Effects of Gastric Bypass Surgery in Patients with Obesity and Type 2 Diabetes

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Cover illustration: Rod of Asclepius, symbol of healing and medicine

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To my teachers and my parents

«Ὁκόσα φάρμακα οὐκ ἰῆται, σίδηρος ἰῆται˙ ὅσα σίδηρος οὐκ ἰῆται, πῦρ ἰῆται˙ ὅσα δέ πῦρ οὐκ ἰῆται, ταῦτα χρή νομίζειν ἀνίατα»

Those who cannot be cured by medications can be cured by surgery, what surgery cannot cure, is being cured by cauterization, what cauterization cannot cure, they should be considered incurable

Hippocrates 460-377 BC

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ABSTRACT

Background: The effects of Roux-en-Y gastric bypass (GBP) have not been adequately explored in patients with concurrent obesity and type 2 diabetes mellitus (T2DM) to the same extent as has occurred for individuals with obesity alone. The overall aim of this thesis is to thoroughly examine the effects of GBP surgery in patients with obesity and T2DM in terms of cardiovascular disease and mortality, changes in various comorbidities, risk factors, and renal function as well as reporting adverse events.

Method: The reported studies are based mainly on merging data from two nationwide quality registries in Sweden (the National Diabetes Register and Scandinavian Obesity Surgery Register) as well as other national databases. Our study population of individuals with T2DM who had undergone GBP was matched with respect to baseline parameters such as sex, age, body mass index (BMI), and calendar year with controls who did not undergo surgery. The risks of postoperative outcomes were assessed using Cox regression models adjusted for various factors depending on endpoints.

Results: Assessing data for 6,132 patients in each group from 2007 to 2014, we found a 58% relative risk reduction in overall mortality, a 59% lower risk of cardiovascular death, and a 49% lower risk of fatal or non-fatal myocardial infarction in the GBP group compared to controls. Following GBP, there were beneficial changes in BMI, hemoglobin A_{1c}, blood lipids, and blood pressure compared to controls despite less frequent use of antidiabetic, antihypertensive, and antihyperlipidemic medications. The improvements in risk factors might contribute to the reduction of mortality risk after GBP in individuals with obesity and T2DM, but the main effect seems to be mediated through the decrease in BMI.

New analyses of data for 5,321 individuals during 2007 to 2015 confirmed lower incidences of all-cause mortality and cardiovascular disease, demonstrated beneficial effects on severe kidney disease, and showed increased risks (2-fold to 9-fold) for several short-term postsurgical complications compared to controls. There were long-term adverse consequences of GBP compared to controls: there was a 92% higher risk of anemia, a 3-fold increase in nutritional deficiencies, a 33% higher risk for psychiatric diagnoses, and a 3-fold increase in

alcohol abuse. The risk rates for most outcomes relating to renal function were lower after GBP. Risks of a composite of severe renal disease or halved estimated glomerular filtration rate (eGFR), and cardiovascular and renal mortality, were generally lower after GBP in all eGFR strata, even in patients with the lowest eGFR.

Conclusion: The benefits of GBP for patients with obesity and T2DM on mortality, cardiovascular risk, and a broad spectrum of clinical diagnoses might be associated to changes in several risk factors; however, the main effect seems to be mediated through weight reduction. Interestingly, the positive effects of GBP are found for almost all categories of renal function, at the same time delaying deterioration to end-stage renal disease. However, the panorama of both short- and long-term adverse events suggests a more effective selection of patients who genuinely are eligible for such an intervention.

Keywords: Gastric bypass; bariatric surgery; obesity; type 2 diabetes mellitus; cardiovascular disease; mortality; risk factors; renal disease; adverse events

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Effekterna av *Roux-en-Y gastric bypass*, den mest etablerade fetmakirurgiska metoden, har mestadels utvärderats vid fetma men inte tillräckligt hos personer med samtidig typ 2-diabetes mellitus. Det övergripande syftet är att noggrant utforska effekterna av denna behandlingsmetod hos patienter med fetma och typ 2-diabetes gällande hjärtkärlsjukdom och mortalitet, förändringar i olika komorbiditeter, riskfaktorer och njursjukdom samt förekomsten av sidoeffekter.

Metoder: Studierna baseras främst på samkörning av två rikstäckande kvalitetsregister i Sverige, Nationella Diabetesregistret och *Scandinavian Obesity Surgery Register* samt andra nationella databaser. Våra studier omfattar individer med diabetes som hade genomgått *Roux-en-Y gastric bypass* matchade med patienter med fetma och diabetes som inte genomgått kirurgisk behandling. Riskerna för postoperativa utfall värderades med Cox regressionsmodeller.

Resultat: Vi identifierade och följde 6132 patienter i två grupperna från år 2007 till 2014. Risken för total mortalitet var 58% lägre, för hjärtkärlsjukdom 59% lägre och för dödlig eller icke-dödlig hjärtinfarkt 49% lägre i den opererade gruppen jämfört med kontrollerna. *Roux-en-Y gastric bypass* hade positiv påverkan på vikten, HbA1c, blodlipider och blodtryck jämfört med kontrollerna trots färre glukosänkande, blodtrycks- och lipidsänkande behandlingar. Dessa förbättringar i olika riskfaktorer kan bidra till att lägre mortalitet hos individer med fetma och diabetes, men den huvudsakliga effekten förefaller förmedlas genom viktminskningen i sig.

Vi genomförde nya analyser med data från 2007 till 2015, då vi identifierade 5321 individer med fetma och typ 2-diabetes som genomgick *Roux-en-Y gastric bypass*. Vi bekräftade lägre risk för total dödlighet och kardiovaskulär sjukdom, men påvisade också fördelaktiga effekter på allvarlig njursjukdom. Vi visade också 2- till 9-faldigt ökade risker för sjukhusinläggning för flera postoperativa komplikationer. På lång sikt sågs 92% högre risk för anemi, tre gånger ökad risk för malnutritionstillstånd, 33% högre risk för psykiatriska diagnoser och tre gånger ökad risk för alkoholrelaterade tillstånd jämfört med kontrollgruppen. Förekomsten av olika njurrelaterade tillstånd var lägre efter *Roux-en-Y gastric bypass*. Riskerna för sammansatt utfallsmått av allvarlig njursjukdom eller halverad beräknad njurfunktion, men också för kardiovaskulär och mortalitet relaterad till njursjukdom, var i allmänhet lägre efter *Roux-en-Y gastric bypass* oavsett njurfunktionsnivå jämfört med de icke kirurgiskt behandlade patienterna.

Konklusion: Fetmakirurgisk behandling med *Roux-en-Y gastric bypass* för patienter med fetma och typ 2-diabetes mellitus har visat positiva effekter avseende mortalitet, kardiovaskulär risk och ett brett spektrum av kliniska diagnoser. Gynnsamma förändringar av flera riskfaktorer ses, men den huvudsakliga effekten förefaller medieras av viktminskningen. De positiva effekterna av *Roux-en-Y gastric bypass* ses vid alla njurfunktionsnivåer och förefaller bevara njurfunktionen. Riskerna för oönskade sidoeffekter på kort och lång sikt är argument för ännu effektivare urval av patienter inför kirurgisk fetmabehandling, och strukturerad uppföljning postoperativt.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Eliasson B, Liakopoulos V, Franzén S, Näslund I, Svensson AM, Ottosson J, Gudbjörnsdottir S. **Cardiovascular disease and mortality in patients with type 2 diabetes after bariatric surgery in Sweden: a nationwide, matched, observational cohort study.** *Lancet Diabetes Endocrinol.* 2015;3(11):847–54.

II. Liakopoulos V, Franzén S, Svensson A-M, Zethelius B, Ottosson J, Näslund I, Gudbjörnsdottir S, Eliasson B. **Changes in risk factors and their contribution to reduction of mortality risk following gastric bypass surgery among obese individuals with type 2 diabetes: a nationwide, matched, observational cohort study.** *BMJ Open Diabetes Res Care*. 2017;5(1):e000386.

III. Liakopoulos V, Franzén S, Svensson A-M, Miftaraj M, Ottosson J, Näslund I, Gudbjörnsdottir S, Eliasson B. **Pros and cons of gastric bypass surgery in individuals with obesity and type 2 diabetes: nationwide, matched, observational cohort study.** *BMJ Open.* 2018; 9(1):e023882.

IV. Liakopoulos V, Franzén S, Svensson A-M, Sattar N, Miftaraj M, Björck S, Ottosson J, Näslund I, Gudbjörnsdottir S, Eliasson B. **Change in renal, cardiovascular and mortality outcomes after gastric bypass in type 2 diabetes - cardiorenal risk reductions exceed atherosclerotic benefits.** 2019 (submitted).

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ABREVIATIONS

BMI	Body mass index
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
GBP	Roux-en-Y gastric bypass
GLP-1	Glucagon-like peptide-1
HbA_{1c}	Glycated hemoglobin A_{1c}
HDL	High-density lipoprotein
HR	Hazard ratio
ICD-10	International Classification of Diseases-10
LDL	Low-density lipoprotein
LISA	Longitudinal Integration Database for Health Insurance and Labour Market Studies
LVCF	Last value carried forward
MDRD	Modification of diet in renal disease
NDR	National Diabetes Register
RYGB	Roux-en-Y gastric bypass
SBP	Systolic blood pressure
SD	Standard deviation
SG	Sleeve gastrectomy
SOS	Swedish Obese Subjects
SOReg	Scandinavian Obesity Surgery Register
T2DM	Type 2 diabetes mellitus
WHO	World Health Organization

1. INTRODUCTION

Obesity started to be a problem for humanity when it was realized that it was associated with different public health scourges and later when it was found that the mortality due to obesity surpassed the incidence of death due to starvation (1). Obesity, as a chronic disease, escalated to a global epidemic in parallel with economic development, lifestyle changes, and the altered dietary as well as physical habits of modern individuals. It is a complex phenomenon based on diverse genetic, behavioral, environmental, and socioeconomic factors, which are found in both developed and developing countries. The increasing prevalence of different morbidities and consequent mortality is the main problem of obesity, contributing to socioeconomic consequences worldwide.

Overweight and obesity was considered to be a sign of prosperity and fertility in prehistoric and historic periods, as only the wealthy were able to achieve this 'status'. In the Greco-Roman period, obesity started to be perceived as exceptional rather than a normal condition. Obesity often generated irony and sarcasm, and assumed the characteristics of caricature and satire, confirming the pattern of an idle person. The ancient Greeks were the first to realize the dangers of obesity and its association with disease. The Greek physician Hippocrates understood that the health risks of obesity led to infertility and early death, and recommended diet, exercise, lifestyle change, and use of emetics and cathartics. These recommendations have actually remained unchanged to the present day, when increased urbanization, sedentary working conditions, and availability of processed and high amounts of food have led to a sharp increase in obesity. It is tragic that all this development opposes the maintenance of ideal body weight and creates a further need for more effective methods of weight loss. The management of obesity also involves its associated co-morbidity, which includes diabetes.

This thesis examines the medical control of obesity and diabetes through gastric bypass surgery intervention with respect to effectiveness and potential problems.

Obesity: definition, epidemiology, and associated factors

Obesity is simply defined as excess body weight for height, but this definition provides a false impression when considering obesity as a disease (2). Practically, it only takes into account body mass index (BMI), the metric definition of obesity, rather than the nature of disease. At this point the criticism of the definition of obesity as a disease is referred to BMI, which introduced for its association to mortality without taking into consideration possible underlying biological mechanisms or body composition (3). BMI cannot define either "excessive fat accumulation" or related functional impairments, as World Health Organization (WHO) presents. BMI was

introduced in 1832 by Quetelet to quantify obesity as there is a curvilinear relation between this scoring system and the proportion of body fat (4), constituting until nowadays the way of expression underweight (BMI < 18.5 kg/m²), normal weight (18-24.9 kg/m²), overweight (25-29.9 kg/m²) and obesity (>30 kg/m²). To define obesity as a disease, the health status of the individual needs to be assessed by clinical characterization, laboratory and endocrine measurements, and body adiposity distribution and composition (5). More simply, we approach obesity through the prism of BMI because of its relationship with mortality for BMI values >25 kg/m², as indicated by large epidemiological studies (6-10). Specifically, one of these studies found that persons who were overweight or had class I obesity did not have a significant increase in mortality risk (7), while most studies presented a J-shaped association of BMI with all-cause mortality (mainly resulting from major cardiovascular events, cancer, and respiratory diseases) and an inverse association regarding mental, behavioral, and accidental events for BMI between 24 and 27 kg/m² (8).

According to WHO (11), the prevalence of obesity has nearly tripled between 1975 and 2016, to 1.9 billion overweight adults and 650 million with obesity. In Europe, 23% of women and 20% of men have been estimated to have obesity, while the proportion in Sweden was 17.3% and 19.9%, respectively. The prevalence of obesity in individuals >20 years of age was 18.6% according to WHO in 2013. This compares to 39.8% in the USA for corresponding statistics in 2016. A recent study (12) showed that trends in BMI have flattened in many high-income countries, while they continue increase in developing countries, independently of sex or age.

Obesity occurs from a complex relationship of biologic, psychosocial, and behavioral factors resulting from genetic predisposition, socioeconomic status, and cultural influences. Naturally, the imbalance of incoming energy versus expenditure plays its role but it is not a sufficient condition for weight gain. Overfeeding studies (13) have highlighted that there is a significant concordance in weight gain among twin pairs as well as a high degree of similarity in adipose tissue distribution (14), which is likely to be caused by genetic and epigenetic factors. Genetic susceptibility within a population seems to determine those who have the possibility to manifest obesity when environmental factors are also fulfilled. Identification of those genes should provide insights into the pathophysiological mechanisms of higher BMI and differentiation of fat distribution. Most genetic studies have concentrated on single-nucleotide polymorphisms and short insertions or deletions that influence a genomic product. The first monogenic studies have demonstrated the role of the appetite-regulating leptin-melanocortin pathway in the central nervous system in body weight gain (15). In recent years, genetic biobanks have been developed, from which large genome-wide association studies have identified more than 300 genetic loci in relation to obesity, while an epigenetic focus on DNA methylation and histone modification has tried to establish associations with different gene expressions that might affect adiposity phenotype (16, 17). Although, the research on genetics

develops with significant associations, the genetical effects on BMI variations or waist-to-hip ratio cannot contribute more than 20%-25% (18, 19).

Predictions on interactions between genes and environmental factors are difficult to make. Factors such as physical activity, metabolic rate, or regulation of energy balance by paracrine hormones, neurotransmitters, gut-brain peptides, and appetite modulators all play a role in fat deposition, but with unknown proportions with respect to causality (20). The role of gut microbiota and its composition is also being investigated with respect to effects on nutrient metabolism, energy balance, and BMI (21). Finally, cultural characteristics, high-fat diets, and different types and deposition patterns of adipose tissue have also been considered as important factors, with the latter – accumulation of visceral adipose tissue – being the focus of metabolic abnormalities known as metabolic syndrome.

Clinical features and complications of obesity – a link to type 2 diabetes mellitus

Hippocrates wrote "Corpulence is not only a disease itself, but the harbinger of others", recognizing that obesity is a medical disorder that also leads to many comorbidities, deteriorates quality of life, and reduces life expectancy.

Obesity is an integral part of a cluster of metabolic abnormalities called metabolic syndrome including insulin resistance (22), dyslipidemia (23), and hypertension (24) that together culminate in an increased risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) (25). Specifically, increased visceral fat is accompanied by increased lipolysis, which leads to increased gluconeogenesis and, further, to hyperinsulinemia and decreased muscle insulin sensitivity. When compensation by β-cells becomes insufficient, hyperglycemia and T2DM occur (26). A meta-analysis of 18 prospective studies (27) demonstrated a 7-times higher risk of diabetes in persons with obesity and a 3-times higher risk in overweight individuals compared to those with normal weight. The strongest and most linear association of weight gain appeared for T2DM, although there were also associations with other major chronic diseases such as CVD and cancer as well as non-traumatic death (28). Conversely, individuals who were classified as metabolically healthy subjects with obesity were younger, with smaller waist circumference, and were associated with a lower risk for diabetes and CVD. Only one third of these individuals changed to a high-risk phenotype (29).

The cardiovascular consequences of obesity have been highlighted in several studies (25, 30, 31) as well as the association with higher risk of all-cause mortality (8-10). Stratification into different age groups showed that adults with obesity had earlier onset of CVD, a greater proportion of lives exposed to CVD morbidity, and shorter survival than normal-weight individuals (31). For each 5 kg/m² increase in BMI above 25 kg/m², all-cause mortality increases by 30% with the highest proportion attributed to CVD, diabetes, kidney disease, non-neoplastic hepatic disease, neoplastic disease,

and respiratory disturbance (9). Diabetes and obesity are powerful predictors of cardiovascular morbidity and mortality, which is related to atherosclerotic disease, the inflammatory status of obesity, and elevated adrenal activity with an upregulated renin-angiotensin-aldosterone system (32, 33). The underlying pathophysiological mechanism is complex.

The combination of obesity and T2DM also seems to be responsible for an increased incidence of cancer. It is estimated that approximately 6% of cancer diagnoses worldwide in 2012 were attributed to diabetes and high BMI with higher incidences of liver and esophageal adenocarcinomas as well as endometrial cancers (34). The proposed mechanism is similarly complex to that proposed for increased CVD with hyperinsulinemia and the chronic inflammatory burden appearing to act in the pathogenesis. There are several other clinical conditions that have been attributed to the combination of obesity and T2DM where the mechanism is not fully understood. For example, osteoarthritis is a clinical complication of both obesity and diabetes, but also of each disease separately (35). Literature contains many other clinical complications related to obesity such as restrictive lung disease, hypoventilation, sleep apnea, gastrointestinal and liver consequences, fertility and menstruation problems, and neurological and psychiatric disorders. A lot of these conditions are also associated with T2DM.

Type 2 diabetes mellitus – before the link with obesity

T2DM is simply characterized by insulin resistance and impaired insulin secretion. It is a complex disease that involves cellular and molecular mechanisms leading to dysregulated glucose homeostasis. Multiple factors including genetic predisposition, insulin resistance, increased insulin secretory demand, dysregulation of glucose and lipid metabolism, impaired incretin release/action, amylin accumulation, and decreased β-cell mass play a causative role in progressive β-cell dysfunction and inadequate insulin secretion (36, 37).

According to WHO in 2016, the number of individuals living with diabetes has almost quadrupled since 1980 to 422 million adults globally (38). Estimations from the International Diabetes Federation indicate that the number with diabetes will increase to 642 million (uncertainty interval 521-829 million) by 2040, while the number of deaths attributable diabetes was 5.0 million between 1990 to 2015 (39). In Europe, 66 million people suffer of diabetes which translates to a prevalence of 9.1% and an age-adjusted estimate of 6.7%. In Sweden, it is estimated that the prevalence of diabetes will rise from 6.8% in 2013 to 10.4% by 2050, with 940,000 subjects affected and a constant incidence of 4.4 per 1,000 (40). T2DM is the most common type of diabetes, accounting for around 90% of all cases of diabetes. All this data confirms the large burden of diabetes, especially in developing countries, and emphasize the problem for the future.

As previously mentioned, diabetes is a multifactorial disease in which genetic factors play a key role; at the same time, there is considerable heterogeneity. A positive family history contributes to 2.4-fold higher risk for diabetes, while twin studies provide higher concordance rates and risks (37). The complexity of diabetes genetics has been demonstrated by genome-wide association studies, which have shown more than 100 genetic associations for the phenotype (41).

A positive energy balance with excess carbohydrate intake leads to high conversion of fat in the liver. Fat increases in fat tissue as well as in the liver when accumulation in subcutaneous adipose storage surpasses a certain threshold. This also increases circulating fat in the form of very low density lipoproteins and does not suppress the production of insulin. Over time, hyperinsulinemia further increases lipogenesis, deregulates pancreatic β-cells, and deteriorates peripheral tissue sensitivity, leading to hyperglycemia and impaired postprandial insulin secretion. The inhibitory effects of fatty acids and glucose on the islets reach a trigger level where the β-cells become unable to compensate for insulin resistance, leading to a relatively sudden onset of clinical diabetes (42, 43). The individual processes in the mechanism of diabetes development are certainly more complicated, not fully understood, and outside the scope of this thesis.

Treatment of obesity and T2DM – the role of bariatric surgery

The close relationship and the development of obesity and diabetes also imply common methods for treatment. Prevention and treatment of the combination of obesity and diabetes – also called diabesity (44) – is an imperative with clinical and economic public health consequences globally. All treatment strategies have more or less concentrated on weight reduction with lifestyle, medical, or surgical intervention.

The Look AHEAD Study, for example, randomized 5,145 patients with obesity and diabetes to intensive lifestyle intervention through decreased caloric intake and to 175 minutes of moderate-intensity physical activity every week over a median 10.2-year follow-up. It showed a significant initial weight reduction of 7%-10% followed by gradual regain, improvements in CVD risk factors (45, 46), and a reduction in CVD morbidity depending on the magnitude of weight loss (47, 48). A systematic review looked at the maintenance of weight loss in adults with obesity and assessed the evidence for the effectiveness of behavioral lifestyle interventions (49). The evidence was limited beyond 24 months after the initial weight loss even after addition of weight-loss medication, orlistat, which partially prolonged the effect but with inhomogeneous final results. Use of liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, in the LEADER Study (50) also showed greater weight loss (6.1% at 160 weeks) and reduced risk for T2DM, but this was limited by the short follow-up duration and adverse events from the medication. Recently, a randomized, placebo-controlled, double-blind study (CAMELLIA-TIMI 61) examined the effect of

lorcaserin, a selective serotonin 2C receptor agonist, that influences appetite (51). After a median 3.3-year follow-up, lorcaserin resulted in improvements in glycated hemoglobin A_{1c} (HbA_{1c}), which was related to weight loss (5% at the first year), discontinuation of antidiabetic agents, and a lower risk for microvascular outcomes based mainly on the effects on microalbuminuria. Actually, there are several other studies providing evidence of weight loss based on conservative therapies, however emphasizing also the limitations (52, 53).

Bariatric or metabolic surgery is the most effective treatment for obesity and T2DM in the terms of maintenance of weight loss, impact on comorbidities, improvement of quality of life, and reduction of all-cause mortality (54-56). Surgeons hypothesized that shortening of the intestine should have an effect on weight loss. In 1952, a Swedish surgeon, Dr Viktor Henrickson, performed the first bariatric operation after his observation of weight reduction in patients that underwent intestine surgical treatment for other diseases. Historically, there have been six dominant procedures in bariatric surgery. In chronological order, they are jejunoileal bypass, Roux-en-Y gastric bypass (GBP), vertical banded gastroplasty, biliopancreatic diversion and its variation duodenal switch, adjustable gastric banding, and sleeve gastrectomy (SG) (57, 58). Because of unacceptable complications of jejunoileal bypass, Dr Mason developed the technique of GBP in 1967, which is actually a development of Billroth II resection and constitutes the most common and effective method used today.

Comparisons with SG have demonstrated heterogeneous results. The STAMPEDE Study (59), for example, found higher weight reduction in GBP patients at 5 years. However, there was no significant difference between the methods with respect to glycemic control, although use of antidiabetic medication was lower in the GBP group. There were no significant differences with respect to blood pressure and low-density lipoprotein (LDL)-cholesterol, while adverse events were relatively similar between the techniques. Likewise, the SLEEVEPASS Study (60) showed greater percentage weight loss among GBP patients; however, 8.3% of SG patients needed reoperation compared to 15.1% for GBP. A Swiss study that also randomized patients to the two techniques did not show significant differences in weight or metabolic changes (61), although there was a higher rate of reoperation/intervention among those who received GBP. SG seems to gaining ground in surgeons' preferences, mostly due to lower complication rates, despite the lack of confirmation of long-term efficacy.

Gastric bypass – effects on weight, comorbidities, and mortality

This thesis concentrates on the effects of GBP because it was the dominant technique used during the study period as well as for the completeness and availability of the data in Sweden. In practice, the indications for bariatric surgical treatment and GBP have been in accordance with the Interdisciplinary European Guidelines on Metabolic

and Bariatric Surgery (62), the National Institute for Health and Care Excellence (63), and the 1998 US guidelines (64). Nevertheless, the final decision for using bariatric surgery and the appropriate technique should always be based on the individuals and their needs.

GBP surpasses other methods concerning efficacy for weight reduction. The Swedish Obese Subjects (SOS) Study, a prospective observational study since 1987, showed a mean (± SD) weight loss compared to baseline of 25±11% for GBP, 16±11% for vertical-banded gastroplasty, and 14±14% for banding after 10 years. After 15 years, the corresponding values were 27±12%, 18±11%, and 13±14%, respectively (65). The maximum weight loss occurred after 1 year: 38±7%, 26±9%, and 21±10%, respectively (66). Large comprehensive meta-analyses have confirmed the effectiveness and superiority of GBP with significant weight reduction and relative maintenance for more than 2 years (54, 67). King et al. (68) presented information on the percentages of patients with weight regain after bariatric surgery. The highest rate of weight regain occurred 1 year after reaching nadir weight and gradually continued thereafter, i.e. 43.6% increased ≥5 mg/kg^2 5 years after reaching their nadir weight loss. This highlights the importance of setting realistic expectations on obesity resolution after surgical treatment and specifies the need of long-term multidisciplinary follow-up or renewed intervention.

Furthermore, bariatric surgery and GBP have shown effectiveness for various comorbidity and mortality endpoints independently of the existence of T2DM. There are few randomized or observational studies that have studied the effects of GBP on study populations with both obesity and T2DM. In the SOS Study, for example, only 7% of 2,010 patients in the GBP group had concurrent T2DM. Randomized studies (59, 69-71) showed significant findings with respect to comorbidities and CVD, but they had low power and they did not assess mortality. Analysis of the diabetes population in the SOS Study (72) showed a reduced incidence of myocardial infarction but no effect on stroke. The first meta-analysis of observational studies on the effects of bariatric surgery on CVD and mortality suggested a more than 50% reduction in mortality, myocardial infarction, and stroke compared to non-surgical controls; however, there was an unknown proportion of patients with diabetes (73). A large Swedish study, also with an unclear number of T2DM patients, was derived from the Scandinavian Obesity Surgery Register (SOReg): it presented outcomes related to various comorbidities such as T2DM, hypertension, dyslipidemia, depression, and sleep apnea at 1, 2, and 5 years after primary GBP (74). The most profound improvements occurred for T2DM and sleep apnea based on changes in laboratory data and medical prescription. More recently, a retrospective observational study, which investigated the time to occurrence of macrovascular disease after bariatric surgery in patients with severe obesity and T2DM, found a 40% risk reduction for macrovascular events but no significant effect on cerebrovascular disease at 5 years (75). Finally, the beneficial effect of different types of bariatric surgery was a 56% lower risk of microvascular disease, which was assessed through

hospital admission or treatment in outpatients clinics in the SOS Study (76, 77), and among patients who experienced T2DM remission an almost 30% lower risk in incidence of microvascular disease in an recent American retrospective study, which included 4,683 patients with T2DM followed up to 7 years (78).

Likewise, there are few studies that have estimated mortality as it seems that a longer follow-up duration is required to produce clear results. Most randomized and observational studies are designed to investigate remission for diabetes and comorbidities after bariatric surgery rather than mortality. The SOS Study (65) showed a 24% lower risk of mortality in an unadjusted model and 29% lower risk after adjustment for sex, age, and risk factors. The lower risk in the surgery group was mainly attributed to the long-term weight loss. In a retrospective cohort study of 7,925 matched patients who had undergone GBP, Adams et al. (79) showed a decreased risk of all-cause mortality (40%) and for cause-specific mortality from coronary artery disease (56%), diabetes (92%), and cancer (60%), over a mean follow-up of 7.1 years. Mortality rates by accidents or suicide were 58% higher in the GBP group. The existence of diabetes may play a role in mortality for patients who receive GBP. A stratified study of patients with or without diabetes showed a significantly lower mortality rate for patients with T2DM compared to those without after GBP. They were also less likely to die from CVD, diabetes, or respiratory disease (80). Irrespectively of diabetes remission, effects on other classic CVD risk factors or the weight loss by itself are eventually components of such evolution (81).

Effects on renal disease

The burden on renal function attributed to obesity (82, 83) or T2DM (84, 85) present two distinct situations that have been extensively investigated. The combination of both factors accelerates the risk of albuminuria, chronic kidney disease (CKD), and end-stage renal disease (ESRD). Hemodynamic changes related to activation of the sympathetic nervous and renin-angiotensin systems as well as inflammatory abnormalities and oxidative stress from both obesity and metabolic syndrome are consistent with glomerular hyperperfusion and hyperfiltration, leading to albuminuria and renal impairment (86-88).

The effects of bariatric surgery, and especially of GBP, on renal function and development of CKD or ESRD have not been adequately investigated in a population with concurrent obesity and T2DM. A recently published retrospective, matched cohort study (89) observed T2DM patients for a median follow-up of 4.3 years after bariatric surgery and showed a 59% lower risk for nephropathy for the surgical group. Another study found resolution of albuminuria in 51% of T2DM patients over a mean follow-up of 61 months following bariatric surgery (90). The STAMPEDE Study (59) only showed a significantly lower urinary albumin-creatinine ratio in SG patients. Change in BMI seems to be the most reliable predictor of this renal function change,

particularly in the first year when patients reach their lowest postsurgical weight (91-93). The SOS Study showed a more than 50% lower risk for albuminuria compared to conservative treatment; however, it failed to show a lower incidence for albuminuria in GBP patients, even though GBP resulted in greater weight loss (94).

It is noteworthy that albuminuria is attenuated when weight is reduced either conventionally (95) or by bariatric surgery (96), meaning that patients with different levels of renal function could experience either an improvement or reversal of the progression of renal dysfunction. Shulman et al. (97) demonstrated a protective role by bariatric surgery against stage 4 CKD or ESRD during 18 years of monitoring, while Alexander et al. (98, 99) reported resolution, improvement, or stabilization of renal function after surgery in patients with CKD or following kidney transplantation. Prospective or randomized studies should more robustly evaluate the beneficial effect of GBP on different levels of estimated glomerular filtration rate (eGFR).

Adverse events of gastric bypass

Bariatric surgery is thus the most effective method of weight loss and regression of associated comorbidities; nevertheless, it is still a surgical method with complications and undesirable effects. Several cohort studies have reported various hospital readmission rates depending on bariatric technique, type of complications, and different duration of follow-up. Specifically for GBP, the hospital readmission rate has ranged from 0.6% to 11.3% within 30 days (100-104), with low mortality (0-0.16%) (100, 105, 106), 3% major adverse events (105) but 21.4%-65.9% long-term outcomes (such as adhesive bowel obstruction, hernia, or psychiatric disorders) during longer time of observation (101).

Adverse events of GBP have been evaluated through observational and randomized studies; however, this has not been sufficiently addressed in patients with concurrent T2DM in surgical populations. The randomized STAMPEDE Study and the Diabetes Surgery Study have reported the adverse events of GBP and SG and, as expected, were more serious than conventional management (59, 70, 107). Strictures, bowel obstructions/ileus, ulcers, gastrointestinal leaks, and reflux disease were the most frequent complications in the first year, and hypoglycemia, anemia, nutrient deficiencies, and depression during the entire follow-up. A Swedish observational study based on the Scandinavian Obesity Surgery Register (SOReg) also demonstrated a higher risk of internal hernia and gallstone disease, as well as a 12-fold increased risk for additional gastrointestinal surgery after primary intervention (101). In addition, they highlighted the value of preoperative weight loss, which reduced the overall risk of postoperative complications by 13%-18%, concerning different types of complications (108). Finally, large US studies (104, 109, 110) have confirmed the aforementioned early postoperative outcomes as well as some of the

long-term deficiencies such as hypoglycemia and psychiatric disorders; however, the study populations only included low proportions of patients with T2DM.

2. AIMS

The main aim of this thesis is to study the effects of GBP surgery on patients with obesity and T2DM. The specific aims of the individual studies are present below.

I. The aim of the first study was to investigate the risk of cardiovascular events and mortality in patients with obesity and T2DM who had undergone GBP compared to patients with same characteristics who did not undergo surgical treatment.

II. The scope of the second study was to thoroughly describe the changes in weight, glycemic control, cardiovascular risk factors, and use of medication as well as to assess the effect of such changes on cardiovascular disease and mortality after GBP.

III. The objective of the third study was to identify the clinical benefits and the short- and long-term adverse effects of GBP in patients with obesity and T2DM compared with matched individuals not undergoing surgery.

IV. The aim of the fourth study was to explore the effects of GBP on renal function in individuals with obesity and T2DM as well as to examine the overall safety of such surgery in patients with different levels of renal disease.

3. PATIENTS AND METHODS

DATA SOURCES

This thesis is based on several data sources provided by different national registries in Sweden. The main registries were the National Diabetes Register (NDR) and the SOReg. Both registries are linked to the National Board of Health and Welfare, which also stores data from the Swedish Inpatient Register (1997-2015). Due to the unique advantage of the personal identity number in Sweden, we can also link to other registries such as the Cause of Death Register (1996-2016), the Prescribed Drug Register (2005-2015), and Statistics Sweden (Figure 1).

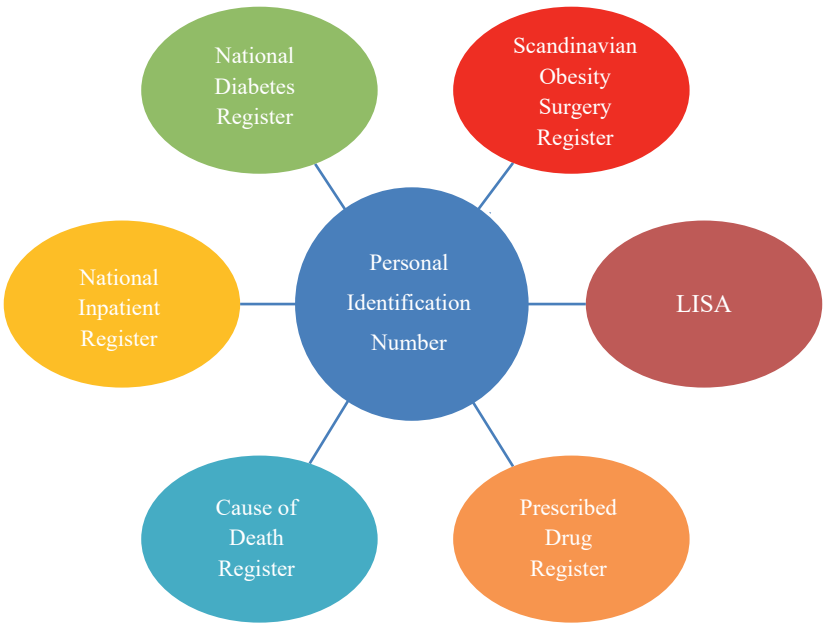

Figure 1. Data sources linked by personal identification number

We submitted our data (NDR and SOReg) and personal identity numbers to the National Board of Health and Welfare for the years 1996-2015 and 2007-2014, respectively. All the personal identity numbers were then replaced by anonymized serial numbers. The coded data were linked to the National Inpatient Register, Prescribed Drug Register, and Cause of Death Register and forwarded to Statistics

Sweden for linkage with the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA), which provides socioeconomic data. The linked data were then returned to us for validation and analysis.

NDR

The National Diabetes Register was launched in Sweden by Swedish Society of Diabetology in 1996 to gather patient data for research purposes and the development of evidence-based treatment for diabetes. Physicians and diabetes nurses report data such as clinical information, medical measurements, and blood tests related to diabetes from outpatient clinics and primary care centers nationwide at least annually. Patients are informed about the scope of registering in the NDR as well as the facilitation of patient self-participation in diabetes care, so that they can provide oral consent or refuse inclusion in the register. Overall, more than 500,000 patients with diabetes are included in the NDR, covering ~90% of patients with T2DM and ~95% of patients with type 1 diabetes mellitus in Sweden.

SOReg

Scandinavian Obesity Surgery Register was started in May 2007 as a quality and research register for patients who receive bariatric surgery in Sweden. Since 2010, it has covered all bariatric procedures in Sweden. The aim of the register is to enhance the application of surgical treatment in patients with obesity, to improve surgical conditions and indications, and to upgrade postsurgical follow-up. All bariatric centers report presurgical characteristics, surgical complications, short-term postoperative and longitudinal effects. Recently, the follow-up time of patients in SOReg has been extended up to 10 years after surgery.

Other Registries

The National Inpatient Register started as National Patient Register in the 1960s and initially included clinical information regarding in-patients from public hospitals. It appeared in its present form since 1987 and includes all in-patients who are cared for in Swedish hospitals with complete coverage of discharge diagnoses.

The Cause of Death Registry belongs to National Board of Health and Welfare, is based on death certificates, and provides statistics for time and cause of death with full coverage since 1961.

The Prescribed Drug Register was established in 2005 to increase knowledge on the effects of prescribed medications. It records all filled prescriptions from all pharmacies nationwide, including information on specific drug (e.g. package size,

dosage instructions, date of drug dispensing), and both patient and prescriber characteristics with also complete coverage.

Finally, the Statistics Sweden, which provides the LISA database, supply demographic, vital status, and socioeconomic data (e.g. educational levels, marital status, occupation, income, ethnicity) and has covered the entire Swedish population since 1990.

PROCEDURES

Studies I and II

These observational, retrospective, cohort studies included adult patients (≥18 years) who had undergone GBP at hospitals in Sweden between January 1, 2007 and December 31, 2014. The studies merged data from SOReg and NDR, which provided a unique study population with three properties – GBP surgery, obesity, and T2DM. We also linked with other national registries such as the National Inpatient Register, the Cause of Death Register, and Statistics Sweden to study various outcomes. All databases have been described and validated (111, 112) (Table 1).

We matched these patients 1:1, without replacement, to patients from NDR with obesity and T2DM but not undergoing GBP. The matching was based on sex, age, BMI, and calendar year of database entry. For this type of matching, we used different categories of age (0-41, 42-49, 50-55, and ≥56 years), BMI (<28, 28 to <35, 35 to <38, 38 to <43, and ≥43 kg/m²), and calendar time (2007-2008, 2009-2010, 2011-2012, and 2013-2014).

The baseline variables for studies I and II were: sex, age, BMI, type and duration of diabetes, HbA_{1c} concentration, LDL- and high-density lipoprotein (HDL)-cholesterol concentrations, blood pressure, antidiabetic, antihyperlipidemic, and antihypertensive treatment, smoking status, history of myocardial infarction, congestive heart failure, and stroke, baseline annual income (in Swedish Krona), marital status, and educational level [low (up to school year 9 of compulsory comprehensive school), mid (years 10-12 of upper secondary school), or high (college or university)].

Obesity is always defined as BMI ≥30 kg/m², but we included all patients who had received GBP independently of BMI in our studies. T2DM was defined epidemiologically as onset of diabetes at ≥40 years of age and treatment by diet, antidiabetic drugs, insulin, or any combination thereof. Smoking was defined as current use of tobacco. In study I, we defined history of myocardial infarction, stroke, or congestive heart failure as admission to the hospital due to these diagnoses before baseline and using codes from the International Classification of Diseases-10 (ICD-10) [I20-25, I61-64, and I50, respectively]. In study II, we defined remission of diabetes as HbA_{1c} <6.5% (<48 mmol/mol) and physical activity as low intensity of

training for ≥30 min 3 times/week. The analyses of all laboratory concentrations (HbA_{1c}, and LDL- and HDL-cholesterol) are quality assured nationwide and expressed in SI units.

Table 1. Overview of the cohorts and some patients' characteristics

	Study I		**Study II**		**Study III**		**Study IV**	
Study design	Cohort		Cohort		Cohort		Cohort	
Study period	2007-2014		2007-2014		2007-2015		2007-2015	
Exposure	GBP	Controls	GBP	Controls	GBP	Controls	GBP	Controls
Data sources	SOReg + NDR	NDR	SOReg + NDR	NDR	SOReg + NDR	NDR	SOReg + NDR	NDR
	Swedish Inpatient Register, Cause of Death Register, LISA		SOReg, NDR		Swedish Inpatient Register, Cause of Death Register, LISA		Swedish Inpatient Register, Cause of Death register, Prescribed Drug Register, LISA	
Patients (n)	6,132	6,132	6,132	6,132	5,321	5,321	5,321	5,321
Sex (females %)	61	61	61	61	60.5	63.8	60.5	63.8
Age (years)	48.5	50.5	48.5	50.5	49.0	47.1	49.0	47.1
BMI (Kg/m²)	42.0	41.4	42.0	41.4	42.0	40.9	42.0	40.9
Outcomes	All-cause mortality, cardiovascular death, myocardial infarction		Changes in BMI, HbA_{1c}, LDL, HDL, SBP, DBP, blood pressure-, lipid- and glucose-lowering medication, smoking, physical activity		Variety of diagnoses after admission to the hospitals		Renal diagnoses and cardiovascular disease after admission to the hospitals, s-creatinine, eGFR, micro- and macroalbuminuria	
Mean follow-up time (years)	3.7	3.3	3.7	3.3	4.7	4.6	4.7	4.6

Studies III and IV

As in the first two studies, we merged data from SOReg and NDR. However, we included patients (18-75 years of age) who had received GBP from January 1, 2007 until December 31, 2013. They were followed until December 31, 2015. Relevant data were also derived from other registries such as the Swedish Inpatient Register, the Cause of Death Register, and Statistics Sweden, and, additionally for study IV, the Prescribed Drug Register (Table 1).

Patients with obesity and T2DM who had undergone GBP were matched on propensity score (1:1) with patients from NDR who had obesity and T2DM but did not undergo GBP. Matching was based on sex, age, BMI, and calendar time.

In study III, we used ICD-10 diagnoses as recorded in the National Inpatient Register. In study IV, we assessed renal function using eGFR determined according to the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. In addition, we used serum creatinine concentration in mmol/l and micro/macroalbuminuria with the clinical definition of urine albumin/creatinine ratio (>3-30 and >30 mg/mmol). Development of renal dysfunction included macroalbuminuria, halved eGFR value compared to baseline, and renal disease diagnoses as presented by ICD-10 classification.

OUTCOMES

Studies I and II

Patients were followed from the index date (date of GBP surgery or a random date within 2 calendar years for controls not undergoing GBP) until the first occurrence of myocardial infarction or stroke, until December 31, 2012 (for data from the Inpatient Register), or until death or until December 31, 2014 (for data from the Cause of Death Register). Primarily, we were interested in fatal or non-fatal myocardial infarction, cardiovascular death, and all-cause mortality. Secondarily, we looked at changes in various risk factors in first year after baseline for those who underwent GBP. We assessed the changes in the control group 1 year after the index date with a range of 90 days before and 180 days after, to avoid multiple imputations.

In study II, we monitored patients in the terms of weight, HbA_{1c}, lipid profile (LDL- and HDL-cholesterol), systolic (SBP) and diastolic blood pressure (DBP), pharmacological treatments, smoking, and physical activity through the whole follow-up period (maximum 7.99 years). Furthermore, we evaluated the effect of the aforementioned factors on the risk of overall mortality, cardiovascular death, and myocardial infarction using causal mediation analysis.

Studies III and IV

In study III, we monitored GBP and control patients from baseline until admission to the hospital due to specific diagnoses related to CVD (acute myocardial infarction, stroke, and peripheral vascular disease), atrial fibrillation, congestive heart failure, and valvular disease as well as diagnoses related to diabetes mellitus or generally to obesity or GBP (e.g. cancer, anemia, malnutrition, alcohol abuse, psychiatric disorders) and all-cause mortality. We also looked at postsurgical diagnoses such as bleeding, complementary gastrointestinal surgery, leakage, ulcers and reflux disease, hernias, bowel obstruction, gall bladder disease, and pancreatitis as well as additional

plastic surgery. Monitoring of the two groups was conducted for up to 9 years (mean 4.6 years). Control patients were censored at the treatment date in the surgery group.

In study IV, patients were primarily assessed for the time to hospital admission due to various diagnoses (renal dysfunction, development of macroalbuminuria, or halved eGFR value) or censored at the end of the study (December 31, 2015) compared to baseline in both groups. Specifically, we were interested in diagnoses of acute and chronic kidney failure, hemodialysis and peritoneal dialysis, kidney transplantation, and diabetic nephropathy. Secondarily, we stratified our groups to different levels of eGFR and estimated the same outcomes. We also investigated the risk for development of severe renal disease or halved eGFR, CVD, congestive heart failure, specific mortality due to CVD or renal disease, and all-cause mortality. Finally, we calculated changes on several renal variables (e.g. creatinine, eGFR etc.) 1 and 2 years after GBP.

STATISTICAL ANALYSIS

Study I

Missing baseline data in SOReg were imputed from a multivariate normal model with a Monte Carlo Markov chain approach. The NDR database for controls is very large, making multiple imputations less feasible on the entire dataset. In addition, it would have been difficult to retain strong within-patient correlation for variables with a high missing data percentage, such as LDL- and HDL-cholesterol (42%). So, we used the last value carried forward (LVCF) method that preserves high within-patient correlations for many variables. Controls that remained without value after the LVCF imputation were excluded from the matching and subsequent regression analysis.

Due to use of rather wide intervals for the matching variables, there may be more than one registration date that can be selected as the index date in controls. For that reason, we selected a random registration date for a matched control during the 2 years when the GBP patient received surgery. Matching of controls was undertaken without replacement, which means NDR patients who were selected as controls in one time period could not be selected as controls in later periods; however, they could be treated surgically later, in which case they were censored at the time of treatment.

To compare the groups in descriptive statistics, we used absolute and mean values and standardized mean differences, as we only described the observed populations and therefore we used a measure tailored for this, independent of the sample size. P-values concern the population's means and the hypothesis test. We calculated p-values to express the significant changes in risk factors in the first year using a mixed repeated measure model for continuous variables, McNemar's test for discrete variables, and χ^2 test for binary variables for diabetes remission. A Cox regression model with Kaplan-Meier survival analysis was used to calculate cumulative all-cause mortality on the

basis of BMI changes 1 year after GBP. Log-rank test was used to estimate survival beyond 1 year of diabetes remission.

Furthermore, we tried to estimate the effect of GBP treatment on outcomes by fitting a Cox regression model to the data, including the treatment indicator and all the baseline variables. As estimator, we used number of events, events rates, and hazard ratios (HRs) with or without adjustment for multiple baseline characteristics. Using Cox regression analysis, we also estimated the number of patients needed to be treated at 5 years of survival based on median values of all covariates.

Finally, we also conducted a sensitivity analysis to search for unobserved confounding factors in relation to the outcome using the method suggested by Greenland (113, 114).

Study II

In study II, we used the same baseline characteristics as in study I. To evaluate the changes of variables during the 7.99-year follow-up, we constructed a linear mixed repeated measure model for BMI, HbA_{1c}, LDL-cholesterol, HDL-cholesterol, SBP, and DBP, and a generalized mixed repeated measure model for variables such as smoking and use of antihypertensive or antihyperlipidemic drugs. We assumed as yearly mean values, measurements performed between months 6-18 as the first year, months 18-30 months as the second year, etc.

In order to investigate the contribution of changes of various risk factors to our outcomes (all-cause mortality, cardiovascular death, and myocardial infarction), we used a new statistic method named causal mediation analysis (115). This method is formulated as a linear structural equation model and tries to identify mediators namely factors that eventually lie in the causal pathway between the treatment (GBP) and the considered outcomes. The potential mediators we examined were changes in risk factors such as BMI, HbA_{1c}, SBP, and LDL- and HDL-cholesterol.

We constructed separate Cox regression models that combined with multinomial logistic regression models to estimate the direct and indirect effect of the mediator to exposure and outcome. The direct effect is the effect of treatment without the corresponding effect of the mediator and indirect effect is the effect of the change in the mediator that is associated with the exposure but without changing the actual exposure. All models were adjusted for previous myocardial infarction, chronic heart failure, or stroke, HbA_{1c}, SBP, DBP, smoking status, use of antihyperlipidemic, antihypertensive, and antidiabetic drugs, income, and educational and marital status.

Study III

In contrast to the previous studies, we matched groups using a propensity score for longitudinal exposure, which was assessed though descriptive statistics. The GBP patients and controls differed substantially prior to matching. It was difficult to find closely matching controls for all GBP patients so the matching process consequently

resulted in only an approximate match. We therefore included potential confounders not balanced after the matching process in the analysis model. The matching has the benefit of selecting an index date for the controls and the balance after matching was enough to make regression adjustment feasible. The propensity score model was set up as a Cox proportional hazards model with time varying covariates and exposure to GBP as the event of interest. The propensity score model contained covariates for sex, age, and BMI.

We presented descriptive statistics with means with standard deviation (SD) for age and BMI, median with quartiles for income, and absolute values with percentages for all other variables. Incidence rates for each outcome were estimated using counts and person-years. In terms of time, we made comparisons between GBP patients and controls by constructing a Cox regression model adjusted for sex, age, BMI, and socioeconomic factors (income, marital status, educational level, and country of birth). We did not make any adjustments for multiple inferences.

An additional Cox regression model was used to separately estimate outcomes in the distribution of men and women.

Study IV

Baseline characteristics were described by absolute frequencies or mean values with percentages or SDs, respectively. As in the previous studies, we used standardized mean differences to describe the comparability of distributions of our groups.

We evaluated the endpoints using number of events and incidence rates per 10,000 person-years together with exact 95% Poisson confidence intervals (CIs). The two groups were compared using HRs estimated with a Cox regression models adjusted for sex, age, BMI, eGFR, marital status, income, educational level, and country of birth. First- and second-year postoperative clinical characteristics are described using descriptive statistics and compared between groups using ANCOVA and logistic regression models including covariates at baseline.

ETHICAL CONSIDERATIONS

The overall aim of this thesis was to gain knowledge on patients who undergo GBP and, at the same time, are diagnosed with T2DM and obesity. Such knowledge can be best accessed using organized databases which contain considerable clinical information on patients with specific characteristics of the diseases we are interested in. All four studies used data from the aforementioned databases while adhering to the conditions that such research procedure require according to the rules and processes dictated by the Swedish health system. The linkage of data from various registries to the NDR was performed by the National Board of Health and Welfare, coded, and then delivered as anonymous data to the researchers.

Ethical aspects of register research primarily concern privacy and data security. Register research generally entails minimal risk for patients, risks that can, in principle, be eliminated by adequate security and coding/de-identification of data. In the registries which we used, the patients have largely been informed about possible participation in different studies at the time of first visiting outpatient or primary care clinics. At that time, they have the right to refrain from participation in research projects. The NDR and SOReg are large research institutions that preserve the privacy and integrity of participants through data de-identification and group-level data analysis without nationality discrepancy or arbitration.

The ethics application for our studies approved by the Regional Ethical Review Board in Gothenburg.

4. RESULTS

Mortality and cardiovascular risk in patients with obesity, diabetes mellitus, and GBP

This study compared 6,132 patients with obesity and diabetes who had undergone GBP with equal number of patients with obesity and diabetes who did not undergo such treatment between January 1, 2007 to December 31, 2014. The median follow-up for the groups was 3.5 years (maximum 7.99 years). At baseline (shown in the attached paper), there were some minor differences between the groups in several characteristics. Matching only provided similarity between the groups in terms of sex, duration of diabetes, and HbA_{1c} and LDL-cholesterol concentrations.

Analysis revealed significant differences in all-cause mortality, cardiovascular death, and myocardial infarction between the groups (Figure 2). Fewer patients died overall in the GBP group compared to controls (82 *vs* 288 patients), with a risk reduction of 58% as shown by Kaplan-Meier curves. There were 13 cardiovascular deaths in the GBP group compared to 67 in the control group, with a risk reduction of 59%. The HR for myocardial infarction in patients was 0.51 (95% CI, 0.29-0.91). Similar risk reductions were observed when we excluded patients with prior CVD or congestive heart failure. The 2-year and 5-year absolute risk of all-cause mortality was 0.4% (95% CI, 0.3%-0.6%) and 1.8% (95% CI, 1.5%-2.2%) in the GBP group, respectively, compared to 1.8% (95% CI, 1.4%-2.4%) and 5.8 % (95% CI, 5.0%-6.8%), respectively, in matched controls. Based on the 5-year absolute risk for patient with median values of various covariates, we calculated the number of patients needed to be treated was 76.6.

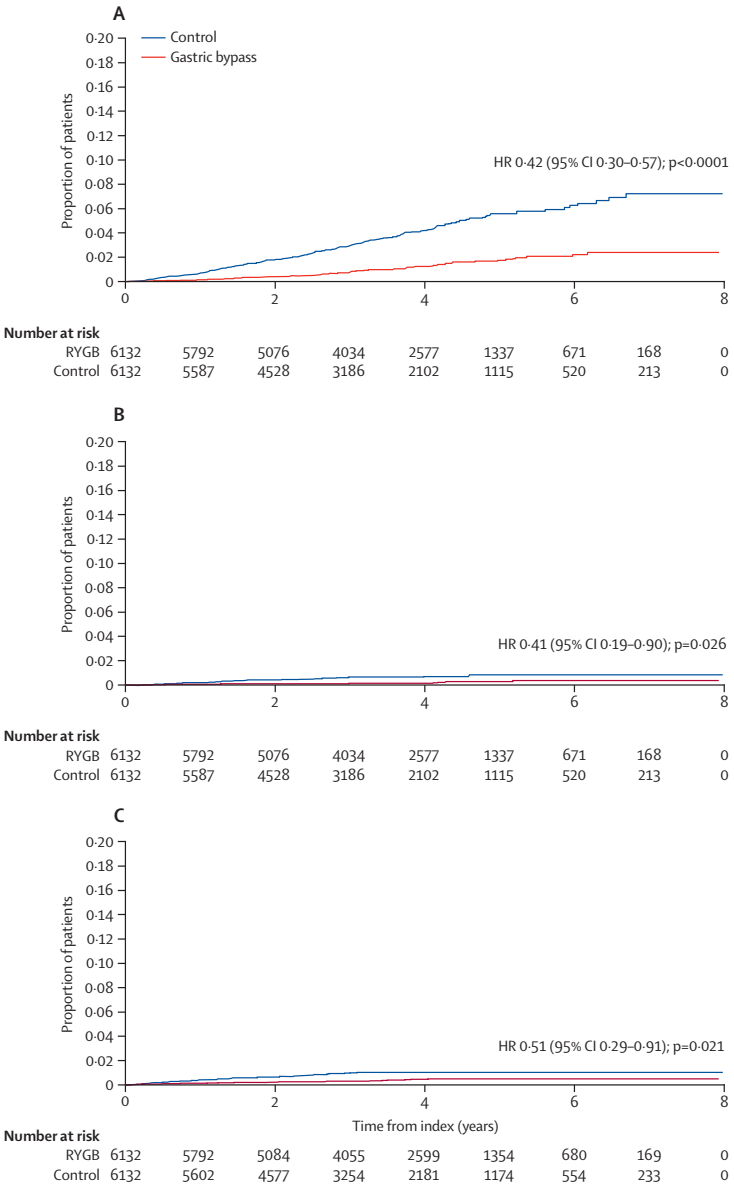

Figure 2. Cumulative incidences of mortality (A), cardiovascular mortality (B), and fatal or non-fatal myocardial infarction (C). From Eliasson et al., *Lancet Diabetes Endocrinol*. 2015;3(11):847–54. Reprinted with permission.

There were significant differences in all parameters (BMI, HbA_{1c}, LDL- and HDL-cholesterol, SBP, DBP, and antidiabetic and antihypertensive drug use) apart from antihyperlipidemic drug use and smoking. Twenty-three percent of GBP patients had HbA_{1c} <6.5% (<48 mmol/mol) at baseline, which increased to 52% at 1 year after

surgery. Corresponding values were 25% and 29% in controls, with the between group change being significant ($p<0.0001$).

The Cox model evaluating cumulative all-cause mortality in relation to different BMI changes in the first postsurgical year. This showed no significant mortality reduction in patients who did not have weight reduction or had the lowest BMI reduction (<2 kg/m²). There was mortality reduction among those with BMI reductions of 2-9 kg/m² ($p=0.0027$) or >9 kg/m² ($p=0.0005$). The risk of mortality during diabetes remission in the first year showed a risk reduction of 38% ($p=0.0066$) compared to the patients not in remission.

In additional analysis, a Cox regression model that included all the baseline factors (presented in the supplementary appendix of the original study) found that age, previous heart failure, and smoking were independent predictors for all-cause mortality. GBP, being female, and being married were protective factors. Age, previous myocardial infarction, and heart failure increased cardiovascular death, while GBP and being female were protective factors. The risk of myocardial infarction also increased with high SBP values.

Finally, to detect potentially unobserved confounders, we conducted sensitivity analysis which arbitrarily tested for the existence/prevalence of an unknown factor that might influence mortality risk. No additional significant effect was found.

Changes in risk factors after GBP and their contribution to mortality reduction

In continuation from the previous study, we used the same cohort to look deeper at the changes of baseline characteristics and risk factors after GBP and over a shorter observation period. The maximum time for which we presented data was up to 6 years, with a median of 3.7 years for GBP patients and 3.1 years for controls. In contrast to the previous study, we decided to present data for this duration of follow-up because of relatively stable mean values and narrow CIs for at least 6 years.

We used a more advanced model for repeated measurements to investigate the changes of various risk factors from baseline. BMI reached its nadir in the second year in the GBP group at 31.9 (95% CI, 31.7-32.1) kg/m² and remained significantly lower than matched controls during the 6-year follow-up. The lowest value for HbA_{1c} was seen in the first year 6.32% (95% CI, 6.27%-6.38%) and also remained significantly lower throughout the whole follow-up period. Compared to the results of the previous study, we found different remission rates for diabetes (36.8% and 9.3% in GBP patients and controls, respectively, in the first year), whereas a different mixed repeated measure model was used for analysis.

Lowering of LDL-cholesterol was significant through the first 3 years in the GBP group, which was independent of the higher consumption of lipid-lowering drugs in the control group. HDL-cholesterol increased gradually and plateaued until the end of

observation in the GBP group. SBP showed the same pattern of change as LDL-cholesterol in the GBP group, but was maintained significantly lower than controls for 4 years. DBP was also reduced in the GBP group, but for a shorter duration despite the more prevalent use of antihypertensive agents in the control group.

The proportion of smokers was significantly lowered in the first 2 years and physical activity was increased for 5 years in GBP group.

Causal mediation analysis, a new statistical method, was undertaken to try and find an explanation for the reduction in all-cause mortality, cardiovascular death, and incidence of myocardial infarction after GBP. In this model, we examined the indirect and direct effect of factors (e.g. BMI, HbA_{1c}, SBP, HDL- and LDL-cholesterol) if we assume that they work or do not work as mediators in the relation between GBP and outcome (Table 2). We found that the lower all-cause mortality and cardiovascular death were significantly mediated through the BMI reduction (an indirect effect). There was no significant effect on myocardial infarction. In contrast, the direct effect of the GBP procedure that was not mediated through the BMI reduction provided a significantly higher risk of all-cause mortality and lower risk of myocardial infarction. Changes in the other factors did not have any significant indirect effect on outcome.

Table 2. Causal mediation results for patients treated with gastric bypass

Causal mediation with Cox regression for patients treated with gastric bypass									
	Overall mortality			Cardiovascular death			Myocardial infarction		
Variable (effect)	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
BMI (direct)	1.956	1.002-3.821	0.0494	1.737	0.594-5.082	0.3133	0.317	0.133-0.756	0.0096
(indirect)	0.384	0.179-0.821	0.0136	0.145	0.028-0.750	0.0213	1.068	0.377-3.030	0.9014
HbA1c (direct	0.329	0.193-0.560	<0.0001	0.292	0.062-1.375	0.1195	0.488	0.230-1.037	0.0620
(indirect)	1.361	0.930-1.993	0.1123	0.988	0.350-2.789	0.9821	0.841	0.468-1.513	0.5641
SBP (direct)	0.611	0.398-0.938	0.0241	0.263	0.051-1.358	0.1109	0.531	0.247-1.143	0.1054
(indirect)	0.948	0.672-1.339	0.7631	0.776	0.296-2.036	0.6069	0.889	0.537-1.472	0.6479
HDL (direct)	0.493	0.280-0.868	0.0143	0.304	0.050-1.839	0.1948	0.521	0.222-1.227	0.1358
(indirect)	1.024	0.649-1.616	0.9197	0.748	0.236-2.370	0.6222	0.681	0.383-1.211	0.1910
LDL (direct)	0.567	0.346-0.930	0.0245	0.187	0.026-1.326	0.0935	0.347	0.156-0.772	0.0095
(indirect)	1.023	0.703-1.491	0.9041	1.664	0.553-5.010	0.3648	1.079	0.592-1.967	0.8038

From Liakopoulos et al., *BMJ Open Diabetes Res Care*. 2017;5(1):e000386. Reprinted with permission.

Clinical benefits and postoperative short- and long-term effects of GBP in patients with obesity and T2DM

To study both the advantages and disadvantages of GBP surgery in patients with obesity and T2DM, we merged data from SOReg and NDR as in previous studies but we included surgery patients from January 1, 2007 until December 31, 2013. They were followed until December 31, 2015. Median follow-up time was 4.6 years (maximum 9 years) and the number of patients in each group was 5,321.

With respect to the clinical benefits of GBP, there were lower incidences of all-cause mortality, CVD, acute myocardial infarction, and congestive heart failure, as partially shown in the first study. Moreover, hospitalization for diagnoses related to diabetes such as hyperglycemia, amputation, and kidney disease was characteristically less frequent after GBP. Cancer diagnosis also appeared less frequent in the GBP group.

Events rates for hospital admission due to anemia (2- fold higher), malnutrition (3-fold higher), alcohol abuse (3-fold higher), and psychiatric disorders (HR 1.33; 95% CI, 1.13-1.58) differed significantly compared to the matched controls. As expected, there was a higher risk of short-term postoperative adverse events among the patients who underwent GBP surgery. Postoperative effects potentially occurring after GBP

were abdominal pain, bowel obstruction, gallstones, gallbladder disease, pancreatitis, gastrointestinal ulcers, reflux, hernia, gastrointestinal leakage, wound complications, and bleeding. Additional gastrointestinal intervention after GBP occurred in 17.6% of cases and reconstructive plastic surgery was also more frequent.

When the sexes were considered separately in a different model with the same adjustments, we noted that men had significantly higher hospitalization risks for fatal CVD, atrial fibrillation, congestive heart failure, and additional gastrointestinal surgery, and women for psychiatric disorders after GBP.

GBP surgery and changes in renal function in patients with obesity and T2DM

Effects of bariatric surgery on renal function have partially been investigated, but there is no clear information on the effects of GBP in patients with obesity and T2DM. With this aim, we used same cohort as in study III to determine the risk of hospitalization due to renal disease and to investigate the changes in renal function after such intervention.

The risk of hospitalization for acute (HR 0.57; 95% CI, 0.36-0.90) or chronic kidney disease (HR 0.45; 95% CI, 0.30-0.67) for patients who had undergone GBP was lower compared to matched controls. The same was found for diabetic nephropathy (HR 0.22; 95% CI, 0.10-0.47), which is a separate diagnosis in the ICD-10 classification. Six patients were admitted to hospital with a diagnosis of hemodialysis or peritoneal dialysis compared to 27 patients in the control group but there was no difference in patients requiring kidney transplantation. Combination of kidney diagnoses, which included common outcomes of severe renal disease, also showed lower risk (HR 0.50; 95% CI, 0.37-0.68) in GBP group.

The lower mortality risk has already been presented. For this reason, we extended analysis by using a new outcome, which combined mortality and kidney failure. We concentrated on death events that happened within 28 days after renal diagnosis, as we think that should better describe the mortality associated with renal disease. We found an HR of 0.48 (95% CI, 0.22-1.04). Death related to CVD was likewise lower (HR 0.36; 95% CI, 0.22-0.58) in GBP group (Table 3).

Table 3. Number of events, incidence rates per 10,000 person-years, and adjusted HRs

Endpoint	Gastric bypass (n=5321)	Control (n=5321)	Hazard ratio with 95% CI	p-value
Half eGFR (MDRD) (ml/min/1.73 m²)	51 (20.43)	120 (49.00)	0.63 [0.45, 0.89]	0.0076
Half eGFR (CKD-EPI) (ml/min/1.73 m²)	40 (16.02)	105 (42.86)	0.58 [0.40, 0.85]	0.0046
Macroalbuminuria	305 (127.22)	575 (252.33)	0.55 [0.47, 0.65]	<0.0001
Acute kidney failure	52 (20.85)	74 (30.14)	0.57 [0.36, 0.90]	0.0147
Chronic kidney disease	52 (20.84)	114 (46.62)	0.45 [0.30, 0.67]	0.0001
Diabetic nephropathy	17 (6.79)	53 (21.59)	0.22 [0.10, 0.47]	<0.0001
Severe renal disease	98 (39.49)	187 (76.87)	0.50 [0.37, 0.68]	<0.0001
Severe renal disease or half eGFR value (MDRD)	135 (54.57)	260 (107.39)	0.56 [0.44, 0.71]	<0.0001
Severe renal disease or half eGFR value (CKD-EPI)	124 (50.09)	245 (101.14)	0.54 [0.42, 0.70]	<0.0001
Hemodialysis or peritoneal dialysis	6 (2.39)	27 (10.97)	0.25 [0.08, 0.72]	0.0104
Kidney transplantation	6 (2.39)	6 (2.43)	0.62 [0.12, 3.39]	0.5854
Fatal kidney disease	12 (4.79)	32 (12.97)	0.48 [0.22, 1.04]	0.0636
Cardiovascular disease	291 (120.10)	346 (145.29)	0.74 [0.61, 0.89]	0.0015
Non-fatal cardiovascular disease	286 (117.91)	333 (139.69)	0.82 [0.70, 0.97]	0.0184
Congestive heart failure	86 (34.56)	233 (96.40)	0.33 [0.24, 0.46]	<0.0001
Fatal cardiovascular disease	31 (12.36)	93 (37.69)	0.36 [0.22, 0.58]	<0.0001
All-cause mortality	183 (72.90)	351 (142.06)	0.58 [0.47, 0.72]	<0.0001

Apart from the clinical outcomes, there were beneficial effects on laboratory findings during the follow-up period. We found risk reductions of 45% for macroalbuminuria, 37% for halved eGFR calculated with the MDRD equation, and 42% for eGFR calculated with the CKD-EPI equation (Figure 3).

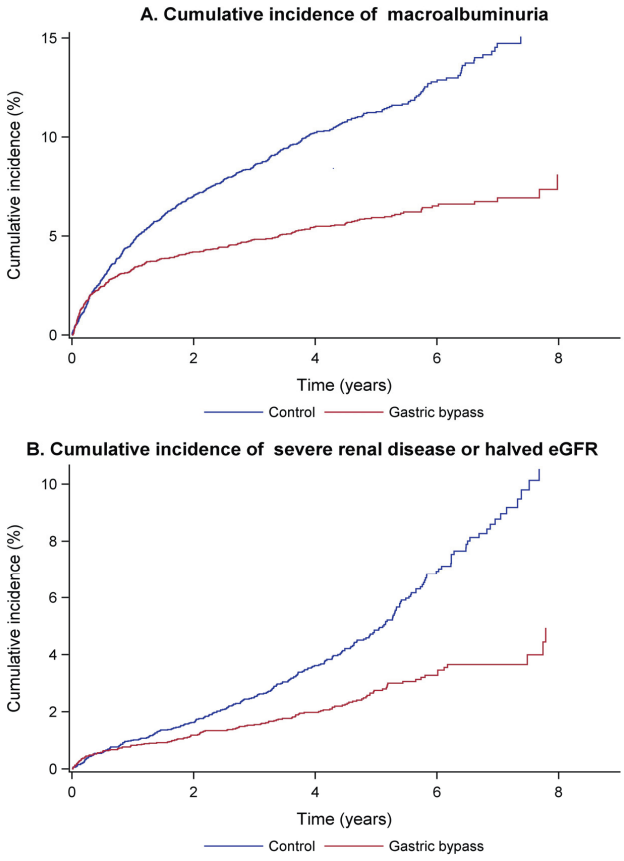

Figure 3 Cumulative incidences during the 9 years follow-up

When we looked more closely at the change in macroalbuminuria during the first 2 years of follow-up, we only found significantly lower values compared to baseline in the second year. However, creatinine and eGFR changed inversely from the first year of observation. HbA_{1c} followed the pattern of BMI change from baseline and was significantly different compared to the control group.

We also analyzed the same outcomes according to different levels of renal function, i.e. stratification according to different eGFR levels. The adjusted model showed that, in patients with normal renal function (eGFR >90 ml/min/1.73 m²), there was a lower risk in the GBP group for acute kidney failure, diabetic nephropathy, severe renal disease, macroalbuminuria, CVD and CVD mortality, congestive heart failure, and all-cause mortality. For intermediate eGFR levels (30-60 ml/min/1.73 m²), there was a lower risk in the GBP group for chronic kidney disease, partially for a composite of severe renal disease or halved eGFR and CVD events, and also partially for heart failure and all-cause mortality. All the results from these categories should be interpreted cautiously because of the low number of the subjects and the broad CIs.

For low eGFR levels (<30 ml/min/1.73 m²) who underwent GBP regardless of the relative contraindication for bariatric surgery, there was a lower risk for hospitalization due to chronic kidney disease compared to the controls (HR 0.28; 95% CI, 0.16-0.47). Lower risks were also noted for diabetic nephropathy, severe renal disease, hemodialysis or peritoneal dialysis, fatal kidney disease and CVD, macroalbuminuria, halved eGFR value, hospitalization of congestive heart failure, and all-cause mortality. Incidence rates for CVD were similar in both groups with many patients suffered.

5. DISCUSSION

Gastric bypass: in the service of reducing mortality and cardiovascular risk

Analysis of nationwide Swedish data on patients with obesity and diabetes who had undergone GBP showed significant reductions in all-cause mortality, cardiovascular death, and myocardial infarction compared to matched controls with obesity and diabetes who did not undergo surgery. Most previous studies on bariatric surgery have generally focused on populations with a small proportion of patients with diabetes. Randomized studies published in the last 5 years generally have a short follow-up, which does not allow the derivation of answers related to mortality.

Our findings are consistent with studies that have recently started to address questions related to mortality by examining longer follow-up (80). Previous reports in the literature, such as the SOS Study (65) and the Look AHEAD Study (48), have suggested benefits with respect to mortality and cardiovascular events that appeared after 4-5 years of follow-up. Specifically, the SOS Study demonstrated a 24% risk reduction of all-cause mortality, 53% for cardiovascular death (116), and 44% for myocardial infarction (72) during a follow-up period up to 16 years. However, it did not clarify the mechanism of bariatric surgery with respect to favoring improved survival. The intensive lifestyle intervention in the Look AHEAD Study contributed to the reduction of cardiovascular morbidity and mortality, in those who lost more than 10% of their bodyweight in the first year of study. The ADAPT Trial, which randomized patients to an 18-month weight loss intervention through dietary counseling and lifestyle modification, found a 50% risk reduction for overall mortality over a mean 8-year follow-up (117). This supports the hypothesis that long-term weight reduction is the factor related to lower all-cause mortality regardless of the method by which weight is reduced.

Apart from weight reduction as a comprehensive factor for risk reduction, a constellation of factors, e.g. anatomical, physiological, hormonal, behavioral, may potentially cooperate (118, 119). GBP in patients with diabetes contributes to changes in incretin secretion, especially for GLP-1, which remains a focus of research. Higher levels of GLP-1 after weight reduction, especially after bariatric surgery, has been suggested to play a key role in increased insulin secretion by ameliorating of impaired β-cell function (120). Improved glucose tolerance is noted (mostly due to a negative energy balance resulting from weight loss), which improves first hepatic and later peripheral insulin sensitivity in combination with increased postprandial insulin secretion elicited particularly by exaggerated GLP-1 responses (121). Other incretins such as glucose-dependent insulinotropic polypeptide that decreases after GBP contribute most to lipolysis rather to increasing insulin secretion (122). Existing assays do not provide robust conclusions about precise mechanisms of action.

Some of the beneficial effects on glucose concentration and HbA_{1c} after GBP maybe attributed to the changes of GLP-1 and other hormones. At the same time, we found a clear reduction in the use of antidiabetic medications and in the proportion of patients with diabetes remission (52% at 1-year postsurgically). Randomized studies have also noted the effects of GBP in T2DM control on improved remission rates, although they used different criteria for remission, type of surgery, and duration of diabetes presurgically (59, 69, 70). It is remarkable that patients with better glycemic control have higher use of antihypertensive and antihyperlipidemic drugs showing the improved care and frequent post-operative control. Of course, we should not overlook the role of changes in diet and lifestyle and their contribution to impacting cardiovascular morbidity and mortality in patients with T2DM (123).

Our study demonstrated a lower mortality rate as well as a lower rate of cardiovascular death and fatal or non-fatal myocardial infarction, despite the low prevalence of cardiovascular events. A possible explanation might be the fact that patients died outside of hospitals, which means they are not always recorded in the Inpatient Register but only in the Cause of Death Register. This is likely to affect the accuracy of diagnoses of death as it does not take into account the medical background of patients. However, the results remain unaltered when patients with previous cardiovascular history are excluded from the analysis.

Changes in risk factors attributed to GBP in patients with diabetes

Further to the previous study, we followed the course of several risk factors that have been traditionally associated with cardiovascular disease after GBP in patients with obesity and diabetes, and we compared them to patients who received conventional non-surgical treatment. We found significant improvements in BMI, HbA_{1c}, and HDL-cholesterol during the entire follow-up period, and a partial improvement in LDL-cholesterol, blood pressure, smoking use, and physical activity. The more advanced model used for repeated measurements, compared to the simple model in previous study, allowed us to demonstrate significantly lower consumption of medications in the surgery group. As in the first study, the use of antihyperlipidemic agents was increased compared to baseline in the GBP group.

Almost all studies of bariatric surgery and GBP have shown decreases in BMI over time. Observational studies such as the SOS Study, the Utah Study, or that of Courcoulas and colleagues (66, 124, 125) as well as randomized studies (59, 69, 70, 126-128) have shown a mean weight reduction ranging from 16.1% to 33.3% over different observation or randomization periods from 2 to 10 years. All these studies report clear weight loss from the first postoperative year of observation, as we also reported, which was highest in the second year and maintained during the entire follow-up period. The same pattern of change was followed by HbA_{1c}, but we could not identify this as clear factor on the effect on all-cause mortality according to our

causal mediation analysis. The effect of the GBP procedure is only mediated through weight reduction and not through the changes in HbA_{1c}, SBP, and LDL- and HDL-cholesterol. Changes in these traditional risk factors contribute to lower risk of atherosclerotic vascular and cardiovascular disease, however they do not fully explain the reduction in incident CVD, and the mechanisms behind this effect remains elusive, as suggested previously (129-131).

The diabetes remission rate in the first postoperative year was lower (36.8%) in study II than study I (52%). This is due to the different models used for repeated measurements taking into account the parameter of time. Notably, we had comparable remission rates as reported in randomized studies (69, 126), meta-analysis (132), and reviews (133). It is now generally accepted that GBP and bariatric surgery are effective methods for treating diabetes in patients that have an indication for surgical treatment. The weight loss in combination with diabetes remission as well as the possible improvements in other metabolic parameters, blood pressure, and lipid profile actually translates into reduced macro- and microvascular events.

The insulin-resistant metabolic environment that accompanies excess body fat is actually the basis of hyperlipidemia noted in individuals with obesity. The delayed metabolism of very low density lipoproteins implies high levels of triglycerides and LDL-cholesterol, and increased activity of hepatic lipids facilitates HDL-cholesterol clearance (23, 134). The effect of GBP on LDL-cholesterol in our study was limited to the first 3 years of observation, while HDL-cholesterol increased significantly during the entire follow-up. This is in line with studies such as the Look AHEAD Study (45, 46), which investigated cardiovascular risk factors and moderate weight loss, but differed compared to the Utah Study (135), which investigated severe obesity and higher proportions of weight reduction. Possible explanations might be the higher consumption of antihyperlipidemics compared to baseline and the higher use in controls compared to the treatment group, as well as a healthier lifestyle after the surgery.

Both SBP and DBP follow the course of LDL-cholesterol change despite the lower use of antihypertensive medication compared to baseline and the control group. The issue of higher consumption of antihypertensives by the controls is a confounding factor. The effects of bypass surgery on the prevalence of hypertension are variable, procedure-related, and time-dependent. During the active weight loss phase, blood pressure decreases and antihypertensive drugs are often discontinued (136). After weight stabilization, the results are less clear with more factors which could play a significant role such as age, number of preoperative antihypertensive medications including diuretics (137), and preoperative duration of hypertension. A meta-analysis of 22 studies using a variety of bariatric surgical approaches found the mean relative risk of hypertension was reduced by 46% between 24 and 50 months and hypertension risk reached a nadir when BMI was also reached its lowest level with a 10 mg/m^2 reduction (55). The SOS Study did not show a significant reduction in

hypertension compared to baseline and there was an increase from the sixth year of follow-up (66).

The Framingham Heart Study (138) as well as other studies (139) have established the role of smoking cessation in reducing cardiovascular risk and mortality. We showed a lower incidence of smokers than in controls, but we could not draw any conclusions on the effect with respect to survival. The same occurred for physical activity, which was significantly higher during almost the entire follow-up; however, this was not included in the mediation analysis model to examine whether there was a mediated effect on mortality and other outcomes. There may be other factors that we did not analyze which may play a key role in lowering mortality and cardiovascular risk in patients who undergo GBP. It is also very likely that the factors we did examine jointly contribute to enhancing outcome according to the hypothesis of multifactoriality.

Beneficial effects and adverse events of GBP in patients with T2DM

In this comprehensive observational retrospective study, we presented some of the previously shown beneficial effects of GBP as well as the spectrum of both short- and long-term adverse events from such treatment in patients with obesity and T2DM. Specifically, we investigated hospitalization due to various diagnoses potentially related to GBP.

Admission rates due to cardiovascular diagnoses such as CVD, fatal CVD, fatal coronary heart disease, acute myocardial infarction, and congestive heart failure were significantly lower in the GBP group during the entire follow-up. Cardiovascular risk in combination with lower all-cause mortality has already been discussed previously on the basis of our previous work (140, 141). The incidence of congestive heart failure after GBP has not been adequately studied. There is a Swedish register study that shows similar results for postsurgical heart failure (HR 0.54; 95% CI, 0.36-0.82) in an unknown number of patients with T2DM over a median duration of 4.1 years (142). We also believe that the lower cardiovascular risk with lower incidence of myocardial infarction in addition to improvements on diabetes and hypertension could provide a convincing answer to this result.

The results show that hospitalization due to diagnoses related to diabetes decreases after GBP. Incidences of hyperglycemia, kidney disease, and amputation mainly due to diabetic foot are most beneficially influenced by improved glycemic control. Inpatient care for hypoglycemia after GBP was not significantly different compared to controls: this might depend on the existence of diabetes and antidiabetic treatment in both groups, thus factors which are not taken into account by studies listing the side effects of gastric bypass. Otherwise, accelerated emptying of nutrients from the stomach to the intestine, increased insulin secretion because of increased incretin hormones, increased islet functional activity, and increased insulin sensitivity after

GBP are used to explain the slightly higher prevalence of hypoglycemia (143). The exact prevalence for such diagnoses varies (144, 145).

Renal disease after GBP is the most frequently studied among microvascular diseases (94, 96, 146). We showed a 42% lower relative risk of hospitalization due to severe renal disease. The STAMPEDE Trial showed a lower albumin/creatinine ratio in the surgery group (59) and, in a recent study of microvascular outcomes, surgical treatment in patients with stage 3 and 4 CKD had significant improvements in eGFR, especially among those who underwent GBP (146). These findings could be applied in such patients with higher burden of disease and impaired renal function, as improvements on glycemic and blood pressure control could as well contribute to lower consumption of antidiabetic and antihypertensive drugs, decreasing the progression rate of renal dysfunction.

Abdominal pain, gastrointestinal leakage, bleeding, bowel obstruction, gastrointestinal ulcers, and reflux are often reported as complications shortly after GBP. These adverse effects mainly occur in the first 30 days postsurgically, as seen in other studies (102, 147). Increased incidences of hernia, gallbladder disease, and pancreatitis occur in the first year of follow-up. An almost 3-times higher risk for gallbladder disease has been observed in parallel with a 3.5-times higher risk of cholecystectomy presented in a large cholecystectomy study (148). Weight reduction in combination with defective gallbladder emptying postoperatively and change in production of bile components have been suggested as possible mechanisms (149). It is remarkable that additional gastrointestinal surgical treatment after GBP is increased 12 fold (101). In our study, 17.6% of patients in the GBP cohort underwent complementary surgery due to various complications from the primary operation. Incidences of rehospitalization due to postsurgical diagnoses are comparable with other studies that had not included a large proportion of patients with diabetes, implying that diabetes *per se* does not raise the complication rate (150). Finally, except for the slightly higher incidence of additional surgical procedures in men, there were no major differences between men and women with respect to complication risk.

Long-term adverse events consisted of diagnoses such as malnutrition, anemia, psychiatric disorders, alcohol abuse, and cancer. We studied diagnoses after hospitalization and we may have therefore missed diagnoses that are usually registered during primary care. We found 3- and 2-fold higher incidences of hospitalization for malnutrition and anemia, respectively, compared to controls despite the possible underestimation of these diagnoses. Prior to GBP, the patient must be made aware of the increased need for post-operative treatment. It is also, therefore, important to adhere to the established indications for GBP. It is also well known that GBP is associated with increased incidences of iron, vitamin B_{12}, folate, calcium, vitamin D, and, less frequently, vitamin A deficiencies (151). Iron and folate deficiencies are the factors most correlated with anemia, although long-term vitamin B_{12} deficiency should not be overlooked (152). Anatomical and physiological changes

alone should not be considered as solely responsible for the occurrence of nutritional deficiencies: postoperative non-compliance by patients should also be considered.

Hospital admission due to psychiatric disorders was observed 33% more often after GBP overall and, in particular, 51% more often in women. We have not yet specified the main diagnoses among the psychiatric disorders, but previous studies were mostly focused on depression, suicidal tendency, and alcohol/substance addiction. Characteristically, they have shown that depression progresses along with suicidal attempts, primarily if there is a diagnosis of self-harm or depression in the patient's previous medical history (153, 154). The SOS Study demonstrated initial improvements in depression and health-related quality of life that gradually deteriorated as follow-up lengthened; however, after 10 years, there was still an improvement compared to baseline values (155). Neuroendocrine alterations, exacerbations of depression and anxiety, nutritional deficiencies, or eating disorders might contribute to suicide ideation. In addition, the higher incidence of alcohol abuse might be related to the physiological alterations induced by GBP. Patients undergoing GBP surgery seem to be more prone to developing alcohol abuse disorders, which is possibly related to the altered uptake and metabolism of alcohol seen after GBP (156, 157).

Cancer incidence and death rates due to all -type of cancers are correlated with increasing BMI (158). This association is accentuated when obesity is combined with diabetes (6% of cancer cases worldwide) (34). Our study showed a 22% lower risk of hospitalization due to all -types of cancer after GBP in patients with T2DM. This effect was not similar in men and women, as previously observed in SOS, suggesting differences in body composition and hormonal alterations as plausible explanations (159). A recent systematic review showed unclear results regarding cancer-related outcomes of randomized studies, but significantly reduced risk in non-randomized and cohort studies (160). The heterogeneity of the included studies, as well as methodological differences, did however not allow firm conclusions.

With our study, we tried to thoroughly demonstrate the pros and cons of GBP surgery. Crucially, there may be a need for more robust criteria along, possibly with scoring systems or algorithms that could be applied by multidisciplinary teams on assessing indication for bariatric surgery in individual patients. The indications of bariatric surgery have been repeatedly updated by the National Institute of Health since 1991; however, the risks of such treatment are still significant and affect the final outcome.

Renal disease and renal function after gastric bypass in patients with T2DM

We also demonstrated a lower incidence in various categories of renal disease and adverse renal parameters after GBP in patients with obesity and T2DM compared to controls. We again report the beneficial effect of GBP on cardiovascular outcomes and mortality in patients with relatively normal renal function, supporting the validity

of our findings in our previous studies. The positive effects seem slightly weaker in patients with intermediate eGFR values and stronger in patients with eGFR lower than 30 ml/min/1.73 m².

The relationship of obesity and CKD, independently of diabetes and hypertension, has been well documented (82, 161). A review and meta-analysis from Italy (162) revealed that obesity is a significant predictor for CKD by increasing the risk of new-onset low eGFR by 28% and albuminuria by 51%. Hemodynamic factors (increased renal blood flow and hypertension) and metabolic changes (e.g. hyperleptinemia, increased free fatty acids, hyperinsulinemia, insulin resistance), which cause sympathetic nerve stimulation, increased vascular tone, endothelial dysfunction, and renal sodium retention have been proposed in the mechanism of hyperfiltration, albuminuria, and glomerulosclerosis (163). The relationship between T2DM and renal disease has also been well studied in the United Kingdom Prospective Diabetes Study (UKPDS) (164), which showed an almost 40% incidence of albuminuria and 30% for renal disease over a 15-year exposure to high blood glucose (85). Both conditions affect renal function, which in turn can be affected by weight reduction (91, 94, 141). Positive changes in fat distribution, insulin secretion and resistance, glucose, HDL-cholesterol, and triglycerides can predict additional improvement in albuminuria and renal function (94).

We believe that the aforementioned mechanisms are reasonable for our findings, as almost all the examined renal diagnoses and laboratory findings after GBP had lower incidences except for the diagnosis of kidney transplantation, which was equally balanced between the groups. However, the low number of events for kidney transplantation does not allow for a reliable conclusion. It is possible that GBP could act as bridge to renal transplantation; thus, patients who have ESRD might undergo bariatric surgery to improve comorbidities and, concomitantly, create better access to renal transplantation (165).

The most beneficial effects of GBP seem to occur in patients with eGFR>60 and <30 ml/min/1.73 m², as these groups included the highest proportions of patients who underwent surgery, providing effect sizes with power to interpret. On the contrary, we observed that patients who received bariatric surgery in intermediate eGFRs are fewer and have various HRs even though renal function differs little between those eGFR groups. It was impressive that the group with the lowest eGFR, where beneficial results are shown for various endpoints, even though there is a relative contraindication to bariatric surgery in patients with such eGFR levels. Actually, this is not clear from European or American guidelines, but from the uncertainty of anesthesiologists to proceed with anesthesia (166, 167). Unfortunately, there are few studies that have estimated the effect of GBP or bariatric surgery in patients with impaired renal function. Imam et al. (146) assessed eGFR changes in patients with stage 3-4 CKD compared to patients not having bariatric surgery during a 3-year period, and Afshinia et al. (95) showed that weight loss in overweight and patients with obesity led to significant decrease of albuminuria regardless of method of weight

loss. The SOS Study also determined the incidence of stage 4-5 CKD/ESRD (reduced by 65% in the surgery group) as an endpoint in patients that had normal renal function at the baseline and underwent bariatric surgery showing protection against ESRD (97).

Strengths and limitations of the studies

This thesis is based on four observational studies with data derived from quality nationwide databases (NDR and SOReg) using unselected inclusion of all patients with T2DM who undergone GBP in Sweden. This is a major strength of our studies, as both registries have a high rate of coverage for such patients – almost 98% of patients who receive bariatric surgery are recorded in the register. This high participation rate provides high power and external validity, especially for countries that also follow same criteria and the surgical contraindications endorsed by the European and International Association for the Study of Obesity in 2013. The quality of the registries, which is strengthened by previous studies (112, 168) and by validation with medical records (111), increases the internal quality of data, allowing safer conclusions and results that are similar to randomized studies.

The amount of missing data at baseline, which is handled by different models in SOReg and NDR, and the gradual decreased recording of data postoperatively were the main limitations of our studies. Baseline data which are not completed by the imputation procedure remained out of the regression models. To handle the missing follow-up data implies successful input into mixed repeated measures models, providing adequate description of changes of risk factors and, thus, keeping stable mean values and narrow CIs.

Matching of the groups either 1:1 or with a propensity score provided comparable groups for most variables; however, there were some minor differences in baseline characteristics which we tried to eliminate using adjusted regression models. We used all the characteristics in the models and, especially for the first study, we conducted a sensitivity analysis to examine the potential importance of unknown factors and the results were unchanged. Of course, the selection of patients who need GBP may itself be subject to bias, increasing the effect sizes of several outcomes. This translates to residual confounding, which we cannot rule out from our studies. Measurement's standard errors cannot also be excluded in case of more frequent follow-up of surgical patients than the controls.

Finally, we did not exclude patients with multiple comorbidities, which may affect the results. We did this in order to maintain the power and heterogeneity of patients undergoing the procedure, resembling as much as possible the clinical reality of such interventions. Nonetheless, we described the trend of such comorbidities. Additionally, we only included patients undergoing GBP and not other bariatric

methods. This was done consciously as there is insufficient data during the study period and evidence of alternative methods to date.

6. CONCLUSION

This thesis has presented the effects of GBP surgery in patients with obesity and T2DM as a result of the opportunities offered by two large quality register databases in Sweden. The first and most important finding is a more than 50% relative risk reduction in all-cause mortality, cardiovascular death, and fatal or non-fatal myocardial infarction. It is noteworthy that the best effects on cumulative mortality appeared with the highest BMI reductions, as well as in patients who had diabetes remission during the first year of follow-up, supporting the use of GBP as a credible therapeutic tool to impact obesity and T2DM.

Expansion of the study on GBP to examine specific cardiovascular risk factors revealed significantly reduced risk for HbA_{1c} and HDL, which followed the BMI reduction through the entire follow-up period, and transient changes of LDL-cholesterol and blood pressure. These effects were significantly affected by GBP compared to the controls despite the lower consumption of antidiabetic, antihyperlipidemic, and antihypertensive agents. BMI reduction remained significantly lower long-term and, thus, we believe it is the most important factor to have a positive effect on all-cause and cardiovascular mortality. The other factors, as we concluded from the mediation analysis, did not have mediated effect. The risk reduction of fatal or non-fatal myocardial infarction could not be attributed to the change of any single factor.

Apart from the beneficial effects on all-cause and cardiovascular mortality, as well as on myocardial infarction, we also showed lower postoperative risk of hospitalization due to various cardiovascular morbidities, severe kidney disease, and cancer. Analyses using a different cohort, but with the same characteristics and longer follow-up, showed a higher risk of postoperative complications, i.e. 17.6% of patients needed additional surgical treatment after GBP. Long-term consequences of GBP that caused frequent hospital admission were a 2-fold higher risk of anemia, a 3-fold higher risk of malnutrition and alcohol abuse, and a higher incidence of psychiatric disorders. All these postoperative adverse effects impose a more careful screening of patients before undergoing GBP.

Additionally, GBP was found to be a beneficial factor that lowers the risk of renal disease postoperatively in patients with obesity and T2DM. A wide spectrum of adverse renal parameters showed lower incidence after GBP. This association remained when we looked at different strata of preoperative renal function covering all stages of kidney insufficiency. Because of the lower power for intermediate levels of eGFR, we cannot derive solid conclusions, although there were beneficial effects in patients with normal renal function and those with the most impaired renal function. Except for the lower incidences of renal diagnoses, the adjusted model revealed lower

CVD and all-cause mortality, adding support for the importance of obesity on cardio-renal axis.

Loss of weight, achieved by GBP, results in numerous positive health effects, although there is a risk of surgical and post-operative complications. It seems reasonable to suggest that careful selection of patients for GBP, and optimized monitoring post-surgery could further improve the results of this treatment.

7. FUTURE PERSPECTIVES

The present thesis discussed the beneficial effects of GBP in patients with obesity and T2DM, mainly with respect to mortality, cardiovascular risk, and kidney dysfunction, as well as a range of short- and long-term adverse events compared to patients not receiving GBP.

GBP has been established as the most effective method of weight loss, and in order to continue to be applied, future studies should focus on research into new algorithms and metrics that could more accurately determine the indications of how and to whom GBP should be applied. Multidisciplinary centers with specialized teams should identify patients who have the need for such treatment, enhancing safety and efficacious monitoring postoperatively.

It is true that other bariatric methods are developing, but research on GBP should go on, since it serves as a reference method. International guidelines have indeed incorporated bariatric surgery into the treatment of diabetes, so future research could focus on, e.g., the effects in various groups of patients. The observational studies of this thesis, involving large samples of the general population, with and without diabetes, can be considered as precursors of and promote prospective studies.

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