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MORBIDITY AND MORTALITY AFTER BARIATRIC SURGERY IN SWEDEN

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Front cover : Venus from Willendorf, a 25 000 year old venus figurine discovered in 1908 in Austria.

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Corpulence is not only a disease itself,
but the harbinger of others.
Hippokrates (460 BC-370 BC)

ABSTRACT

Overweight and obesity has increased in Sweden and in the rest of the world during the last decades, probably due to a more sedentary lifestyle and changes in diets. Body mass index (BMI) is a commonly used index of weight-for-height for classifying adult individuals. BMI is weight in kilograms divided by the square of the height in meters (kg/m^2). BMI between 18.5 and 25 is called normal weight. Overweight is defined as a BMI over 25 and obesity as BMI over 30. A BMI over 40 is sometimes referred to as morbid obesity. Obesity is associated with several diseases such as diabetes type 2, hypertension, obstructive sleep apnea and different cancers. Obesity is also associated with an increased risk of preterm mortality. Intentional weight-loss, by any mean, may lead to resolution of the obesity related diseases and to a reduction in mortality risk. Weight-loss can be achieved by modification of life-style factors, diets, pharmacological treatment or surgery. For morbidly obese people surgical treatment is the most effective method to attain sustainable weight reduction. For this reason surgery has become increasingly popular with increasing number of operations being performed annually.

The overall objective of the studies comprising this thesis work was to investigate morbidity and mortality after weight-loss (bariatric) surgery. Specific aims were to: 1) Study long-term outcome after laparoscopic Vertical Banded Gastroplasty with regards to weight-loss and long-term postoperative complications; 2) study short- and long-term mortality after bariatric surgery; 3) study if bariatric surgery could lower mortality in an obese group of men compared to an obese group of non-operated men; and, 4) to study morbidity- and mortality rates after the most common bariatric procedure in Sweden today, the gastric bypass.

This thesis work is based on data from one quality registry held at Danderyd Hospital and on nationwide data sets created by record linkage between the Swedish inpatient care registry, the registry of the total population and other national registries.

This thesis covers the time period 1980 to 2006. During these years there has been an increase in bariatric procedures with the most rapid increase seen during the last 5 years. Throughout the time-period early postoperative mortality in Sweden has been low, comparable to expert centers in the United States. Mortality within the first year after surgery was found to be higher among men raising the question whether any long-term gains in survival advantage attained through the weight-loss surgery would be "wiped out" by the increased early mortality. However, when comparing mortality between a cohort of surgically treated obese men and a cohort of obese non-operated men a survival advantage was seen in the surgical cohort. During years covered by the datasets used in this thesis work there has been a shift towards more complex procedures. Vertical banded gastroplasty is a restrictive procedure that was popular in the 1990:es and later on reintroduced with a laparoscopic approach. The long-term result regarding weight-loss was modest and rates of surgical reinterventions, either due to complications or insufficient weight-loss was high. With a failed vertical banded gastroplasty conversion to a gastric bypass gave the best results. Gastric bypass is the predominant procedure in Sweden today mostly conducted by a laparoscopic approach.

The laparoscopic approach is considered technically more challenging than the open approach, which has raised concerns whether complication rates would be higher after laparoscopic surgery. There was no difference in mortality between the two approaches and no major differences regarding postoperative morbidity. However, much higher complication rates were noted after revisional procedures, when a previous bariatric procedure was converted to a gastric bypass.

In summary, bariatric surgery can be performed safely on a national level. Men have a survival advantage after bariatric surgery compared to obese non-operated men yet it remains elevated compared to the general population. High revisional rates were seen after laparoscopic vertical banded gastroplasty. Laparoscopic gastric bypass is as safe as open gastric bypass; however revisional procedures, by any approach, have much higher complication rates. Therefore, it is important to make an evidence-based choice when bariatric surgery is conducted for the first time.

LIST OF PUBLICATIONS

I. Marsk R, Jonas E, Gartzios H, Stockeld D, Granström L, Freedman J. High revision rates after laparoscopic vertical banded gastroplasty. *Surg Obes Relat Dis* 2009;5:94-98

II. Marsk R, Freedman J, Tynelius P, Rasmussen F, Näslund E. Antiobesity surgery in Sweden from 1980 to 2005: a population-based study with a focus on mortality. *Ann Surg* 2008;248:777-781

III. Marsk R, Näslund E, Freedman J, Tynelius P, Rasmussen F. Weight-loss surgery reduces mortality in Swedish men. *Submitted*

IV. Marsk R, Tynelius P, Rasmussen F, Freedman J. Short-term morbidity and mortality after open versus laparoscopic gastric bypass surgery. A population-based study from Sweden. *Obesity Surgery 2009, DOI 10.1007/s11695-009-9942-3*

CONTENTS

LIST OF ABBREVIATIONS

BMI	Body Mass Index
BPD	BilioPancreatic Diversion
CI	Confidence Interval
CT	Computed Tomography
DNA	DeoxiriboNucleic Acid
DS	Duodenal Switch
EWL	Excess Weight Loss
GB	Gastric Banding
GBP	Gastric ByPass
GI	Gastro Intestinal
GLP-1	Glucagon-Like Peptide-1
HDL	High Density Lipoprotein
HR	Hazard Ratio
ICD	International Classification of Diseases
LABS	Longitudinal Assessment of Bariatric Surgery
OR	Odds Ratio
PYY	Peptid YY
SBU	Statens Beredning för medicinsk Utvärdering
SOS	Swedish Obese Subjects
VTE	Venous ThromboEmbolism
WHO	World Health Organization
WHR	Waist-Hip Ratio

1 INTRODUCTION

1.1 DEFINITIONS AND EPIDEMIOLOGY OF OBESITY

Obesity is defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation that may impair health. It is considered a chronic disease in Sweden, as well as internationally[1]. Body mass index (BMI) is a commonly used index of weight-for-height for classifying adult individuals. BMI is the weight in kilograms divided by the square of the height in meters (kg/m^2).

The WHO defines overweight as a BMI equal to or more than 25 and obesity as a BMI equal to or more than 30. Obesity is further subdivided into classes where class 1 is a BMI of 30-34.9, class 2 a BMI of 35-39.9 and class 3 a BMI >=40. A BMI from 18.5 to 25 is desirable in adults. The classification system is based on data indicating that optimal BMI with respect to long-term survival is between 18.5 and 25 and that mortality risk increase at a BMI above 25[1] . Other non-WHO used definitions are morbid obesity (BMI 40-50) and super-obesity (BMI>50). BMI is an approximate index since no consideration is taken to which body compartment the weight comes from. As an example a muscular man can be classified as overweight or even obese. However, in a clinical setting this is not a major issue. BMI correlates strongly with percentage of body fat on a group level and is a useful, noninvasive and inexpensive measure of fatness[1]. Other methods for measuring obesity include waist-hip ratio (WHR) or waist circumference which focuses on abdominal obesity. In American literature excess weight is expressed as a percentage from the "ideal" body-weight. The ideal weight is based on standard height-weight tables constructed by the Metropolitan Life Insurance Company. It is still common to see results regarding weight-loss presented as percent excessive weight-loss (%EWL).

It has been estimated that in 2005 at least 400 million adults were obese and the projection for 2015 is that 700 million will be obese worldwide[2]. Obesity has previously been thought of as a problem only in high-income countries; however, there is a dramatic increase seen in low- and middle-income countries as well[2]. In Sweden, the prevalence of obesity is estimated at more than 10% of the adult population (men as well as women) and during the 30 years from 1969-1974 to 2000-2005, the prevalence of obesity in the range BMI 30-34.9 almost quintupled while obesity in the range >=35 increased 10-fold among men 18-19 years of age according to a recent nationwide study[3]. There is no clear gender difference with regards to obesity in Sweden or the rest of the world[2].

1.2 CAUSES OF OBESITY

The epidemic of obesity seen during the last decades is likely caused by lifestyle and environmental changes including increased intake of fat-rich, calorie dense food[4]. However, obesity has an underlying genetic component[5]. Monogenetic obesity syndromes such as Prader-Willi have fueled the interest in searching for candidate-genes associated with non-syndromic human obesity. Many genes have been identified but the gene currently strongest associated with obesity, FTO, is estimated to account for only 1% of the heritability of obesity[6]. Another growing research field is

epigenetics. Epigenetics is the study of heritable changes in gene expression that do not involve changes to the underlying DNA sequences. Instead, these processes include DNA methylation and changes in packaging of DNA around nucleosomes[7]. These changes could play a role in gene regulation and thus for example explain why an adverse intrauterine environment can be involved in the future development of obesity[8]. The cause of obesity is likely to be multifactorial involving a mix of environmental, genetic and epigenetic factors.

1.3 CONSEQUENCES OF OBESITY

1.3.1 Morbidity & mortality

Several diseases are associated with obesity. The metabolic syndrome is a cluster of risk factors identifying individuals with increased risk of diabetes as well as cardiovascular disease. Different definitions exist of the syndrome, including abdominal obesity (waist circumference), elevated plasma triglyceride levels, reduced high density lipoprotein (HDL), elevated blood pressure and elevated fasting glucose[9]. Although the use of the metabolic syndrome as a tool for predicting individuals at high risk for diabetes or cardiovascular disease have been challenged during recent years, at least in an elderly population[10], the individual components are established risk factors.

The risk of hypertension is up to five times higher among obese than among normal weight individuals[11] and numerous studies have shown an intimate relationship between obesity and type 2 diabetes[12-14]. Obesity is an independent risk factor for cardiovascular disease[15-17]. Cancers of the esophagus, colon, breast, kidney and endometrium have been linked to obesity and it has been estimated that a quarter to a third of all those cancer cases are caused by obesity and inactivity[18]. Obstructive sleep apnea is also associated with obesity[19] and the condition is *per se* a risk factor for cardiovascular disease[20]. Furthermore, obesity reduces fertility in both sexes[21, 22] and osteoarthritis is more common among obese individuals[23]. Excess bodyweight is the sixth most important risk factor contributing to the overall burden of disease worldwide[24].

With this increase in morbidity it is not surprising that obesity is associated with an increase of early mortality. Obesity decreases life expectancy by 7 years at age 40 at a BMI of >30[25] and in a recent meta-analysis, a BMI between 22.5-25 was associated with the lowest overall mortality. Above this range, each 5 higher BMI was associated with about a 30% higher all-cause mortality[26].

The increase in morbidity causes a great impact on healthcare costs. The total costs for obesity related issues has been estimated to be more than $90 billion/year in the United States, approximately 9% of the total healthcare expenditures[27].

1.4 TREATMENT OF OBESITY

1.4.1 Non-surgical treatment options

1.4.1.1 Diet, life style

Nutritional management of obesity remains controversial and numerous different diets exist, boosted by an enthusiastic daily press. *The Swedish council on technology*

assessment in health care (Statens Beredning för medicinsk Utvärdering (SBU)) evaluated in 2002 existing evidence on treatments of obesity and concluded that changes in dietary habits can lead to weight reduction in the range of 3-10 kg during the first year. The long-term effects are more uncertain [28]. In a Cochrane review from 2007, a low glycemic diet was found more beneficial than other diets, but differences were small and follow-up in the included studies were short[29]. In a recently published randomized controlled trial weight-loss after a Mediterranean diet or a low carbo-hydrate diet was at least as good as with a low fat diet[30]. Patients included in dietary intervention trials are generally in a BMI range of 25-35 and long-term follow-up studies are scarce. Exercise is associated with improvements in cardiovascular risk factors, but is not as potent as dietary changes for losing weight[31].

1.4.1.2 Pharmacological treatment

In Sweden, two different groups of pharmaceuticals are available for the treatment of obesity (June 2009).

Orlistat (Xenical®, alli®) is a potent selective inhibitor of gastrointestinal lipases. By binding to gastric- and pancreatic lipases, orlistat makes the enzymes unable to hydrolyse triglycerides to free fatty acids. This decreases the amount of dietary fat absorbed in the gastrointestinal canal. The most common side-effects are related to the gastrointestinal tract with fatty/oily stools and fecal urgency[32]. Orlistat has in studies been shown to reduce diabetes incidence[33]and to decrease blood pressure[34]. The effect regarding weight-reduction has been modest with a weight-loss of 3-6 kg compared to placebo[33, 35].

Sibutramin (Reductil®) modifies central nervous system neurotransmission by acting as an inhibitor of noradrenaline, serotonin and to some extent dopamine reuptake in the brain. It promotes weight-loss by increasing the sense of satiety. Side-effects of sibutramine are increases in systolic and diastolic blood pressure and an increase in pulse rate[36]. Insomnia, nausea and constipation have also been reported[37]. Weight-loss has compared to placebo been reported at 4-5 kg with a follow-up of up to 4 years[38, 39]. In summary, pharmacological treatment is associated with a weight-loss of 6 kg or less during a follow-up of up to 4 years. No study has shown a positive effect regarding mortality and cardiovascular morbidity[40].

1.4.2 Surgical treatment of obesity

Surgical treatment of obesity, bariatric surgery, was introduced in the 1950s. The first bariatric operation was performed in 1952 by the Swedish surgeon Viktor Henriksson. The procedure was a small bowel resection. Throughout the years numerous different procedures have been introduced (and disbanded). Bariatric surgery can traditionally be divided into restrictive and malabsorptive procedures. The restrictive procedures decrease food intake and promote an early feeling of satiety at meals. Malabsorptive procedures reduce the absorption of nutrients and thereby promote weight-loss. Some procedures are a combination of both.

Standard indication criteria for bariatric surgery in Europe and the United States are: 1) A BMI>40 or 2) a BMI>35 with one or more comorbidities attributable to obesity[41]. All bariatric procedures can today be performed with a laparoscopic approach[42-45]

which has several advantages, such as less postoperative pain, improved postoperative pulmonary function, shorter hospital stay and lower incidence of incisional hernias compared to open surgery[46-48]. There is, however an ongoing debate with regard to differences in complication rates between laparoscopic and open approach in more complex bariatric procedures.

Presented below are the most common bariatric procedures performed. The jejunoileal bypass is not in use today, but is worth mentioning from a historical point of view, as well as for understanding the rationale of biliopancreatic diversion. The most commonly used procedures in Sweden during the last two decades are the vertical banded gastroplasty, gastric banding and gastric bypass. Today 96% of all bariatric procedures performed in Sweden are gastric bypass (Scandinavian Obesity Surgery Registry)

1.4.2.1 Vertical banded gastroplasty (VBG)

The VBG (Fig 1) is a restrictive procedure. A VBG creates a small pouch in the proximal part of the stomach. This pouch is partially separated from the rest of the stomach, with only a small gap remaining. The staple line can be divided or not. The gap between the upper pouch and the rest of the stomach is reinforced with a polypropylene or Gore-Tex™ band to prevent it from stretching. When eating, the small pouch fills up quickly promoting slow eating and small meals otherwise the patient vomits.

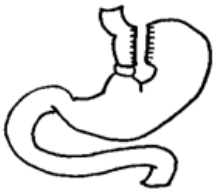

Figure 1: VBG

1.4.2.2 Gastric Banding (GB)

GB (Fig 2) is a restrictive procedure where a constricting band is placed around the top end (cardia) of the stomach and does not involve any partition of the stomach. Modern bands are inflatable allowing for adjustments of the stoma size to regulate food intake. The functional end result has striking similarities to the VBG forcing the patient to eat small amounts of food slowly.

Figure 2: GB

1.4.2.3 Gastric Sleeve

The gastric sleeve (Fig 3) is a restrictive procedure where the stomach is vertically transected and reduced by 75- 85%, thus limiting food intake. It leaves the pyloric valve intact so stomach function and digestion are unaltered. It is generally seen as the first part of a two-part procedure, being followed by either a gastric bypass or a biliopancreatic diversion; however, more recently it has been used as a single procedure. Long-term results of gastric sleeve are limited.

Figure3: Gastic sleeve

1.4.2.4 Gastric bypass (GBP)

The GBP (Fig 4) combines restrictive and malabsorptive techniques. A small pouch is created in the proximal part of the stomach. The small bowel is transected distal to the ligament of Treitz and the distal part of the bowel is pulled up and connected to the

gastric pouch. Gastrointestinal continuity is restored by creating an entero-entero anastomosis approximately 1 meter distally on the small bowel. This technique is called "Roux-en-Y" since the final appearance resembles (although vaguely) the letter Y. The limb of the Y that goes from the pouch is called the alimentary or efferent limb and the limb draining the bile and pancreatic juices is called the biliopancreatic or afferent limb. The pouch and its anastomosis constitute the restrictive part whereas the intestinal segment from the pouch to the entero-entero anastomosis constitutes the malabsorptive part. Since nutrients are unexposed to bile and pancreatic juices, limited absorption takes place in this segment.

Figure 4: GBP

1.4.2.5 Biliopancreatic diversion (BPD)

The BPD (Fig 5) is a modern improvement of the jejuno-ileal bypass. It differs from the jejuno-ileal bypass in that no small bowel is defunctionalized, minimizing the risk of liver failure and bacterial overgrowth. The procedure includes a limited gastrectomy and a long Roux-en-Y limb with a short common alimentary channel of approximately 50 cm where absorption takes place. A modification of the BPD is the BPD with duodenal switch (DS) (Fig 6). This procedure has a more pronounced restrictive component and includes a vertical transection of the stomach, just like the gastric sleeve. The small bowel is transected approximately 250 cm from the colon. The distal end is anastomosed to the proximal duodenum and the proximal end is anastomosed 50-100 cm proximal to the ileocecal junction. The preservation of the pylorus makes the emptying of food from the stomach function in a physiologically normal way.

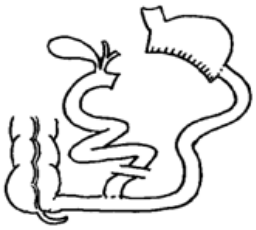

Figure 5: BPD

Figure 6: BPD+DS

1.4.2.6 Jejunoileal bypasss (JIB)

The JIB (Fig 7) is a typical malabsorptive procedure. The proximal part of the small bowel (jejunum) is divided and the proximal limb is anastomosed to the distal part of the small bowel (ileum). The majority of the small bowel is bypassed and a state of malabsorption is introduced. Weight-loss was good but patients developed diarrhea, vitamin deficiencies, kidney stones and osteoporosis. Bacterial overgrowth in the bypassed intestinal segment could cause severe arthritis as well as liver failure. Because of all adverse effects the jejuno-ileal bypass is now abandoned.

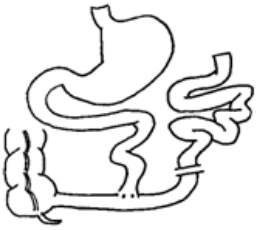

Figure 7: JIB

1.4.3 Outcome of surgical treatment

As of today, no clear guidelines exist for recommending a certain procedure to a certain patient. In a study where patients were divided into sweet-eaters and non-sweet eaters,

better weight-loss were seen among sweet-eaters who had a GBP compared to a VBG[49] thus suggesting that patients eating patterns could be used to guide the surgeon to the "right" procedure. Later studies have been unable to replicate these results[50, 51]. A schematic presentation of outcomes after the various surgical procedures is presented in table 1.

1.4.3.1 Weight

Several studies have shown superior weight-loss with surgical treatment compared to conventional treatment of obesity[52-54]. In the Swedish Obese Subjects (SOS) study a surgical group and a matched control group are followed prospectively. The change in BMI for the surgical group at 10 years follow-up was -6.7 kg/m² while the control group had gained an additional 0.7 kg/m² [52].

Among the different bariatric procedures, BPD seems to offer greater weight loss than GBP[55] and weight loss after GBP is greater than after both VBG[56] and GB[57]. Weight-loss after VBG and GB is of the same magnitude, perhaps somewhat greater after VBG[58, 59]. Weight-loss after gastric sleeve has in one study been the same as after GBP[60]; however, follow-up was only 12 months. Another trial has shown better weight-loss after gastric sleeve compared to GB[61].

Table 1: A schematic presentation of outcome after different procedures regarding weight, morbidity and mortality.

	Weight loss	**Early complications**	**Mortality**	**Late complications**
Vertical banded gastroplasty (VBG)	+	+	+	+++
Gastric Banding (GB)	+	+	+	++
Gastric bypass (GBP)	++	++	++	+
Gastric sleeve	++?	+?	+	?
Biliopancreatic diversion (BPD)	+++	+++	+++	?

1.4.3.2 Surgical complications and postoperative mortality

Complications after bariatric surgery differ between procedures. All procedures except GB have an inherent risk for leakage since they include transection of the gastrointestinal tract. However, leakage has also been reported after GB due to inadvertently causing a rift in the stomach at the placement of the band. Restrictive procedures are in general safer with regards to early complications compared to combined or malabsorptive procedures. One reason is that no anastomoses are created which minimizes the risk for leaks. This is to some extent counterbalanced by a less pronounced weight-loss and available evidence also indicates an increased risk of surgical reinterventions in long-term. Most published series are small with short follow-up and data regarding long-term outcome after laparoscopic VBG and laparoscopic GB

are scarce. Early and common late postoperative complications after GBP are described in detail in the discussion section.

Published data regarding postoperative mortality differs. Several case series have shown a low perioperative mortality[62] and a recent meta-analysis demonstrated a 30-day all-cause mortality of 0.28%[63]. However, few population-based series have been published with regard to early mortality after bariatric surgery. In one series of Medicare beneficiaries from Washington state undergoing bariatric surgery between 1996 and 2002, 30-day and 1-year mortality was found to be 2.0% and 4.6%, respectively[64]. In a second population-based study covering the period 1987 to 2001, 30-day mortality was 1.9%[65]. Thus, there are obviously large differences in reported data. The most common causes of early postoperative death are pulmonary embolism, cardiac events and intestinal leaks with sepsis[66, 67].

Data regarding morbidity and mortality often come from high-volume expert centers, which may not be representative for an unselected population of bariatric patients. It is of interest to study complication rates on a population-level, including all centers performing bariatric surgery. This will give a more accurate picture on the incidence rates of complications, which is important for the individual centers for comparison, as well as, for the patients to have accurate information preoperatively. Furthermore, postoperative mortality data from the United States is often based on in-hospital mortality, which might underestimate death rates, since individuals developing fatal complications after discharge might be missed[68]. Since in-hospital stay for a laparoscopic bariatric procedure is getting shorter or even done as day-surgery[69] in-hospital mortality can give false low mortality rates.

Worldwide, as well as in Sweden, women are much more often undergoing bariatric surgery than men (Fig 8). Available evidence does not support that obesity is more prevalent among women and cannot explain why women are more likely to be operated for obesity[70, 71]. Both postoperative morbidity and mortality is more common among men[72, 73]. One explanation could be that women are more likely to be motivated due to concerns about the body appearance, whereas it is socially more acceptable for a man to be obese[74]. This may lead to men seeking medical attention at a later stage, thus with more co-morbid diseases present at time of referral. Recently it also has been shown that men have higher rates of co-morbid diseases than women in the same BMI range[75]. We have not found any studies focusing specifically on men and as women are overrepresented in the current literature on bariatric surgery it is not evident that results from previous studies can be extrapolated to men.

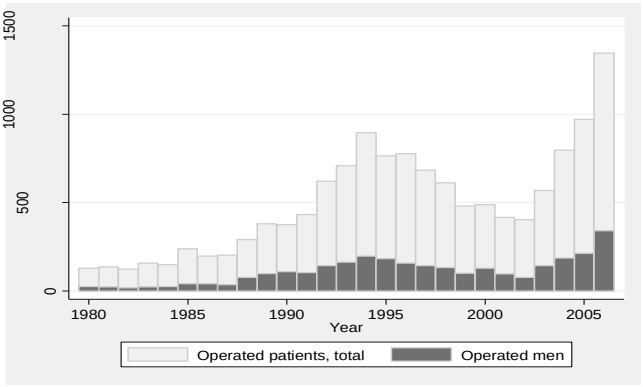

Figure 8: Number of bariatric procedures per year in Sweden 1980-2006.

1.4.3.3 Trends in bariatric surgery

The number of bariatric procedures performed worldwide has shown a dramatic increase during the last decades[76] and the trend is a clear shift from restrictive to more complex procedures[62]. In the late 1980ies restrictive surgery (mainly VBG) was performed in over 50% of all bariatric cases in the United States compared to levels of a few percent in 2004. Gastric bypass is now the most popular procedure[77]. In Sweden about 1500 individuals underwent bariatric surgery in 2006. This is a threefold increase compared to 2001. The trend towards more complex procedures is also true for Sweden, where GBP since 2003 is the predominant procedure and in 2008, 96% of all bariatric procedures performed in Sweden were GBP. In spite of this increase in bariatric surgery there is a need for more. If all individuals who meet the standard indication criteria in Sweden were offered surgery, estimations indicate a need of 10-15 000 procedures performed annually[78].

1.5 IMPLICATIONS OF WEIGHT LOSS

1.5.1 Morbidity

Weight-loss, by any method, leads to improvement of hyperlipidemia, hypertension and diabetes[33, 79-81], all well known risk factors for cardiovascular disease. The effect of weight-loss with regard to the incidence of stroke and myocardial infarction is less clear. One study has shown a lower incidence of myocardial infarction after surgery compared to a non-operated obese control group[82] and another has shown lower mortality in coronary artery disease[83]. The effect of weight-loss on stroke is unclear. Gastric bypass and BPD have been shown to ameliorate type 2 diabetes, even before substantial weight-loss has taken place, suggesting a mechanism other than weight loss itself. Resolution rates as high as 89% have been reported at time of discharge after GBP[84]. The mechanisms are not fully understood but altered gut signaling from the lower intestine as well as no exposure of the duodenum and proximal jejunum to ingested nutrients might be part of the explanation[85]. This high resolution rate of type 2

diabetes has fueled the discussion whether surgery actually is the best treatment for diabetes[86], an idea that would have been considered absurd two decades ago.

1.5.2 Mortality

The effect of weight-loss on mortality has been a matter of debate. Several epidemiological studies has shown an increased mortality after weight-loss[87-89], but without knowledge whether the weight-loss was intentional or unintentional, conclusions are hard to draw since they raise the question about reverse causality. More recently prospective and retrospective cohort studies have shown a reduction in mortality after intentional weight-loss[52, 83, 90]. The SOS-study, with its matching between the control and the surgical cohort, is perhaps to date the best study showing a survival advantage for the surgical cohort with a hazard ratio of 0.71 after a follow-up of just over 10 years[52]. In a retrospective cohort study by Adams et al[83] a GBP cohort was compared to a obese non-operated cohort and with a follow-up period of 7 years the rate of death was 40% lower in the surgical group (hazard ratio 0.60 (95% CI 0.45-0.67)).

2 AIMS

The overall aim of the thesis was to study morbidity and mortality after bariatric surgery in Sweden.

The specific research questions were:

- What is the long-term outcome after laparoscopic VBG? Should we still use it?
- What is the national short- and long-term mortality after bariatric surgery in Sweden?
- What are the effects of bariatric surgery on morbidity and mortality in Swedish men?
- What are morbidity- and mortality rates after GBP in Sweden? Are there differences between a laparoscopic or an open approach?

3 MATERIAL & METHODS

3.1 INFORMATION SOURCES

This thesis is primarily based on data from the following registries:

3.1.1 Quality register held at Danderyd Hospital

Data on all bariatric procedures at Danderyd Hospital have been prospectively registered since 1995 for quality assurances. The registry includes data on date of surgery, type of procedure, approach (laparoscopic/open), pre- and postoperative complications as well as weight data. A manual check was conducted on all included patients files for missing data on weight, complications and revisional surgery. Furthermore a letter was sent to all patients requesting them to send in new weight data, which was verified at later outpatient visits. In spite of these efforts, 13.6% of the patients were lost to follow-up, defined as not returning to the clinic within 2 years as follow-up was every second year. Data from this registry was used in paper I.

3.1.2 Registry of the Total Population

The Registry of the Total Population is a basic registry of the population of Sweden. It is held by Statistics Sweden and includes all individuals with permanent residency in Sweden. It also includes data on emigration and date of death. The registry contains some extra individuals since all births and immigrations are captured while some cases of emigration are missed [91] but the overall quality is regarded as good[92]. Data from this registry was used in paper II-IV.

3.1.3 Swedish Military Service Conscription registry

The conscription registry holds data on all individuals called for conscription. Until approximately year 2001 military conscription was mandatory for all Swedish males at an approximate age of 18 years. The registry includes data on height, weight, blood pressure, and conscription date. The quality of the registry can be regarded as good, but due to changes in data management, part of the data from years 1978, 1984 and 1985 have been lost. Data from this registry was used in paper III.

3.1.4 The Population and Housing censuses

The population and housing censuses were performed in 1960-1990. These censuses were compulsory and non-participation could lead to penalty payment. The last census was in 1990 and had a non-participant rate of 2.5%. Quality can be regarded as good[93]. From the censuses data was collected regarding parental education, parental socioeconomic index and the participants' highest attained education. The information on parental education and socioeconomic index was used as a measure of the individual's socioeconomic position in childhood. Statistics Sweden´s socioeconomic index classification was used where parental occupation was classified into non-manual worker at higher level, non-manual worker at intermediate level, non-manual worker at lower level, farmers, skilled workers, unskilled workers and others (those whom no specific occupation was reported). Data regarding parental- and own educational level as well as socioeconomic index in childhood was included since studies have shown

increased mortality and morbidity in cardiovascular disease among groups with lower socioeconomic status[94, 95]. Data from this registry was used in paper III and IV.

3.1.5 The Swedish inpatient care registry

The inpatient care registry was used from 1969 to 2006. It is held by the Centre of Epidemiology at the National Board of Health and Welfare and covers dates of admission and discharge as well as ICD-8, 9 and 10 codes for diagnoses and surgical procedures from 1964. From the late 1970th most regions in Sweden reported in-hospital care to the registry and as of 1987 the registry comprises essentially 100% of the population. Validation studies of the registry have been conducted in 1986 and 1990 and the quality can be regarded as good[96]. Improvements were noted from 1986 to 1990. Data from this registry was used in papers II, III and IV. Data gathered included pre- and postoperative morbidity regarding co-morbid disease such as hypertension, hyperlipidemia, diabetes mellitus, angina pectoris, myocardial infarction and stroke. Preoperative data was used for descriptive purposes and for adjustments in statistical analyses (see 3.3 below). In paper IV data was also collected regarding postoperative complications and surgical procedures during follow-up.

3.1.6 The cause of death registry

This registry is held by the Swedish National Board of Health and Welfare and includes date of death and causes of death since 1961. The quality is good although deaths among emigrated individuals might be missed[97]. Approximately 0.5% has no registered cause of death. Quality regarding cause of death is validated on a regular basis and is considered better in young and middle aged individuals than among old people.

3.2 COHORTS

Basic characteristics of the surgical cohorts are presented in table 2

Table 2: Basic characteristics of the surgical cohorts in paper I-IV

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Patients Men (%) Women(%)	486 78 (16%) 408 (84%)	12 379 2675 (22%) 9614 (78%)	1216 1216 (100%) 0	4701 1097 (23%) 3604 (77%)
Controls	NA	NA	Obese: 5327 General : 1 492 863	NA
Age at surgery (years)	40.7 ±10.3	41.3 ±10.9	32.2 ±8.3	41.1 ±10.1
Type of procedure (%)	VBG (100%)	VBG or GB (68 %) GBP (25%) Other (7%)	VBG or GB (62%) GBP (32%) Other (6%)	GBP (100%)
Follow-up (years)*	3.0 (1.0-6.0)	10.7 (5.7-14.7)	9.2 (3.8-13.2)	2.1 (0.9-4.7)

* Median (25-75% quartile), NA=not applicable

The surgical cohorts in papers II-IV were identified from the Swedish in-patient care registry by using the Swedish version of the Classification of Surgical Procedures (NOMESKO), searching for surgical procedure codes related to bariatric surgery (4750-53, 4759, JFD00, JDF00, JDF01, JDF10, JDF11, JDF 20, JDF21). A confirmatory International Classification of Diseases (ICD) -code with obesity was mandatory (277.99, 259X, 278A, E66.0, E66.1, E66.8, E66.9). Individuals who, according to additional ICD-codes in their records, had undergone bypass surgery for inflammatory bowel disease or gastrointestinal cancers were excluded.

3.3 STATISTICS

The STATA software (version 9, StataCorp LP, College Station, Texas) was used for data management and all statistical calculations.

3.3.1 Cox regression

Cox proportional hazards regression model[98] was used in papers III and IV for calculating relative risks (estimated by hazard ratios) for mortality and postoperative morbidity while controlling for patient characteristics. In all instances where we used Cox´s regression model, the proportional hazard assumption was checked graphically and we found no evidence that it was violated.

3.3.2 Multiple logistic regression

Multiple logistic regression was used in paper IV calculating relative risks (estimated by odds ratio) for early postoperative complications (within 30 days), while controlling for patient and hospital characteristics.

3.3.3 Confounders

In papers III & IV Cox regression and multiple logistic regression analyses were used allowing for adjustments for potential confounders. As previously mentioned, data on parental and own highest attained education was gathered from the population and housing censuses since cardiovascular morbidity and mortality is known to be higher in lower socioeconomic classes. Furthermore when estimating postoperative morbidity we adjusted for preoperative morbidity in the same disease. When estimating postoperative mortality, adjustments were made for preoperative morbidity of all studied diseases. Age at surgery is likely to influence both morbidity and mortality and was also adjusted for. In paper IV we created a model for estimating institutional experience at the various hospitals performing GBP. This was an attempt to take into account effects of a learning curve. During the study period there was a dramatic increase in GBP surgery in Sweden and the laparoscopic approach was also introduced during this time. From the inpatient care registry, data regarding operating hospital and operating date were collected. At each hospital all open and laparoscopic procedures were consecutively numbered (separately regarding approach) and each case thereafter assigned an institutional volume category. Low volume was defined 50 or fewer operations of a specific approach at the institution, intermediate as the 50-100 operations and high volume as more than 100 operations.

4 RESULTS

4.1 RESULTS PAPER I

486 consecutive patients operated at Danderyd Hospital with an attempted laparoscopic VBG. Median (range) follow-up time was 36 (0-132) months. Data regarding weight-change was recorded as was any complications or reinterventions during follow-up. The greatest weight-loss was achieved during the first post-operative year where the mean BMI-change was -10.5±4.7. After the first year of weight-loss a trend of weight-regain was noted. 104 (21.4%) patients required revisional surgery 114 times during follow-up and 15 patients underwent surgery for incisional hernias. The three most common reasons for revisional surgery were vomiting/food intolerance (44%), insufficient weight loss (19%) and staple line rupture (19%). Of the 104 patients, 49 were converted to a GBP, 31 had a repeat VBG and 24 had their band removed. Ten (32%) of the patients who had a repeat VBG required further surgery. Seven of those were converted to a GBP and 3 had their band removed. In summary, of 486 patients operated with a VBG, 56 (11.5%) were converted to a GBP and 27 (5.6%) had their band removed. Of the patients converted to a GBP, good weight-loss was achieved at least during the first two years of follow-up.

4.2 RESULTS PAPER II

From the Swedish in-patient care registry we identified 12 379 patients who had undergone bariatric surgery in Sweden between years 1980 and 2005. The record was then linked to the registry of total population as well as the cause of death registry. A majority of the patients (78%) were women and a majority of the procedures were restrictive (68%). A total of 751 (6.1%) individuals died during follow-up. Cumulative all-cause mortality was estimated during the first 30, 90 and 365 days after surgery and was found to be 0.2, 0.3 and 0.5%, respectively. There was a slight downward trend in early mortality during the study-period and a significant increase in GBP and decrease in restrictive procedures since the mid-nineties. One year mortality was higher in patients older than 50, but when stratifying by sex this was only evident in men (2.9% for men and 0.6% for women over 50 and 0.7% for men and 0.3% for women under 50 ($P < 0.01$ for men and $P = 0.11$ for women)). Mortality was higher among men throughout the follow-up period. When death within the first postoperative year was excluded, the age-adjusted mortality rate ratio was 1.8 (95% CI, 1.5-2.1) in favor of women. The most common causes of mortality after 12 months were malignancies and myocardial infarction.

4.3 RESULTS PAPER III

In this paper we studied postoperative morbidity and mortality in a cohort of operated obese men compared to a non-operated obese cohort of men and a general control cohort of men. All men identified in paper II as having had bariatric surgery and who was found in the military conscription registry with a recorded BMI between the years of 1969 and 2000 created the surgical cohort (n=1216). Controls were any man with a year of birth and a date of conscription ± 1 year of any man in the surgical cohort. Controls were assigned pseudo-surgical dates corresponding to their counterpart in the

surgical cohort. From this large general population cohort (n=1 492 863) an obese non-surgical cohort was created consisting of all men with a BMI>35 at time of military conscription (n=5327). The three cohorts were followed in the in-patient registry from conscription to date of surgery/pseudo-surgery and from date of surgery/pseudo-surgery to end of study, date of emigration or death, whichever came first. Regarding pre- and postoperative morbidity we focused on disease linked to the metabolic syndrome (diabetes, hypertension, myocardial infarction, angina pectoris, stroke and hyperlipidemia). The preoperative incidence of co-morbid disease is presented in table 3. However, to account for the fact that the surgical cohort had increased chances of being diagnosed with a co-morbid disease around the time of surgery, all first time diagnosis within a year of the date of surgery were disregarded for diabetes, hypertension, hyperlipidemia and angina pectoris. This correction was performed in all three cohorts to treat them equally. Pre- and postoperative incidence rate ratios and hazard ratios are presented in table 4. Lower risks postoperatively were seen for the operated cohort regarding diabetes and hyperlipidemia compared to the obese non-operated cohort. No differences were detected regarding cardiovascular diseases. When comparing the operated cohort and the general control cohort, the relative risks of in-patient care were increased for all studied diseases, with the exception of hyperlipidemia. The relative risks of myocardial infarction and stroke were 2.2 (95% CI 1.3-3.8) and 4.2 (95% CI 2.6-6.7), respectively. When comparing all-cause mortality between the operated cohort and the obese non-operated cohort, the adjusted mortality risk ratio was 0.7 (95% CI 0.5-1.0) (p=0.039). Comparison between the operated cohort and the general control cohort yielded an adjusted mortality risk ratio of 1.5 (95% CI 1.1-2.0).

Table 3: Preoperative incidence rates per 10 000 person years among the cohorts in paper III & IV

Co-morbid disease	**Paper III Surgical cohort**	**Paper III Obese non-surgical cohort**	**Paper III General control cohort**	**Paper IV Laparoscopic GBP**	**Paper IV Open GBP**
Diabetes	42.5	17.3	3.1	59.3	46.5
Hyperlipidemia	12.4	2.0	0.8	14.8	9.3
Hypertension	47.0	7.1	2.0	71.5	50.0
Angina pectoris	4.5	1.0	0.9	7.6	6.2
Myocardial infarction	4.0	1.4	0.9	5.7	4.9
Stroke	2.5	1.8	1.1	3.8	2.9

Table 4: Preoperative incidence rate ratios (IRR) and corresponding postoperative hazard ratios (HR) of co-morbid disease with corresponding 95% confidence intervals in cohorts from paper III

Co-morbid disease	Surgical vs obese non-surgical, IRR (95% CI)	Surgical vs obese non-surgical, HR (95% CI)	Surgical vs general control, IRR (95% CI)	Surgical vs general control, HR (95% CI)
Diabetes	1.1 (0.7-1.7)	0.4 (0.3-0.5)	6.2 (4.3-8.6)	2.0 (1.4-2.8)
Hyperlipidemia	4.6 (1.7-13.5)	0.4 (0.2-0.9)	10.5 (5.6-18.1)	1.6 (0.8-2.9)
Hypertension	4.5 (2.8-7.3)	1.2 (0.9-1.7)	9.8 (6.7-13.8)	5.5 (4.3-7.0)
Angina pectoris	4.4 (1.3-16.8)	1.0 (0.5-1.9)	5.0 (2.3-9.5)	3.3 (2.1-5.1)
Myocardial infarction	2.8 (0.9-9.1)	0.8 (0.4-1.6)	4.2 (1.8-8.4)	2.2 (1.3-3.8)
Stroke	1.4 (0.4-4.5)	1.0 (0.6-2.0)	2.7 (1.1-6.6)	4.2 (2.6-6.7)

4.4 RESULTS PAPER IV

In the Swedish in-patient care registry, we identified 4701 patients who had a GBP between years 1997 and 2006. Of these, 3852 were primary procedures while the remaining 849 were revisions from previous bariatric surgery. A total of 35% of all GBP operations were completed with a laparoscopic approach. Data from the in-patient registry was extracted regarding co-morbid disease and postoperative complications. Comparisons were made regarding open and laparoscopic approach as well as for primary and revisional (conversion to GBP from previous bariatric surgery) procedures. Preoperative co-morbidities in the open and laparoscopic cohorts are presented in table 3. We could not detect any difference in 30-day, 90-day and 1-year mortality between open and laparoscopic approach, neither between primary and revisional procedures. Surgical re-intervention due to anastomotic leaks was higher after laparoscopic GBP compared to open GBP with an odds ratio of 2.1 (95% CI 1.3-3.6). However, subgroup analysis showed higher leak rates after revisional laparoscopic procedures compared to revisional open (OR 4.1; 95% CI 1.5-11.2), whereas after primary GBP no statistically significant difference was seen between laparoscopic and open approach (OR 1.7; 95% CI 1.0-3.1) (p=0.07). In general, complications were more common after conversion from previous bariatric surgery (OR 1.9; 95% CI 1.5-2.4) as estimated by 30-day re-admission.

5 DISCUSSION

Surgery is today the most effective treatment of obesity, leading to sustained weight-loss and decreased morbidity in obesity associated co-morbidity and ultimately decreased mortality[52]. Numerous different surgical procedures have been attempted throughout the years and today at least 5 different methods are in use (GB, GBP, Gastric sleeve, BPD w/o duodenal switch). Traditionally bariatric procedures have been classified into restrictive, malabsorptive or a combination of the two.

5.1 RESTRICTIVE SURGERY

Restrictive procedures such as VBG and GB have been considered safe and easy to learn, but long-term results have been a matter of debate. Series have shown a trend of weight-gain over time[99, 100] and also high rates of revisional surgery[99, 101], which is in accordance with our results after long-term follow-up of VBG. In our VBG-series, the two most common causes for revisional surgery were food intolerance/vomiting and insufficient weight-loss. The problem with vomiting might be due to problems for the patient to adapt to new eating habits and the insufficient weight-loss due to patients switching to high-calorie liquid diets[50]. For some patients a restrictive procedure will produce good results with a sustained weight-loss at a minimum of risk. The problem is that we do not yet have any effective methods for identifying those patients. It seems reasonable to extrapolate the disappointing long-term results for VBG to GB due to the similarity of their functional result. And, indeed, in a study by Balsiger et al[101] cumulative reoperation rates was 32% after GB within 7 years. However, results after adjustable GB vary. In Australia results after GB are very good with long-term weight loss[102]. The reasons behind the variable results seen after restrictive surgery may be due to the follow-up protocols. Gastric sleeve has gained popularity during the last few years with good initial weight-loss[103], and in one study even better than after GBP[60], however, long-term data are lacking.
The rates of revisional surgery are of importance when evaluating different procedures, since revisional surgery is associated with much higher complication rates, as shown in papers I & IV in this thesis. The rational to choose a safe and "easy" restrictive procedure is counterbalanced when considering that 20+% will be converted to GBP, with an almost 5 times increased risk for anastomotic leakage compared to a primary GBP, within 5-7 years.

5.1.1 Is there a role for restrictive surgery in the future?

The concept of simply restricting food-intake might be a too simple solution for such a complex problem as obesity. The GBP is a combined restrictive and malabsorptive procedure with the malabsorptive part being the roux-limb, from the gastric pouch to the entero-entero anastomosis, where little nutrient absorption takes place since bile and pancreatic enzymes are lacking. Varying lengths of the roux limb are in use, with a "normal" roux-limb being approximately 100 cm. The results regarding weight-loss after use of longer roux limbs (>150 cm) compared to "normal" ones are not consistent. Intuitively, the longer the roux-limb the greater the weight-loss should be. Interestingly many studies have shown no improvement in weight-loss when using longer limbs in patients being less than superobese (BMI>=50 kg/m²)[104-106]. This suggests the

possibility that malabsorption might not be the major factor explaining the superior sustainable weight-loss seen after GBP compared to restrictive procedures. So why and how does it work? Is dumping part of the answer? The dumping syndrome consists of varying different symptoms including nausea, dizziness, profuse sweating, hypotension and diarrhea. The dumping syndrome is thought to be caused by the jejunum being exposed too quickly to hyperosmolar food from the stomach, which is the case in GBP since the pylorus is excluded. Foods high in sugar and fat usually trigger dumping. The unpleasant symptoms are thought to steer away the patients from such foods and thus promoting a healthier diet. However dumping is not prevalent in all GBP patients and no clear relationship seems to exist between dumping severity and weight-loss[107]. Accumulating evidence now suggests that alterations in gut hormones after bypass procedures such as GBP and biliopancreatic diversion at least in part can explain the greater weight-loss after these procedures compared to restrictive procedures[108]. Recent evidence also shows differences in gut hormone response between patients with poor weight-loss after GBP compared to patients with good weight-loss[109] further supporting the importance of the endocrine response following surgery. The complex mechanisms that regulate energy homeostasis include several different hormones. Three hormones that recently have gained attention are ghrelin, peptide YY (PYY) and glucagon-like peptide-1 (GLP-1). Ghrelin is an orexogenic hormone released from the stomach and upper intestine. It is rapidly suppressed by food intake proportionate to the amount of calories ingested. After GBP there is conflicting data with regards to levels of ghrelin. There have been studies reporting both unchanged, decreased and increased ghrelin levels after GBP[110]. Both PYY and GLP-1 are hormones released from the lower intestine following food ingestion and are involved in signaling satiety[111]. Several studies have demonstrated increased post-prandial plasma concentrations of GLP-1 and PYY after GBP[112, 113]. Their different pathways and actions are not completely understood today but with increased knowledge perhaps more efficient pharmacological therapies can emerge.

Interestingly, there is recent data showing that the gastric sleeve might be more than just another restrictive procedure[60]. Changes in levels of ghrelin and PYY after gastric sleeve could explain the good weight-loss seen (at least short-term) and could also result in sustainable weight-loss over time. The hormonal changes seen may be explained by the gastric resection. It includes most of the fundus where many ghrelin-producing cells are located. The remaining gastric tube will give incomplete digestion due to decreased gastric acid secretion. This means that the duodenum will get exposed to undigested foods with a higher pH. PYY is released from the distal gastrointestinal tract, but it has been shown that intraduodenal infusion of lipids in humans leads to rising PYY-levels[114].

5.2 GASTRIC BYPASS

During the past decade there has been a rapid increase in the numbers of bariatric procedures performed in Sweden, as well as in the rest of the world[76] fueled by the evident benefits regarding morbidity and mortality. Gastric bypass is the predominant bariatric procedure in Sweden with good long-term results regarding weight-loss. When studying the outcome of bariatric surgery it is not only weight-reduction that is of interest. Postoperative complications and postoperative mortality is of great

importance. Some of the most common complications of GBP surgery are discussed below.

5.2.1 Postoperative bleeding

Early postoperative complications after GBP include bleeding. The source could be port-sites, mesenterial edges or from either of the two anastomoses. Bleeding into the intestine can potentially cause obstruction of the biliary limb by blood-clots blocking the entero-enteroanastomosis. This could cause a blow-out of the gastric remnant. However most cases of bleeding stops without any other intervention than substituting blood. In our nationwide GBP material, hemorrhage requiring surgical intervention was seen in 0.7-0.9% of the patients with no difference regarding open or laparoscopic approach.

5.2.2 Leaks

Leakages from the gastrointestinal tract usually come from either the gasto-enteral anastomosis or less common the entero-entero anastomosis. Symptoms signaling a leak can be vague and a high degree of clinical suspicion is warranted. Abdominal pain is not always present, neither is fever. Sometimes the only signs signaling the leak are tackycardia and/or tachypnea. Diagnostic options include upper GI contrast examination and CT scans. However, even when combined, the two modalities could miss up to one third of the leaks[115]. Re-exploration is a appropriate diagnostic option when a leak is suspected[116] allowing irrigation, placement of drains and sometimes placing extra stitches reinforcing the anastomosis. More recently another treatment option has emerged. Endoscopically placed covered stents have been used, both in acute leaks as well as on more chronic fistulas with good results[117] thus avoiding long-term parenteral nutrition. Leakage from the gastric remnant can be treated with drainage and a gastrostomy. Some small contained leaks can be treated with nil per mouth and percutaneous drains.

The frequency of leaks varies in the literature between 0.4-3.2%[118, 119] in part explained by different study populations. Whether leak-rates are higher after laparoscopic than open surgery is a matter of debate and conflicting results exist in the literature. One large study including more than 25 000 patients operated with an open approach presented a leak rate of 0.4%[118]. A more recent study by Nguyen et al concluded that leaks were more common among open than laparoscopic bypasses with leak-rates of 1.7% and 0.6% respectively. From our nationwide GBP material anastomotic leaks requiring surgery was 2.0% among laparoscopic GBP and 1.3% among open GBP, which is significantly in favor of the open approach. Our material included revisional surgery, which has higher complication rates. Leak-rates in revisional series is often in the range of 10-15%[120, 121] and in our GBP material the risk of leak was 3-fold higher after revisional compared to primary procedures, with 7.4% and 2.2% in the laparoscopic and open group, respectively. When analyzing primary procedures alone we could not detect a significant difference in leak-rates between the two approaches (OR 1.7; 95% CI 1.0-3.1). In our material we could only detect leaks requiring surgical interventions. In other published data it is not clear whether all leaks are included or if it is just leaks requiring interventions. Thus caution is required when comparing the numbers.

Laparoscopic GBP is a technically demanding procedure involving intra-corporeal suturing as well as dissection under less than optimal circumstances and it has been shown that leak-rates decline with the surgeons experience[122, 123]. Once the skill is mastered it seems unlikely that results regarding leaks would differ between approaches.

5.2.3 Venous thromboembolism (VTE)

Venous thromboembolism is a complication to most abdominal procedures and pulmonary emboli can be fatal. Obesity per se is a risk factor for VTE as well as age (>50 years), smoking, history of VTE and other complications such as leaks[124]. The incidence of VTE is reported in the range of 0.2-0.8%[125, 126] after GBP and open surgery has been associated with a higher risk[127]. In a recently published series from the LABS group including primary GBP operations no significant difference regarding the incidence of VTE was seen between open and laparoscopic approach [128]. That was also the case in our material, but we did find an increased risk after revisional surgery compared to primary surgery (OR 6.2; 95% CI 2.3-16.8), perhaps in part due to the higher frequency of leaks.

5.2.4 Internal hernias

Internal hernias are a well known complication to GBP and is the herniation of small bowel through a mesenteric defect. It is more common after laparoscopic GBP, probably due to fewer adhesions postoperatively resulting a more mobile small bowel. Two or three potential mesenteric defects are created during a GBP (fig 9). The retrocolic retrogastric approach creates transverse mesocolon (A), Petersen´s defect (B) and jejeunojejunostomy (C), whereas the antecolic antegastric approach creates only two mesenteric defects: Petersen´s defect (B) and jejunojejunostomy (C). Internal hernias can present early or several years after the primary procedure and symptoms are quite variable. The most common symptoms include abdominal pain, nausea and vomiting. Complications of missing an internal herniation include bowel ischemia and perforation as well as intestinal gangrene. Diagnostic radiography includes contrast-enhanced CT scans of the abdomen. A diagnostic laparoscopy can be both diagnostic and therapeutic allowing the hernia to be reduced and the mesenteric defect closed. The incidence of internal herniation is around 2-3%[129] and seems more common when using the retrocolic retrogastric approach[129, 130]. In our GBP material 4.2% of the laparoscopic patients were hospitalized for small bowel-obstruction during follow-up. We have no data regarding ante- or retrocolic approach. We could not detect a difference between the laparoscopic and open approach regarding frequency of surgical intervention for bowel-obstruction.

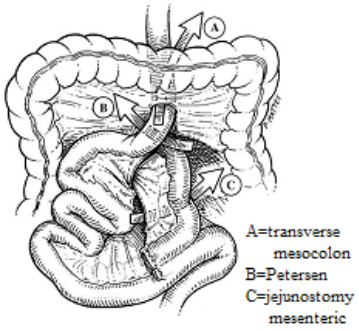

Figure 9: Potential mesenteric defects. Repreinted with permission of Schweitzer MA et al (2000). Laparoscopic closure of mesenteric defects after Roux-en-y gastric bypass. J Laparoendosc Adv Surg Tech 10:173-175

5.2.5 Incisional hernias

Incisional hernia is a common complication to midline laparotomies. Bariatric surgery is not an exception. In a review by Podnos et al[131] incisional hernias were seen in 0.5% of the laparoscopic and 8.6% of the open cases. This was also the case in our material with much lower incidence rates in the laparoscopic group (IRR 0.4; 95% CI 0.3-0.6). 9.7% of the open GBP had surgery for incisional hernia during follow-up compared to 2.2% in the laparoscopic group.

5.3 MALABSORPTIVE PROCEDURES

The bileopancreatic diversion (BPD) with or without duodenal switch is not commonly used in Sweden. Internationally it has gained popularity for treating super-obese individuals. Weight-loss seems to be somewhat better than after GBP. Early complications are similar to GBP. BPD induces malabsorption to a varying extent, which can lead to micronutrient deficiencies. Mortality after BPD is the highest among all bariatric procedures[62], which in part can be explained by the fact that it is usually the procedure for the most obese and thus the sickest patients.

5.4 MORBIDITY AFTER BARIATRIC SURGERY

In paper 3, preoperative and postoperative morbidity was estimated in a male surgical cohort, a male obese non-surgical cohort and a male general control cohort. As expected, preoperative morbidity was higher in all studied diseases in the surgical cohort compared to the general control cohort. Comparisons regarding preoperative morbidity between the two obese cohorts showed higher incidences of hyperlipidemia, hypertension and angina pectoris in the surgical cohort. In the other studied diseases no significant differences were noted. This implies, also as expected, that individuals selected for bariatric surgery have more co-morbidities than other obese individuals. Regarding postoperative morbidity, throughout the follow-up period there was as increased risk of in-patient care for all studied diseases in the surgical cohort compared to the general control cohort. Somewhat more surprisingly, hazard ratios were in favor of the surgical group compared to the obese non-surgical cohort for in-patient care regarding diabetes and hyperlipidemia but not for the other studied diseases. This might be due to high proportion restrictive procedures with less weight-loss, short follow-up time or low statistical power because of few cases. The results are in accordance with the results from the SOS-study[81] where a majority of the patients are women implying similar resolution of co-morbidities between the sexes.

5.5 MORTALITY AFTER BARIATRIC SURGERY

Mortality after any surgical procedure must be low, particularly when considering benign "prophylactic" surgery such as bariatric surgery. As mentioned in the introduction there are large differences in reported early postoperative mortality. Mortality is dependent on type of procedure and patient selection. In general, the highest mortality rates are reported from studies covering many centers whereas the lowest comes from single center series. Established patient-dependent risk factors are weight, gender and age[72, 73, 132]. Possible risk factors include diabetes[133], hypertension[133], previous thromboembolic events[128] , type of surgical approach[63, 133] and surgical experience[64]. It is noteworthy that the Swedish SOS-study did not get

ethical permission for randomizing patients to surgery or conventional treatment, since the ethics review boards at that time considered it unethical due to high postoperative mortality rates.

In the nationwide Swedish material from 1980-2005 we found the cumulative 30-day, 90-day and 1-year mortality to be 0.2, 0.3 and 0.5%, respectively after all bariatric procedures. Early mortality was higher among men. These numbers compare favorably with many single center series[72] and the results are better than population based studies from the United States[64, 134]. The difference might be attributable to a larger proportion of restrictive surgery in the Swedish material and to more obese patients with more co-morbid disease in the United States. Throughout this thesis we have used 30-day mortality while it is common in the United States to use in-hospital mortality. Both methods have their merits but it seems that in-hospital mortality is more likely to underestimate mortality-rates than 30-day mortality[135]. In paper IV Swedish obese patients, treated with GBP from 1997 to 2006, had a 30-day, 90-day and 1-year mortality of 0.3, 0.4 and 0.6%, respectively. In both paper II and IV, early mortality was higher among men; however, after adjusting for preoperative morbidity this difference diminished, suggesting that preoperative morbidity might be one explanation why different mortality is seen between sexes.

The increased mortality among men has raised the question whether men will actually gain from bariatric surgery, or if the long-term survival advantage seen in mixed studies is cancelled out by the increase in postoperative mortality. The results of paper III showed a survival advantage among operated men compared to an obese group of non-operated men. The reduced mortality risk of 0.7 closely resembles the one seen in the SOS-study[52] implying a similar survival advantage in both sexes.

5.6 HEALTH ECONOMICS

Obesity and related co-morbidities have been estimated to account for 9% of the total U.S. healthcare expenditures[27]. Bariatric surgery will be cost effective if the costs for the procedure, complications, medications and follow-up are less than estimated costs for medication and expected healthcare costs with conservative treatment. Christou et al[90] demonstrated 50 % fewer hospitalizations in a bariatric cohort compared to a non-operated obese cohort during 5 years of follow-up. Different models have been used to assess cost-effectiveness after surgery compared to conservative treatment and it has been shown that bariatric surgery is cost effective[136] even when looking at just one co-morbid disease such as type-2 diabetes[137]. The initial costs have been reported to be covered by downstream savings in as little as 2 to 4 years[138]. More studies are needed, preferably in a Swedish setting, since if bariatric surgery in Sweden is proven cost-efficient more resources may be allocated to this field. Perhaps the real question is whether we can afford not to operate morbidly obese subjects. Money saved now can turn out to be costly in the long run.

5.7 USING REGISTER DATA - PROS AND CONS

Paper I is based on prospectively collected data held in a quality database that was created for quality assurance at Danderyd Hospital. One could argue that this, as a single center series, could possibly lead to underreporting of complications and

revisional procedures if these were taken care of in other hospitals. By using the dataset from paper II all index VBG from Danderyd Hospital were identified and an analyses showed that of all revisional procedures in this group, some 4% were conducted at another hospital. The reported revisional rate of 21.4 % after laparoscopic VBG might thus be an underestimation. The fact that the database only consisted of 486 patients made it possible to manually check and validate the database against all the patient charts to identify any missed complication.

Papers II-IV in this thesis is based on a database created by record-linkage of data from different existing Swedish registries. An obvious advantage is the relative easy which data can be retrieved. Sweden has a long history of keeping nation-wide registries with high quality data. When using nation-wide data, the results are applicable to the whole unselected group of patients who have undergone bariatric surgery. Results from single expert centers might give a too positive picture regarding postoperative morbidity and mortality. When studying rare events, such as postoperative mortality, a prospective study has to include many patients in order to get sufficient statistical power. This is both time-consuming and expensive. One example is the SOS-study, where it took just over 10 years of follow-up to detect a difference in mortality between the two cohorts[52].

When using registry data it is a limitation that the information has not been collected specifically for research purposes, which may have consequences for quality of the data. Some co-morbid diseases may be under-reported in registries created for administrative purposes. Another limitation is lack of information on all potential confounding factors. In this thesis data on height and weight was available from time of conscription examinations, but not at time of bariatric surgery. Such information would have been very useful. When estimating the incidence of co-morbid diseases from the in-patient care registry, diseases such as hypertension, diabetes and hyperlipidemia may be underestimated because these conditions are usually handled by the patient's primary care physician and will only end up in the in-patient care registry if severe enough to generate in-patient care or if the patient recieve in-patient care for other reason. It is more likely that life-threatening conditions such as myocardial infarction and stroke are present in the in-patient care registry since most these cases or events will be admitted to hospital. When comparing surgical and non-surgical cohorts in paper III, we tried to adjust for the increased probability of getting a diagnosis of a co-morbid disease during pre- or postoperative check-ups in the surgical cohort than in the non-surgical cohorts by disregarding all new diagnoses set for diabetes, hypertension and hyperlipidemia within a year of date of surgery (or pseudo-surgery date). However, it is possible that the underestimation of co-morbid diseases may have resulted in some residual confounding in the multivariate Cox regression analyses.

When studying mortality, the Swedish registries are of great help. In many studies from the United States mortality is based on in-hospital mortality only, resulting in underestimations of the true rates of peri- and postoperative mortality. Furthermore, as stated by Buchwald et al[63] in the meta-analysis of mortality, death after 30 days and onwards is likely a gross underestimate due to significant loss to follow-up in case-series. In the Swedish cause of death registry approximately 0.5% has no registered cause of death. Quality regarding cause of death is validated on a regular basis and is

considered better in younger or middle-aged individuals (as in our studies) than in old people.

6 CONCLUSIONS

Bariatric surgery is in an expansive phase in Sweden. Laparoscopic GBP is today the most popular procedure. The number of restrictive bariatric procedures is declining and long-term results after VBG are discouraging with a trend of weight-gain and high rates of revisional surgery. Simple restriction is not enough and perhaps the old terms restrictive and malabsorptive surgery, also are outdated with increased knowledge regarding effect of gut peptides on satiety. The role of gastric sleeve is still unclear due to lack of long-term results.

- VBG should not be performed as a bariatric procedure today.

Obese patients are high risk candidates for any major surgical procedure. Throughout the time-period this thesis covers, mortality rates have been comparable to single expert centers in the USA. This in spite of the shift towards more complex procedures such as GBP where mortality is higher.

- Early mortality after bariatric surgery is low in Sweden.

Postoperative mortality is higher among men. A possible reason is higher rates of co-morbid disease at time of surgery. In spite of that, obese men have a survival advantage after bariatric surgery compared to non-operated obese men. This survival advantage seems to be in the same range as for women. Men also have a similar reduction in co-morbid diseases after bariatric surgery as seen in studies mainly comprised of women.

- More obese men should be encouraged to undergo bariatric surgery

Laparoscopic GBP is as safe as open GBP on a national level. Mortality is low. Risks for complications are highly increased after revisional GBP especially if conducted by laparoscopic approach. Higher incidence rates were observed for anastomotic leaks and other complications such as deep vein thrombosis and pulmonary emboli. This stresses the importance of choosing the best surgical procedure the first time around.

- Laparoscopic bariatric surgery is safe and should be the first choice

7 SUMMARY IN SWEDISH (SAMMANFATTNING)

Prevalensen av fetma i befolkningen har ökat kraftigt i större delen av världen de senaste decennierna. Fetma skattas oftast med hjälp av kroppsmasseindex (BMI). Fetma är kopplad till en rad sjukdomar såsom högt blodtryck och diabetes. Tillsammans utgör de delar av det så kallade metabola syndromet som ökar risken för hjärt-kärlsjukdom. Övervikt eller måttlig fetma kan ofta åtgärdas med kostomläggning och motion och ibland även med farmaka. Vid svår fetma räcker ingen av dessa alternativ. Individer med ett BMI>40 eller ett BMI>35 och en eller flera överviktsrelaterade sjukdomar kan idag erbjudas kirurgisk behandling. Kirurgisk behandling har visat sig vara det mest effektiva sättet att minska kraftigt i vikt. Efter kirurgi ser man positiva effekter på såväl blodtrycket som blodsockret. Senaste åren har det publicerats ett flertal studier som visar bättre överlevnad hos individer som genomgått överviktskirurgi jämfört med överviktiga som inte gjort det.

Kirurgin har traditionellt delats in i restriktiv och malabsorptiv kirurgi. Den restriktiva minskar möjligheten att snabbt äta stora portioner genom att delar av magsäckens volym minskas. Exempel på restriktiva ingrepp är vertikalt bandad gastroplastik (VBG) (fig 1, sid 4) och gastric banding (fig 2, sid 4). Malabsorptiva ingrepp innebär att delar av tunntarmen kopplas om så näringsupptaget försämras. Exempel är biliopancreatic diversion (fig 5&6, sid 5) och tarmshunt (fig 7, sid 5). En tredje variant är ingrepp som kombinerar restriktion och malabsorption. Det idag mest populära ingreppet gastric bypass (fig 4, sid 5) är ett exempel på det.

I denna avhandling har vi undersökt långtidsresultaten efter VBG och funnit ganska nedslående resultat. Viktnedgången har varit bra i cirka ett år men sedan har många börjat gå upp i vikt igen. Andra har haft mycket besvär med kräkningar. Under uppföljningstiden har över 20 % av patienterna behövt genomgå ytterligare operationer. VBG bör därför överges som behandlingsmetod mot kraftig övervikt.

Vidare har dödligheten studerats efter överviktskirurgi i Sverige. Resultaten visar att den ligger på låga nivåer och står sig bra i internationella jämförelser. Män har en högre dödlighet än kvinnor efter kirurgin vilket kan bero på att de har fler överviktsrelaterade sjukdomar innan de hänvisas till operation. Trots det fann man att även män med fetma tjänar på att operera sig. Dödligheten var 0.7 gånger lägre än hos en grupp ickeopererade män med fetma.

I dag görs majoriteten av alla överviktsoperationer i Sverige med så kallad titthålsteknik. Det har flera fördelar, framför allt snabbare postoperativ återhämtning. Det har funnits farhågor att det skulle vara högre komplikationsfrekvens efter titthålskirurgi då denna metod är tekniskt sett mer avancerad. Man har studerat dödlighet och komplikationsfrekvenser hos nästan 5000 patienter som opererats med en gastric bypass. Resultaten visade att det inte var fler komplikationer efter titthålskirurgi. Det var heller ingen skillnad i dödlighet. Däremot var det fler komplikationer vid re-operation, dvs när en tidigare överviktsoperation var tvungen att göras om. Det styrker tesen att VBG bör avvecklas och väcker frågan om man över huvud taget skall ägna sig åt restriktiv kirurgi.

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