

# Surgical treatment of severe obesity with laparoscopic gastric bypass and duodenal switch

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# Abbreviations

ACS	American College of Surgeons
ASMBS	American Society for Metabolic and Bariatric Surgery
BAROS	Bariatric Analysis and Reporting Outcome System
BMI	Body-mass index
%BWL	Percent of body weight lost
CRP	C-reactive protein
%EWL	Percent of excess weight lost
GLP-1	Glucagon-like peptide-1
GSRS	Gastrointestinal Symptom Rating Scale
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
OP scale	Obesity-related Problems scale
SD	Standard deviation
SF-36	Short Form-36 Health Survey
SOS study	Swedish Obese Subjects study
TFEQ-R21	Three-Factor Eating Questionnaire-R21

# Contents

- 1 List of papers ..... 1
- 2 Introduction ..... 2
  - 2.1 Obesity ..... 2
    - 2.1.1 Definitions of obesity, morbid obesity, and superobesity ..... 2
    - 2.1.2 Global and national prevalence trends ..... 3
    - 2.1.3 Impact on health ..... 4
    - 2.1.4 Management ..... 6
  - 2.2 Bariatric surgery ..... 8
    - 2.2.1 Surgical techniques ..... 8
    - 2.2.2 Laparoscopy in bariatric surgery ..... 11
    - 2.2.3 Outcomes after bariatric surgery ..... 13
    - 2.2.4 Weight loss after bariatric surgery in morbidly versus superobese patients ..... 20
- 3 Aims ..... 22
- 4 Methods ..... 23
- 5 Results ..... 32
- 6 Discussion ..... 34
  - 6.1 Methodological considerations ..... 34
  - 6.2 Main findings ..... 37
    - 6.2.1 Establishing laparoscopic gastric bypass ..... 37
    - 6.2.2 Weight loss after gastric bypass and duodenal switch ..... 38
    - 6.2.3 Cardiovascular risk factors ..... 39
    - 6.2.4 Nutritional aspects and eating behavior ..... 40
    - 6.2.5 Gastrointestinal symptoms ..... 41
    - 6.2.6 Quality of life ..... 42
  - 6.3 Who should have bariatric surgery? ..... 42
  - 6.4 Clinical implications ..... 43
  - 6.5 Topics for further research ..... 44
- 7 Conclusions ..... 46
- 8 References ..... 47
- 9 Papers I – IV ..... 72



# 1 List of papers

## Paper I

Søvik TT, Aasheim ET, Kristinsson J, Schou CF, Diep LM, Nesbakken A, Mala T. Establishing laparoscopic Roux-en-Y gastric bypass: perioperative outcome and characteristics of the learning curve. *Obes Surg* 2009; 19(2):158-165.

## Paper II

Søvik TT, Taha O, Aasheim ET, Engström M, Kristinsson J, Björkman S, Schou CF, Lönroth H, Mala T, Olbers T. Randomized clinical trial of laparoscopic gastric bypass versus laparoscopic duodenal switch for superobesity. *Br J Surg* 2010; 97(2):160-166.

## Paper III

Søvik TT, Aasheim ET, Taha O, Engström M, Fagerland MW, Björkman S, Kristinsson J, Birkeland KI, Mala T, Olbers T. Weight loss, cardiovascular risk factors, and quality of life after gastric bypass and duodenal switch: a randomized trial. *Ann Intern Med* 2011; 155(5):281-291.

## Paper IV

Søvik TT, Karlsson J, Aasheim ET, Fagerland MW, Björkman S, Engström M, Kristinsson J, Olbers T, Mala T. Gastrointestinal function and eating behavior after gastric bypass and duodenal switch. *Surg Obes Relat Dis* 2012 (Epub ahead of print).

# 2 Introduction

## 2.1 Obesity

### 2.1.1 Definitions of obesity, morbid obesity, and superobesity

Body-mass index (the weight in kilograms divided by the square of the height in meters) is a commonly used measure of obesity. First named the Quetelet Index after Adolphe Quetelet in 1832, and renamed body-mass index (BMI) in 1972, BMI is widely used in epidemiological studies of associations between excess weight and morbidity or mortality (1;2).

**Table 1.** Classification of underweight, overweight, and obesity according to the World Health Organization (1).

Classification	Body-mass index (kg/m <sup>2</sup> )
Underweight	<18.5
Normal range	18.5 – 24.9
Overweight	≥25.0
Pre-obese	25.0 – 29.9
Obese	≥30.0
Obese class I	30.0 – 34.9
Obese class II	35.0 – 39.9
Obese class III	≥40.0

*Morbid obesity* may be defined as a body weight twice or more the desirable weight based on life insurance tables (2). The currently used definition of morbid obesity was developed in 1991 in a National Institutes of Health (NIH) consensus statement (3). Among other criteria, this definition suggested that patients with class III obesity (Table 1) or class II obesity with high-risk comorbid conditions may be considered for bariatric surgery. The term *superobesity* was proposed in 1987 as a weight exceeding 225% of estimated ideal weight (4). Later,



superobesity was defined as having a BMI  $>50 \text{ kg/m}^2$  (5). In this thesis, superobesity is defined as a BMI in the range of  $50 - 60 \text{ kg/m}^2$ , and *super-superobesity* as a BMI  $>60 \text{ kg/m}^2$ , as suggested by the American Society for Metabolic and Bariatric Surgery (ASMBS) (6).

### 2.1.2 Global and national prevalence trends

To date, the obesity epidemic has not been reversed in any population through public health measures (7). A recent study explored worldwide trends in BMI based on measured weight and height from 9.1 million participants and 960 country-years from 1980 to 2008. In adults, the mean BMI increased by  $0.5 \text{ kg/m}^2$  per decade for women and by  $0.4 \text{ kg/m}^2$  per decade for men. Large differences in BMI rises were observed across regions and between sexes. Worldwide, in 2008, an estimated 1.46 billion adults had a BMI of  $25 \text{ kg/m}^2$  or greater, including some 500 million obese individuals (8).

In the United States, the prevalence of obesity exceeds 30% in both women and men, with recent prevalence figures of a BMI  $\geq 40 \text{ kg/m}^2$  of 8.1% in women and 4.4% in men (9;10). In Norway, the prevalence of obesity is approximately 20% in both women and men (11). In the Nord-Trøndelag health study (HUNT), obesity rates increased from 13.6% in women and 7.8% in men in 1984 – 1986 to 23.2% in women and 22.1% in men in 2006 – 2008 (12).

Little data are available on the prevalence of severe obesity (e.g. BMI  $>50 \text{ kg/m}^2$ ) from measured weight and height (13). In adults, *self-reported* weight is systematically under-reported and height is over-reported (14). Data from telephone surveys in the United States indicate that the prevalence of severe obesity among adults has increased several times faster than the prevalence of overweight and of moderate obesity. For example, the prevalence of a BMI  $>50 \text{ kg/m}^2$  increased by 75% from 2000 to 2005, compared to a 24% increase in the prevalence of a BMI  $>30 \text{ kg/m}^2$  (15;16).

In large case series of patients undergoing bariatric surgery in the United States, about 20 – 25% of patients had preoperative BMIs in the range of  $50 - 60 \text{ kg/m}^2$  (17-19). In a database of patients undergoing bariatric surgery at Oslo University Hospital Aker, about 20% were superobese before surgery (unpublished data).

Although rates of overweight and obesity have increased in children and adults over the last decades (8;20), some recent studies indicate that the obesity prevalence is plateauing and

possibly decreasing, particularly in women and children (9;21-24).

### **2.1.3 Impact on health**

Overall, the disease burden attributable to excess weight is dominated by cardiovascular disease, diabetes, and cancer (25). According to projected obesity trends in the United States and the United Kingdom, millions of additional cases of these preventable diseases may place a serious strain on health systems (26).

Obesity in childhood is associated with an increased risk for obesity in adolescence and adulthood (27;28), and for diabetes and coronary heart disease in adulthood (29-31). As a strong association exists between obesity, glucose intolerance, and hypertension in childhood and increased rates of premature death, prevention of obesity should start at an early age (32). However, little data are available on the effectiveness of intervention programs for overweight children and adolescents (33;34).

#### **Common comorbid conditions and the metabolic syndrome**

In adults, elevated BMI is associated with subsequent development of comorbid conditions such as type 2 diabetes mellitus, hypertension, hyperlipidemia, gallbladder disease, and osteoarthritis (35-38). This risk is also increased in subjects with a BMI in the upper part of the healthy BMI range (22 – 25 kg/m<sup>2</sup>) (39). A positive association between BMI and the risk for ischemic stroke is described regardless of sex and race, but this relationship is attenuated after adjusting for diabetes and hypertension (40). In the National Health and Nutrition Examination Survey (NHANES, 1999 – 2004), the largest increase in the prevalence of hypertension, dyslipidemia, and the metabolic syndrome in obese class III were observed in the age group of individuals between 18 and 29 years (41).

The metabolic syndrome is a constellation of common disorders which confer increased risk for type 2 diabetes, cardiovascular disease, and increased all-cause and cardiovascular mortality (42-44). A commonly used definition of the metabolic syndrome, published by the National Cholesterol Education Program (NCEP), proposes cutoff values for waist circumference, triglyceride levels, low levels of high-density lipoprotein (HDL) cholesterol, blood pressure, and fasting glucose (42). The prevalence of the metabolic syndrome increases with the degree of obesity in children and adolescents (45). In the United States, the

prevalence of the metabolic syndrome was 27% in adults in NHANES data from 1999 – 2000 (46). In a Norwegian cohort of patients eligible for bariatric surgery, 80% had the metabolic syndrome as evaluated by the same definition (47).

### **Other obesity-related disorders**

In population studies, BMI is positively associated with an increased risk for gastrointestinal symptoms, such as gastroesophageal reflux, vomiting, upper abdominal pain, bloating, and diarrhea (48-50). Also, morbidly obese patients may have more hiatal hernias and gastritis (51). The putative mechanisms for upper gastrointestinal disorders include an increased intra-abdominal pressure and decreased lower esophageal sphincter pressure in obese individuals (52;53). Weight loss is associated with a decreased risk for such symptoms (48).

An accelerated colonic transit and colonic dysfunction may contribute to an increased frequency of diarrhea in obese individuals (49). In a series of 120 patients eligible for bariatric surgery (92% women), functional gastrointestinal symptoms were found in 89% of patients, 18% reported diarrhea, and 10% had fecal incontinence (54).

Other studies have found positive associations between BMI and sleep-disordered breathing (55); and an increased risk for adult-onset asthma (56) and infertility in women and men (57;58).

### **Cancer**

Obesity confers an increased risk for several types of cancer, e.g. esophageal adenocarcinoma; and thyroid, colon, renal, endometrial, and gallbladder cancer. The risk for developing some cancers, such as colon cancer, differs among women and men (59;60). The putative mechanisms of the relationship between obesity and carcinogenesis include different hormonal systems that are interlinked through insulin (59).

### **Mortality**

Both overweight and obesity is associated with increased all-cause mortality. In a large study of individuals who had never smoked, and did not have heart disease or cancer, mortality was lowest with a BMI in the range of 20 – 25 kg/m<sup>2</sup> (61). The results were in agreement with a study which included smokers and persons with preexisting cancers (62). These recent data

contradict earlier reports that failed to show an association between overweight (i.e. BMI 25 – 30 kg/m<sup>2</sup>) and increased all-cause mortality (63).

Life expectancy is decreased in severely obese individuals. In white women aged 20 – 30 years with a BMI >45 kg/m<sup>2</sup>, an estimated 8 years of life is lost because of severe obesity, and 13 years of life is lost for white men in the same age group (64).

### **Quality of life**

Previous research has linked obesity and poor physical quality of life in children and adolescents. In one study, severely obese children and adolescents had similar health-related quality of life as those diagnosed with cancer (65). In adults, an association exists between BMI and reduced health-related quality of life, poor physical and mental health, and activity limitations (66). Obesity is also associated with psychosocial dysfunction, and more so in obese women than in obese men (67). Discrimination of morbidly obese individuals is prevalent both at work and in public places (68). Obese persons are also particularly likely to encounter negative stigma from family members and health care professionals (69).

### **2.1.4 Management**

For patients with obesity-related comorbid conditions, even a modest weight reduction of 10% or less is associated with important health benefits such as improved glycemic control, a reduced blood pressure, and lower cholesterol levels (70).

#### **Dietary and lifestyle interventions**

In a study conducted in the United States, 44% of women and 29% of men reported that they were attempting to lose weight, most commonly by modifying their diet (71). However, only about 20% of motivated individuals achieve weight loss maintenance through dietary and lifestyle changes (72). In primary care practices, behavioral interventions through in-person individual contact or remote weight-loss support, such as e-mail solutions, can induce sustained weight loss (73). Commercially available weight loss programs which include regular weighing, dietary advice, and physical therapy might provide greater weight loss than standard treatment in primary care (74).

Within 1 year of follow-up, diets which are low in carbohydrate and high in protein lead to

greater weight loss and more favorable changes in metabolic parameters in overweight and obese individuals than diets which are low in fat and high in carbohydrate (75-77). Also, low-carbohydrate diets reduce hepatic triglyceride content (78), and have little effect on plasma saturated fatty acids concentrations (79).

Although regular physical activity is commonly recommended for weight loss, clinical exercise trials have demonstrated less weight loss effect of such intervention than predicted, possibly because of compensatory mechanisms (80). The effects of exercise may be sex-dependant; exercise of moderate intensity can provide significant weight loss in overweight and obese men, whereas it prevents weight gain in women (81). In obese men, weight loss by diet and exercise induce greater improvements in insulin action than diet alone (82), whereas adding exercise to a diet in obese women does not provide further improvements in metabolic markers (83).

Intensive lifestyle intervention can induce sustained weight loss and improvements in cardiovascular and metabolic parameters in overweight and obese individuals with type 2-diabetes (84). Among severely obese subjects, however, long-term data on the effects of lifestyle intervention are limited. Two recent studies suggest that, within 1 year of follow-up, intensive lifestyle modification in morbidly obese patients increases physical activity levels, substantially reduces weight, and confers positive changes in cardiovascular risk factors and glycemic control (85;86).

## **Pharmacological treatment**

Anti-obesity drugs provide modest weight loss (<5 kg) compared with placebo after 1 to 4 years of treatment (87;88). Most studies on such drugs are funded by pharmaceutical companies, and attrition rates are generally in the range of 30 – 40%. Thus, poor adherence may limit the clinical effectiveness and use of anti-obesity drugs. Changes in cardiovascular risk factors and adverse effects differ between the drugs.

In the Sibutramine Cardiovascular Outcomes (SCOUT) trial, investigators evaluated the effect of a serotonin and epinephrine reuptake inhibitor and lifestyle intervention versus lifestyle intervention alone in overweight and obese patients, aged 55 years or older, with preexisting cardiovascular disease, type 2 diabetes, or both. Sibutramine increased the risk for nonfatal cardiovascular events and was consequently withdrawn (89;90). The Comprehensive

Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial tested whether the selective cannabinoid-1 receptor antagonist rimonabant improved major vascular event-free survival in patients with previous established or increased risk for vascular disease, but was terminated prematurely because of neuropsychiatric effects of rimonabant (91).

Orlistat is one of few drugs approved for pharmacological weight management. In the XENDOS (XENical in the prevention of Diabetes in Obese Subjects) study, orlistat combined with lifestyle changes provided significant weight loss and reduced the incidence of diabetes in obese subjects with impaired glucose tolerance after 4 years of treatment (92). Recently, the U.S. Food and Drug Administration (FDA) approved both the selective serotonin 2C receptor agonist lorcaserin and once daily, controlled-release phentermine plus topiramate (93;94). These drugs are to be used in obese adults, or in overweight adults with at least one obesity-related comorbid condition, in combination with diet and exercise.

Liraglutide, an analog of the incretin hormone glucagon-like peptide-1 (GLP-1), is approved for treatment of type 2 diabetes, but not as an anti-obesity drug. In a recent randomized trial, once-daily subcutaneous injections of liraglutide was well tolerated, provided greater weight loss than orlistat, and improved cardiovascular risk factors (95).

## **2.2 Bariatric surgery**

### **2.2.1 Surgical techniques**

#### **Jejunioleal bypass**

Studies of the metabolic effects of small bowel bypass in animals were published in the 1950s (96). During the next decade, the effects of jejunoileal shunts were reported in morbidly obese patients (97). A modified surgical technique, the jejunioleal bypass, was suggested as an effective and safe operation for inducing weight loss and was applied throughout the 1970s (98-100). This operation combined an end-to-end anastomosis between the proximal jejunum and the distal ileum with an anastomosis between the excluded small bowel and the colon to decompress the bypassed small bowel and prevent reflux of intestinal content into the bypassed segment (101). Long-term follow-up of patients treated with jejunioleal bypass

indicates maintained favorable changes in weight and cardiovascular risk factors. However, the operation was abandoned because of the risk for serious complications, including protein malnutrition, bacterial overgrowth in the bypassed bowel segment, and hepatic failure (2;102-106).

### **Gastric bypass**

Gastric bypass was first performed in 1966 by Edward E. Mason (107). The procedure was modeled after a Bilroth II gastrectomy, as weight loss was frequently observed after this operation. By constructing a small upper gastric pouch, Mason hypothesized that most mucosa containing parietal cells would be located in the distal part of the stomach, thus reducing the amount of acid above the stoma. Consequently, meal-stimulated gastrin production would be suppressed and the incidence of stomal ulcers would be low (108). The anastomosis was initially performed with a narrow gastric outlet and a short proximal loop gastroenterostomy placed retrocolically (109). Later modifications of the procedure included mobilization of the entire fundus in order to create a smaller gastric pouch (110;111), the conversion from loop gastroenterostomy to a Roux-en-Y configuration (112), and the banded gastric bypass (the Fobi pouch) (113).

### **Gastroplasty**

With the gastroplasty, described in the early 1970s, Mason attempted to simplify the gastric bypass (114). The stomach was divided horizontally from the lesser to the greater curvature, leaving a small outlet between the upper and lower gastric pouches. However, weight loss after the procedure was unsatisfactory. Several surgical modifications were proposed, such as gastric partitioning and the vertical banded gastroplasty (115-117).

### **Gastric wrapping**

Also preceded by animal studies, the gastric wrapping technique reduced the reservoir capacity of the stomach by inverting the lesser curvature by combining a large Nissen's fundoplication and a tightly applied mesh (wrap) around the stomach (118;119). The purpose was to develop an alternative bariatric procedure which did not disrupt the continuity of the gastrointestinal tract. However, the operation was associated with dysphagia and gastric perforations after long-term follow-up (120).

## **Gastric banding**

Building on the principle of reducing the reservoir capacity of the stomach, the first gastric banding procedures were performed in 1980 (121). These included the use of a nonadjustable band (i.e. a self-lockable nylon band in a Dacron graft). Short-term analyses of weight loss were promising, but long-term follow-up demonstrated a high rate of reoperations because of esophagitis, weight regain, and also Barrett's esophagus and erosions of the band through the stomach wall (122;123). To overcome complications from tissue reactions of the implanted bands, the original bands were replaced by Dacron reinforced silicon bands. The development of bands containing an inflatable balloon connected to a subcutaneous reservoir by a tube allowed for adjustment of the stoma diameter and pouch size by adding or withdrawing saline from the reservoir (124-126).

## **Biliopancreatic diversion and duodenal switch**

The purpose of the biliopancreatic diversion procedure, as presented by Scopinaro in 1979, was to introduce a safe malabsorptive operation as an alternative to jejunioileal bypass (127;128). The main features were a distal gastrectomy to reduce the risk for stomal ulcers, and a long Roux-en-Y construction with the enteroenteric anastomosis at 50 cm proximal to the ileocecal valve and the gastroenteric anastomosis 250 cm proximal to the valve. Such an arrangement would allow for a selective malabsorption of fat, as this is absorbed in the short common bowel segment. Protein and starch, however, are absorbed throughout the bowel segment between the upper anastomosis and the colon. Mono- and disaccharides, short-chain triglycerides, and alcohol are also probably fully absorbed (129).

A modification of the biliopancreatic diversion, the biliopancreatic diversion with duodenal switch, was developed by Hess in 1988 to reduce the risk for complications in patients with previous bariatric surgery in the upper part of the stomach (130). This technique, which preserves pyloric function, reduced the frequency of complications such as marginal ulcer formation and dumping. The duodenal switch included a vertical gastric resection, possibly reducing parietal cell mass, along a 40 Fr tube (bougie) from a few centimeters proximal to the pylorus to the angle of His. The ileum was anastomosed to the duodenum.

Cholecystectomy and appendectomy were performed concomitantly. Marceau's duodenal switch procedure, a modification of the biliopancreatic diversion with a sleeve gastrectomy and a longer (100 cm) common channel, added further weight loss and reduced the incidence



of malnutrition. However, symptoms of abdominal bloating and malodorous stool and flatus remained unchanged (131-133).

### **Sleeve gastrectomy**

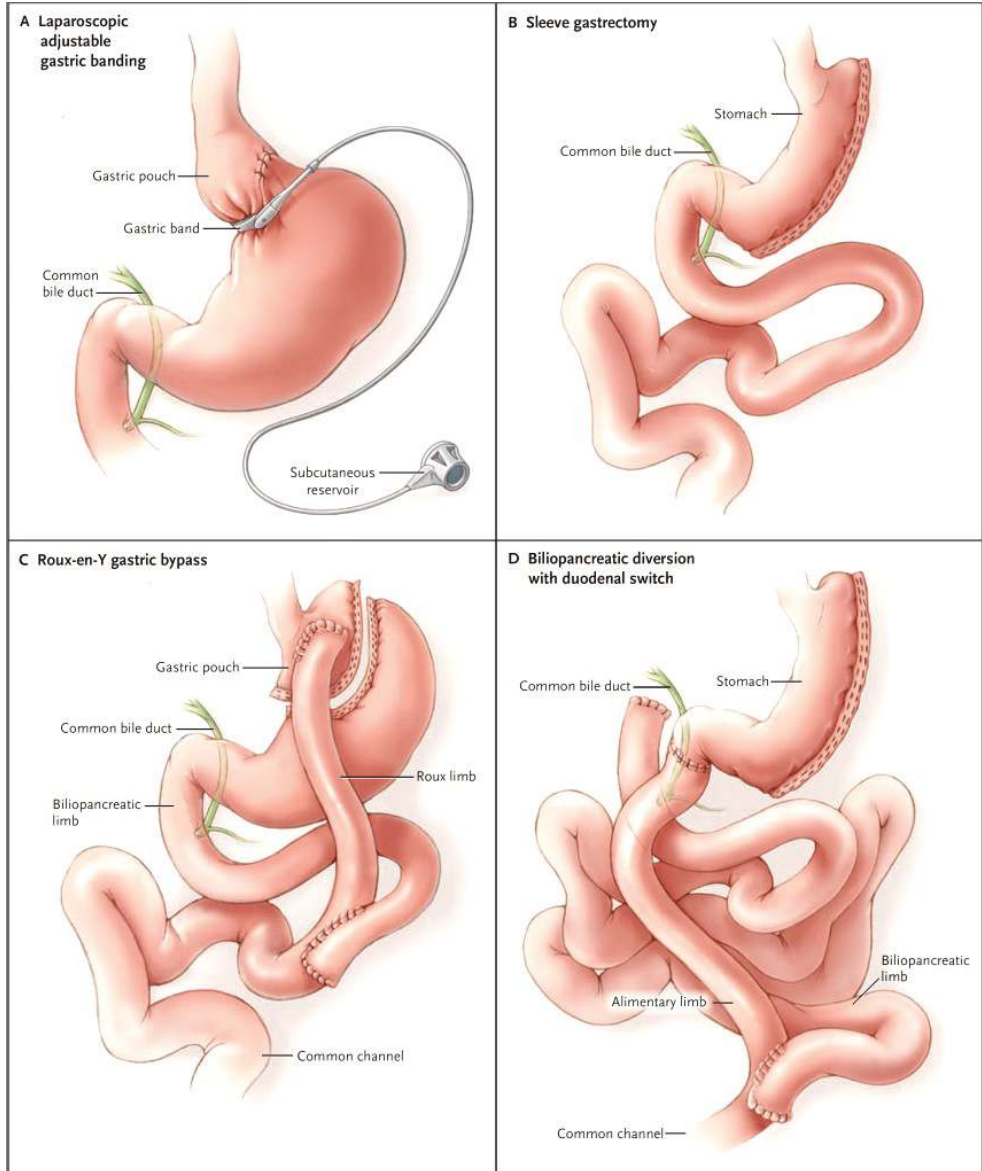
As mentioned, sleeve gastrectomy was proposed as the restrictive feature of the biliopancreatic diversion with duodenal switch. Later, in the setting of two-stage laparoscopic surgery in high-risk patients, the efficacy of sleeve gastrectomy as a stand-alone bariatric procedure was recognized by Gagner and colleagues (134). The procedure was recently approved by the ASMBS as an acceptable primary bariatric operation or first operation in a staged surgical approach (135).

### **Bariatric procedures in current use**

In 2008, gastric bypass accounted for 51% of bariatric procedures performed in North America, followed by adjustable gastric banding (44%), sleeve gastrectomy (4%), and duodenal switch (1%). Correspondingly, in Europe, adjustable gastric banding procedures were performed in 43% of patients, followed by gastric bypass (39%), sleeve gastrectomy (7%), and duodenal switch (5%) (136). Today, most procedures are done by laparoscopy. In recent years, banding procedures are performed less in Europe whereas gastric banding and sleeve gastrectomy are done with increasing frequency in North America (19). Laparoscopic gastric bypass is the most commonly performed procedure in Norway, although laparoscopic sleeve gastrectomy is gaining popularity. Duodenal switch is offered at some centers, both by laparoscopy and by open technique, and accounts for about 5% of bariatric procedures at Oslo University Hospital Aker (137;138).

### **2.2.2 Laparoscopy in bariatric surgery**

The first laparoscopic bariatric procedures were performed in the early 1990s. Reports of laparoscopically placed nonadjustable and adjustable gastric bands (139;140) were followed by studies of the first vertical banded gastroplasty in 1993 (141), laparoscopic gastric bypass in 1994 (142), and laparoscopic duodenal switch in 2000 (143). Studies comparing open versus laparoscopic bariatric surgery suggest that weight loss is similar with both approaches. The advantages of laparoscopic surgery include a shorter length of hospital stay, less postoperative pain, an improved cosmetic result, swifter return to daily activities, and reduced



**Figure 1.** Bariatric surgical procedures in current use. Reproduced from DeMaria (144) with permission. Top left: Laparoscopic adjustable gastric banding, top right: vertical (sleeve) gastrectomy, bottom left: Roux-en-Y gastric bypass, bottom right: biliopancreatic diversion with duodenal switch.

rates of wound infections and incisional hernias (145-150). In a meta-analysis comparing open and laparoscopic bariatric surgery, investigators found no differences in the risks for reoperation, anastomotic leak, or mortality between the two approaches (151).

### **Learning curve in laparoscopic bariatric surgery**

After the introduction of laparoscopy in surgical procedures such as appendectomy, cholecystectomy, and colorectal resections, surgical learning curves for the operations were described. The acquisition of surgical skills is reflected in shortened lengths of surgery and postoperative hospital stay (152-154). However, the number of procedures reported as sufficient for proficiency in a procedure vary widely and are limited by various definitions of a “learning curve”, by reports of results from a surgical team rather than a single surgeon, and by categorizing procedural volumes instead of exploring the effects of procedure volumes as a continuous variable in analyses (155). Also, several reports of learning curves in laparoscopic surgery were published in the early era of laparoscopy. The learning curve for laparoscopic cholecystectomy, for example, has been described to comprise 25 cases, but further improvement is observed beyond 200 cases (156). For laparoscopic gastric bypass, investigators have reported that the learning curve comprises about 100 cases (157).

## **2.2.3 Outcomes after bariatric surgery**

### **Weight loss**

In a meta-analysis of bariatric surgery published in 2004 which included 22094 patients, the mean percent of excess weight lost (i.e. weight loss/excess weight\*100%) was 48% after gastric banding, 62% after gastric bypass, and 70% after biliopancreatic diversion with or without duodenal switch (158). In another meta-analysis, weight loss was also greatest after biliopancreatic diversion, followed by gastric bypass (159). Studies of weight loss outcome after gastric bypass after  $\geq 5$  years of follow-up are shown in Table 2 (articles were retrieved through a nonsystematic search in PubMed).

### **Diabetes**

In 1995, investigators found that in a cohort of over 600 morbidly obese patients undergoing gastric bypass, glucose levels were normalized in 121 of 146 patients (83%) with type 2

**Table 2.** Long-term weight loss outcome after gastric bypass surgery.

Author, year	Procedure	Number of patients	Follow-up, years	Follow-up, %	Outcome	BMI <50 at surgery	BMI ≥50 at surgery
Sugerman (160), 1992	Gastric bypass	162	5	70	%EWL: 60	N/A	N/A
Reinhold (161), 1994	Gastric bypass	153	5	56	%EWL: 51	N/A	N/A
Pories (162), 1995	Gastric bypass	608	14	96	%EWL: 49	N/A	N/A
MacLean (163), 2000	Gastric bypass	274	6	N/A	N/A	BMI: 29	BMI: 35
Jones (164), 2000	Gastric bypass*	352	10	51	%EWL: 62	N/A	N/A
Sugerman (165), 2003	Gastric bypass*	1025	5 – 7	50	%EWL: 59	N/A	N/A
Sjöström (166), 2004	Gastric bypass	34	10	100	%BWL: 25	N/A	N/A
White (167), 2005	Silastic ring/Fobi pouch gastric bypass	342	5	39	%EWL: 70	N/A	N/A
Christou (168), 2006	Gastric bypass*	228	11	84	%EWL: 68	%EWL: 72	%EWL: 60
Magro (169), 2008	Fobi pouch gastric bypass	782	5	47	N/A	N/A	N/A
Suter (170), 2009	Gastric bypass*	625	6	84†	N/A	%BWL: 30	%BWL: 31

Table 2 continued

Author, year	Procedure	Number of patients	Follow-up, years	Follow-up, %	Outcome	BMI <50 at surgery	BMI ≥50 at surgery
Diniz (171), 2009	Gastric bypass	193	5	73	%EWL: 62	%EWL: 66	%EWL: 60
Kruseman (172), 2010	Gastric bypass	141	8	59	%EWL: 56	N/A	N/A
Higa (173), 2011	Gastric bypass*	242	10	26	%EWL: 57	%EWL: 51‡	%EWL: 58‡
Suter (174), 2011	Gastric bypass*	379	7	90	%EWL: 58	N/A	N/A
Awad (175), 2012	Fobi pouch gastric bypass	260	10	69	%EWL: 82	N/A	N/A
	Gastric bypass	218		71	%EWL: 63	N/A	N/A

Mean values are reported for outcomes. BMI is reported in kg/m<sup>2</sup>. %BWL, percent of body weight lost; %EWL, percent of excess weight lost; N/A, data not available.

\*Studies including gastric bypass procedures of various limb lengths. †Percent follow-up at 5 years after surgery. ‡Approximate values read from graph.

diabetes after up to 14 years of follow-up (162). A later meta-analysis showed that 78% of patients with type 2 diabetes had normalized glucose levels after bariatric surgery (176). The prevalence of type 2 diabetes in 136 patients operated at Oslo University Hospital Aker was 34% before and 10% after a mean of 17 months after gastric bypass (47). The beneficial effect of surgery on glucose levels varies with the surgical techniques. Young patient age and short duration of diabetes is associated with the highest remission rates (176-178). Recently, the International Diabetes Federation acknowledged that bariatric surgery can be considered an appropriate treatment for obese subjects with type 2 diabetes who do not reach treatment goals with medication (179).

A substantial proportion of patients with type 2 diabetes may discontinue antidiabetic medication shortly after bariatric surgery (180). Animal studies indicate that this may in part be attributed to the rerouting of nutrients from the upper gastrointestinal tract (foregut exclusion theory) (181). Other investigators have shown that the early improvement in insulin resistance is primarily a result of caloric restriction and an increased nutrient delivery to the hindgut (hindgut delivery theory) (182;183). Increased meal stimulated release of hormones from the hindgut is observed after surgical techniques that include foregut exclusion and those that do not (184). Gastric bypass is associated with increased postprandial concentrations of gut hormones such as peptide YY (PYY) and GLP-1, primarily released from the distal bowel (185). GLP-1 exerts numerous effects on the pancreas and different peripheral tissues resulting in increased insulin sensitivity (186). Over time, weight loss in itself will have a positive effect on insulin resistance.

### **Cardiovascular risk**

Bariatric surgery is associated with amelioration of a wide range of risk factors for heart disease and predicts a substantial long-term cardiovascular risk reduction (187;188). Evaluation of changes in cardiovascular risk after bariatric surgery was reported from the Swedish Obese Subjects (SOS) study. This is a nonrandomized, matched, prospective trial including 4047 patients of whom 2010 have had bariatric surgery and 2037 serve as controls. At 2 and 10 years of follow-up, risk factors such as diabetes, hypertriglyceridemia, low levels of HDL cholesterol, and hypertension changed more favorably in the surgery group than in the control group (166). After a mean follow-up of 15 years, the number of cardiovascular

deaths was significantly lower in the surgery group (28 events versus 49 events in the control group) (189).

## **Cancer**

In the SOS study, after a mean follow-up of 11 years, a significantly lower number of first-time cancers were observed in the surgery group than in the control group. A reduced cancer incidence was observed in women, but not in men. This sex-specific difference in cancer incidence was also reported in a study from the Utah Cancer Registry. 6596 patients who had undergone gastric bypass and 9442 severely obese persons who had applied for driver's licenses were matched for age, sex, and BMI (190). After a mean follow-up of 13 years, the surgery group had a 24% lower incidence of cancer and a 46% lower cancer mortality. The reduction in cancer incidence was greatest for obesity-related types of cancer. This finding was later supported by others (191).

## **Mortality**

Three retrospective studies published between 1997 and 2004 indicated a reduced mortality after bariatric surgery by reducing the risks for a number of conditions such as cardiovascular disease and cancer (192-194). In 2007, one large retrospective study and a report from the SOS study supported these findings, although the absolute differences in mortality were relatively small between the surgery and control groups in both studies (195;196). There is a majority of women in most case series in the bariatric literature, but a later study found a survival benefit also in male patients (197). However, in an analysis of a cohort of high-risk patients (predominantly older men), bariatric surgery was not associated with decreased mortality (198).

## **Other conditions associated with obesity**

Bariatric surgery is associated with an improvement of obstructive sleep apnea syndrome (158;199) and reduced hip and knee pain in patients with osteoarthritis (200). Fertility can improve in women after surgically induced weight loss, including in patients with polycystic ovarian syndrome (201;202). Also, evidence suggests that rates of adverse maternal and neonatal pregnancy outcomes are reduced in women who have had bariatric surgery

compared with rates in nonoperated obese (203). Of concern, some case reports indicate a worsening of sperm parameters in morbidly obese men after bariatric surgery (204;205).

### **Quality of life**

Morbidly obese patients seeking bariatric surgery have reduced health-related quality of life and experience great improvements after surgery (66;206). This is reported across different procedures such as gastric bypass and duodenal switch (207;208). After jejunoileal bypass, patient satisfaction was also surprisingly good in spite of high rates of complications and readmissions (110).

### **Procedure-related morbidity and mortality**

Complications after bariatric procedures include gastrointestinal leaks and bleeding, anastomotic strictures, internal small bowel herniation, and cholelithiasis (209;210). In a prospective, multicenter study of 30-day outcomes in 4776 patients after gastric bypass (mostly performed by laparoscopy) and laparoscopic adjustable gastric banding, 4.3% of patients had a major adverse event and the mortality rate was 0.3% (18).

There is no agreement on how to define complications after bariatric surgery. Rates of complications occurring within 30 days after laparoscopic gastric bypass are reported in the range of 13% – 17% (157;211). Recent studies from high-volume Scandinavian hospitals indicate that this operation may be performed with extremely low morbidity rates (1% – 3%) (212;213). In an analysis of data from an ASMBS database containing 57918 operations, mostly performed by laparoscopy, the morbidity rate after sleeve gastrectomy was higher than after gastric banding and lower than after gastric bypass (17).

In general, laparoscopic duodenal switch case series are smaller than series of laparoscopic gastric bypass and the morbidity rates are higher. In a series of 1000 open and laparoscopic duodenal switch operations, 30-day rates of “minor” and “major” complications after the laparoscopic approach were 8% and 7%, respectively (214). In another series, the 30-day morbidity rate after laparoscopic duodenal switch was 24% in patients with a BMI  $\geq 50$  kg/m<sup>2</sup> (215), similar to the 25% morbidity rate after this operation at Oslo University Hospital Aker (138).



In a 2007 meta-analysis, 30-day mortality rates were lower after laparoscopic gastric bypass (0.16%) than after laparoscopic biliopancreatic diversion with or without duodenal switch (1.1%) (216). In a recent survey of 28616 operations from hospitals accredited by the American College of Surgeons (ACS) – Bariatric Surgery Center Network, the 30-day mortality rate after laparoscopic sleeve gastrectomy (0.11%) was positioned between laparoscopic gastric banding (0.05%) and laparoscopic gastric bypass (0.14%) (19).

Outcome after bariatric surgery is influenced by hospital and surgeon procedure volume, with lowest morbidity and mortality rates in high-volume centers (217-219). In the 2000s, studies raised concerns about high mortality rates after bariatric surgery, particularly for older patients (220). In a large gastric bypass case series published in 2002, male gender and superobesity were identified as predictors of severe complications, and patients >55 years had a threefold-higher mortality rate than younger patients (221). In a recent large series, an extreme BMI value was associated with an increased risk for 30-day major complications, whereas patient age and sex was not (18).

### **Nutritional and metabolic complications**

Low concentrations of several vitamins, such as vitamin B-6, vitamin C, 25-hydroxyvitamin D, and vitamin E are common in morbidly obese patients opting for bariatric surgery (222). Close follow-up of patients after surgery is required to prevent vitamin deficiencies (223-225). High doses of supplementation of fat-soluble vitamins have been proposed after duodenal switch (226). Deficiencies of iron and other micronutrients are common after both gastric bypass and malabsorptive surgery (129;225-230). Protein-calorie malnutrition can be severe after malabsorptive surgery, particularly in patients with a short common channel (50 cm) (129;231). In rare cases, transient hepatic impairment or death from liver failure develops after malabsorptive procedures (232;233). Patients usually respond to treatment with dietary changes or parenteral nutrition, but 1 – 5% eventually require revisional surgery with lengthening of the small bowel available for nutrient uptake (226;231). Hyperinsulinemic hypoglycemia (233), kidney stones and oxalate nephropathy (226;234;235), and visual impairment (236;237) are also known metabolic sequelae after bariatric surgery.

## **Eating behavior**

Although limited, available research indicates that laparoscopic adjustable gastric banding is associated with positive changes in eating behavior (238). However, undesirable eating patterns such as grazing (i.e. continuous eating of small amounts of food over long periods of time) are frequent (239). For gastric bypass surgery, a high ability to intentionally limit food intake (i.e. cognitive restraint) before surgery is associated with greater weight loss after the operation (240). Some studies suggest that gastric bypass is associated with improvements in undesirable eating patterns and, as compared with purely restrictive procedures, a reduced consumption of high-fat foods and an increased intake of fruits and vegetables (241-243). However, bulimic episodes, vomiting, and food aversions are not uncommon (244;245). Malabsorptive operations also seem to confer positive changes in eating behavior (246).

## **Gastrointestinal symptoms and bowel function**

After gastric bypass, early dumping is common within 15 – 30 minutes after meals containing sugar (247). Postprandial sweating and nausea has been attributed to rapid emptying of hyperosmolar foods to the jejunum, followed by a fluid shift into the gut lumen, a fall in plasma volume, and sympathetic stimulation from pressoreceptors (248). Late dumping syndrome is characterized by symptoms such as diaphoresis and impaired consciousness 1 – 3 hours after meals (233). Excessive nausea and vomiting after surgery can cause severe malnutrition and possibly neurological sequelae (249). After gastric bypass, patients can experience relief of a range of gastrointestinal symptoms in the long-term, whereas duodenal switch has been associated with diarrhea, abdominal bloating, and foul-smelling gas and stool (226;250).

## **2.2.4 Weight loss after bariatric surgery in morbidly versus superobese patients**

### **Gastric bypass**

Reports of long-term weight loss results after gastric bypass have demonstrated that a substantial proportion of superobese patients may still be morbidly obese even after peak weight loss. For example, one study found that 43% of patients with a preoperative

BMI >50 kg/m<sup>2</sup> had a BMI >35 kg/m<sup>2</sup> approximately 2 years after surgery (163). Other reports of long-term results support these findings (170).

### **Distal gastric bypass**

Sugerman and colleagues reoperated patients who had insufficient weight loss or correction of comorbid conditions after gastric bypass by performing a so-called *distal* gastric bypass, with a shorter common channel for nutrient uptake. Five of the patients had a 50 cm common channel, and all these eventually had severe protein-calorie malnutrition demanding revisional surgery and two died of hepatic failure (251). Most other published results after distal gastric bypass, but not all (252), show an increased weight loss and risk for complications related to malnutrition (253-257). Apparently, applying a very long alimentary limb in a distal gastric bypass somewhat reduces the risk for serious malnutrition. Nelson et al described a *very, very long-limb* gastric bypass in a report of 257 patients, mostly with a BMI >50 kg/m<sup>2</sup> (235). This technique comprises a common channel length of 100 cm, a biliopancreatic limb of 60 cm, and an alimentary limb of 300 to 500 cm. After an average of 4 years of follow-up, over 80% of patients had lost more than 50% of excessive weight. Patient satisfaction was high although 4% had revisional surgery for protein-calorie malnutrition.

### **Gastric bypass versus duodenal switch**

Meta-analyses have indicated that weight loss is greater following duodenal switch than gastric bypass (158;159), but few studies have directly compared these procedures. Some nonrandomized comparisons show that weight loss is greater after duodenal switch than after gastric bypass (258;259). Others have reported similar weight loss after the procedures (260).

We sought to compare surgical treatment of superobesity with gastric bypass versus duodenal switch in a randomized trial.

### 3 Aims

The aims of this thesis were to evaluate results after establishing a laparoscopic gastric bypass program for the treatment of morbid obesity and to compare outcome of gastric bypass and duodenal switch, both performed by laparoscopy, in superobese patients. This included:

- I An evaluation of perioperative outcome and learning curves for two surgeons during the introduction of laparoscopic gastric bypass at a Norwegian hospital.
- II A comparison of perioperative safety and 1-year weight loss after laparoscopic gastric bypass and laparoscopic duodenal switch in superobese patients.
- III A study of 2-year weight loss and changes in cardiovascular risk factors and quality of life after gastric bypass and duodenal switch in superobese patients.
- IV An evaluation of changes in gastrointestinal symptoms, bowel function, eating behavior, dietary intake, and psychosocial functioning 2 years after gastric bypass and duodenal switch in superobese patients.

# 4 Methods

## 4.1 Patients and study designs

### 4.1.1 Paper I

Morbidly obese patients undergoing bariatric surgery at Oslo University Hospital Aker from June 2004 until October 2007 were evaluated for inclusion in the study. A total of 292 consecutive patients undergoing laparoscopic gastric bypass were included. Patients were excluded if they had biliopancreatic diversion with duodenal switch (n=31), sleeve gastrectomy (n=20), or gastric banding (n=1); or had previously undergone bariatric surgery (n=11).

Data were retrieved retrospectively from patient charts from June 2004 to December 2005. Subsequently, data were collected prospectively on designated case forms. They were stored in a database containing perioperative and follow-up data of all bariatric patients operated at Oslo University Hospital Aker.

### 4.1.2 Papers II – IV

Patients included in a randomized trial of laparoscopic gastric bypass versus laparoscopic duodenal switch were recruited from referrals to treatment of morbid obesity at Oslo University Hospital Aker and Sahlgrenska University Hospital, Gothenburg, Sweden between March 2006 and August 2007. Participants were eligible for inclusion if they had a BMI of 50 – 60 kg/m<sup>2</sup> at referral, were aged 20 – 50 years, and had failed attempts of previous weight loss. Exclusion criteria were a history of previous bariatric or major abdominal surgery, disabling cardiopulmonary disease, cancer, long-term oral steroid treatment, and conditions associated with poor compliance (such as drug abuse or severe psychiatric illness). A signed, informed consent was retrieved from all participants. Participants were consulted, informed, and enrolled by dedicated persons at both centers.

A total of 368 patients were prescreened for inclusion (261). 68 patients fulfilled the inclusion criteria and 7 of these declined to participate. 61 patients were included and randomized.

## **Randomization**

Patients were randomly assigned to laparoscopic gastric bypass or laparoscopic duodenal switch at Sahlgrenska with the LabView software, version 7.1 (National Instruments, Austin, Texas) with stratification according to hospital, patient sex, age (<35 years or ≥35 years), and BMI (<55 kg/m<sup>2</sup> or ≥55 kg/m<sup>2</sup>) by using the minimization method. Blocking was not used. Patients and surgeons were masked to treatment allocation until 1 week before surgery.

## **Surgical interventions**

The patients consumed a low-calorie diet (1000 kcal/d) for 3 weeks before surgery. Operations were performed at both study hospitals with standardized laparoscopic techniques. Total intravenous anesthesia with target-controlled infusion was used for both procedures. Bupivacaine was injected at the trocar sites at the start of the procedure. During surgery, 500 ml dextran was infused as thrombosis prophylaxis, and single prophylactic doses of 1500 mg metronidazole and 400 mg doxycycline were administered. In both procedures, pneumoperitoneum was established by visual introduction of the first trocar 15 cm below the xiphoid. The limb lengths were measured by sequentially placing a 20 cm band adjacent to the small bowel. Mesenteric defects were not closed in either procedure.

In gastric bypass, five trocars were placed and the liver was mobilised with a retractor. The stomach was divided proximally with a gold (3.8 mm) or blue (3.5 mm) linear stapler cartridge to create a small pouch of about 25 mL. The jejunum was measured 50 cm from the ligament of Treitz and anastomosed to the pouch in an antecolic antegastric fashion with a 45 mm long blue stapler cartridge. The anastomosis was completed with running suture. The omentum was not routinely transected. To create the alimentary limb, the jejunum was measured 150 cm distally from the gastrojejunal anastomosis and anastomosed to the 50 cm biliopancreatic limb using a 45 mm long white (2.5 mm) stapler cartridge and closed with running suture. The small bowel was then transected between the 2 anastomoses with a white stapler cartridge to create a Roux-en-Y configuration with a long common channel, allowing food from the alimentary limb to be mixed with bile and pancreatic juices transported in the biliopancreatic limb. The patency and run-off of the gastrojejunostomy was evaluated by instilling diluted methylene blue in a nasogastric tube while clamping the small bowel.

In the duodenal switch, an additional 5 mm trocar was placed below the umbilicus. A sleeve gastrectomy was performed along a nasogastric tube of 30 – 32 Fr with repeated firings of 60 mm long green (4.1 mm), gold or blue stapler cartridges from the antrum to the angle of His. The duodenum was mobilized and transected 4 cm distal to the pylorus with a 60 mm blue cartridge. The small bowel was measured from the cecum to create a common channel of 100 cm and an alimentary limb of 200 cm. The procedure then involved a hand-sewn anastomosis between the duodenum and the ileum, an anastomosis between the biliopancreatic limb and the ileum with a 45 mm long white stapler cartridge and closed with a running suture, and transection of the bowel between the anastomoses. A cholecystectomy was performed in patients with symptomatic gallstone disease. Appendectomy was not performed.

### **Postoperative care**

The patients consumed a liquid diet from the first postoperative day, a semiliquid diet after 1 week, with a gradual return to normal food intake after 2 weeks. Low molecular weight heparin was administered daily according to weight from the day after the procedure until 10 days after discharge. The patients were discharged by the attending bariatric surgeon. Postoperative outpatient follow-up was at 6 weeks, 6 months, and 1 and 2 years by surgeon and dietician.

### **Nutritional supplements**

One week after surgery, all patients were prescribed daily supplements of multivitamins, 100 mg of iron sulfate, 1000 mg of calcium carbonate, and 20 µg of vitamin D3. Patients in the gastric bypass group also received injections of vitamin B12 every 3 months. Ursodeoxycholic acid (500 mg/day) was prescribed for 6 months, except in participants who had had a cholecystectomy.

After surgery, patients received relevant top-up vitamin supplementation if concentrations were below these cutoffs: thiamine, 55 nmol/L; vitamin B<sub>6</sub>, 11 nmol/L; vitamin C, 11 µmol/L; vitamin A, 0.9 µmol/L; 25-hydroxyvitamin D, 37 nmol/L; and vitamin E, 2.2 µmol/mmol (adjusted for serum total cholesterol and triglycerides) (262). Blood samples were repeated after 4 to 6 weeks. Top-up supplementation was discontinued if the vitamin concentration was within the reference interval.

## 4.2 Outcome measures

### 4.2.1 Paper I

As indicators of the surgical learning curve, the lengths of surgery and postoperative hospital stay, and 30-day rates of morbidity, reoperations, and readmissions were evaluated. The learning curve was assessed by the graphs as the point at which all indicators amenable for graphical analysis had levelled off. Previous reports have indicated that the length of the learning curve for laparoscopic gastric bypass is about 100 procedures. We aimed to compare surgical results from the early and late phases of the learning curve and chose to compare the first 40 and last 40 procedures by the surgeons individually. We also compared the first 100 with the subsequent procedures for both surgeons to evaluate the results from procedures performed prior to and following completion of the learning curve for laparoscopic gastric bypass.

### 4.2.2 Papers II – IV

The primary end point of the randomized study of laparoscopic gastric bypass versus laparoscopic duodenal switch in superobese patients was the change in BMI from baseline until 2 years after surgery. Secondary end points included changes in anthropometric measures, cardiovascular risk factors, health-related quality of life, body composition, vitamin concentrations, and adverse events (papers II and III). Paper IV presents other secondary end points, i.e. gastrointestinal symptoms, bowel function, eating behavior, dietary intake, and psychosocial functioning.

Weight was measured with patients wearing light clothing and no shoes, with 1 kg subtracted to account for clothing. Weight change was reported as reduction in BMI units, percent of excess BMI lost ( $[(\text{preoperative BMI} - \text{current BMI})/(\text{preoperative BMI} - 25)] \times 100\%$ ), total weight loss in kilograms, and percent of body weight loss. The number of participants who were classified as class III obese ( $\text{BMI} \geq 40 \text{ kg/m}^2$ ) at 2 years after surgery was also evaluated. Waist circumference was measured halfway between the caudal point of the costal arch and the iliac crest (263). Hip circumference was measured at the level of the femoral great trochanters. With patients in the supine position, sagittal abdominal diameter was measured as the distance from the back to the highest point of the abdomen during normal expiration, as a



proxy for visceral adipose tissue mass (264). Cardiovascular risk factors were evaluated by changes in fasting lipid concentrations (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides), glucose, insulin, C-reactive protein (CRP), and blood pressure. Blood pressure was measured 3 times with an appropriately sized cuff after the participant had rested for 5 minutes, and the last 2 measurements were averaged. Comorbid conditions were diagnosed on the basis of referrals and clinical assessment.

Blood samples were collected after overnight fast. Routine laboratory analyses (glucose, lipids, and CRP) were performed at the Departments of Clinical Chemistry at the two study sites. Hitachi Modular multi-analyzers (Boehringer Mannheim, Germany) were used for these analyses (Model 717 at Oslo University Hospital Aker and 800 at Sahlgrenska University Hospital). Intact parathyroid hormone was measured by chemi-luminoimmunometric assay (Diagnostic Products Corporation, Los Angeles, California) at the Hormone Laboratory, Oslo University Hospital. Insulin was measured with different immunoassays at Sahlgrenska (Insulin Elecsys, Roche Diagnostics GmbH, Mannheim, Germany) and at Oslo University Hospital Aker (Linco Research Inc, St. Charles, Missouri before March 2007 and DELFIA, PerkinElmer Life Sciences, Wallac Oy, Turku, Finland in subsequent analyses). Detailed descriptions of vitamin assays used in the study have been published elsewhere (262).

Body composition was evaluated by changes in fat mass and fat-free mass, as measured by bioelectrical impedance analysis in Norwegian participants (n=30; 2 participants exceeded the 200 kg weight capacity of the apparatus at baseline) by using the BC-418 (Tanita, Tokyo, Japan). In Swedish participants (n=30), total body potassium was estimated as a proxy for fat-free mass by measuring the amount of radioactive K-40 in a whole-body counter (Nuclear Enterprises, Edinburgh, United Kingdom) at the Department of Radiation Physics at Sahlgrenska University Hospital. The ratio of total body potassium to fat-free mass was set at 64.8 mmol/kg for men and 59.6 mmol/kg for women (265). The percent of weight lost as fat-free mass ( $[\Delta\text{fat-free mass}/\Delta\text{body weight}] \times 100\%$ ) was calculated after both body composition studies.

Health-related quality of life instruments are commonly divided into generic (i.e. not specific to age, disease, or treatment group) and condition-specific (266). Generic health-related quality of life was assessed by using validated Norwegian and Swedish versions of the Short Form-36 Health Survey (SF-36) (4-week recall, version 2.0). This self-administered

questionnaire consists of 8 domains, of which 4 reflect physical health and 4 reflect mental health. A score was calculated for each domain on a scale from 0 (worst possible health state) to 100 (best possible health state) (266).

Psychosocial function was evaluated by the Obesity-related Problems scale (OP scale). This is a condition-specific quality of life measure which consists of eight items on a 4-point response scale. It is validated for measuring the effect of obesity on psychosocial functioning and useful for evaluating effects of obesity interventions (67). The participants were asked how bothered they were by their obesity in everyday life activities (e.g. private gatherings, going to restaurants or community activities, trying on and buying clothes, and intimate relations). The responses were summed and the score was transformed to a scale from 0 to 100, where a high score indicates more psychosocial dysfunction.

Gastrointestinal symptoms were evaluated by the Gastrointestinal Symptom Rating Scale (GSRS), which is a validated measure of perceived severity of gastrointestinal symptoms (267;268). The GSRS consists of 15 items; each measured on a 7-point Likert scale where 1 represents no symptoms and 7 denotes the most severe symptoms. Mean values for 5 symptom dimensions (i.e. diarrhea, indigestion, constipation, abdominal pain, and reflux) were calculated.

The participants' bowel function was assessed with a validated questionnaire developed for patients with fecal incontinence and constipation (269), and later modified at Sahlgrenska. The participants were asked about frequency and texture of stool, sensibility for stool, discrimination between gas and stool, deferring time, involuntary leakage of gas, anal leakage of stool, use of pads, physical and social impact of bowel habits, and medication.

The Three-Factor Eating Questionnaire-R21 (TFEQ-R21) is validated for measuring eating behavior in obese persons (270). TFEQ-R21 includes three domains: uncontrolled eating (9 items, the tendency to lose control over eating when feeling hungry or when exposed to external stimuli), cognitive restraint (6 items, the conscious restriction of food intake to control body weight or body shape), and emotional eating (6 items, overeating in relation to negative mood states) (271;272). The domain scores range from 0 to 100. A high score indicates more uncontrolled, restraint, or emotional eating.

The participants recorded their ingested foods and drinks for 4 consecutive days (3 weekdays and 1 weekend day). They were encouraged to continue normal eating habits. They were also instructed to express quantities in common household measures and to provide detailed descriptions of the food items and the preparation of the food. The food records were checked for incomplete data (e.g. type of food or portion size). The total caloric intake and intakes of fat, protein, and carbohydrates were calculated using the DIET32 software (Aivo, Solna, Sweden) with a nutrient database from the Swedish National Food Composition Tables (Livsmedelsdatabas [PC-kost], Statens Livsmedelsverk 1993).

## **4.3 Statistics**

### **4.3.1 Sample size calculation**

In the randomized trial, the sample size was based on changes in the BMI from baseline until 2 years after surgery (primary endpoint). In a review of superobese patients treated at Sahlgrenska, the mean (standard deviation [SD]) reductions in BMI were 18.0 (6.7) kg/m<sup>2</sup> after gastric bypass (n=19) and 24.9 (5.0) kg/m<sup>2</sup> after duodenal switch (n=13) after mean follow-ups of 34 and 31 months, respectively. Thus, 26 participants would give 80% power to detect a significant difference between the groups ( $P<0.050$ ). A total of 60 participants were included to strengthen analysis of secondary outcome. Sample size was calculated in SamplePower 2.0 (SPSS, Chicago, Illinois).

### **4.3.2 Statistical analyses**

Proportions were presented as numbers or numbers (%). Continuous data were presented as mean (SD) or median (range).

Proportions between groups were compared with the chi-square test, the Fisher's exact test or the Suissa–Shuster exact unconditional test. In paper IV, the bowel function questionnaire included outcomes with four ordered categories. After assigning the categories the scores (1, 2, 3, 4), outcomes were compared between the two treatment groups using the exact Wilcoxon-Mann-Whitney test.

In paper I, the association between two continuous variables was estimated with Spearman correlation. To graph the curve for the estimated odds ratio for complication related to patient

BMI, a logistic regression model was used to estimate the odds ratio for complication with a 95% confidence interval, adjusted for age, gender, number of procedures, length of surgery, and surgeon. The odds ratio for complication related to patient age was adjusted for BMI, gender, number of procedures, length of surgery, and surgeon. To graph the probability curves of perioperative complications, the operation dates were sorted in increasing order for each surgeon. The increasing orders were saved in a new variable called “number of procedures”. The probability of complications as a function of surgeon experience was estimated by fitting regression spline curves using the R software function “smooth.spline”, which fits piecewise cubic polynomials to the data.

In papers I and II, a Student’s *t* test or a Mann-Whitney *U* test (if a normal distribution could not be assumed after logarithmic transformation) was used to compare continuous variables. In papers III and IV, linear mixed models were fitted to all continuous outcome variables to account for the repeated measures by patient. Competing models were compared by using the Akaike information criterion and the Bayesian information criterion. Time was modeled by using a piecewise linear spline with a knot at 12 months. Individual participant time points, measured as the number of weeks since inclusion, were used. Two variables presented in paper III (glucose and insulin) had a knot at 6 months instead of 12 months, and 2 variables (systolic and diastolic blood pressures) were modeled with only 1 slope.

In paper III, time and time-by-treatment interaction were fixed effects in all models. All models included a random intercept. For some variables, models also included fixed effects for treatment and site and random slopes by patient. In paper IV, all models included fixed effects for treatment, time, and time  $\times$  treatment interaction. For some variables, models also included fixed effects for site. All models included a random intercept and random effects for time, except the TFEQ-R21 dimension emotional eating, which only included a random intercept. An unstructured covariance matrix was used in all models, except for the GSRS dimension diarrhea, which had an independent covariance matrix structure.

Statistical analyses were performed with SPSS version 15.0 for Windows (SPSS, Chicago, Illinois), Stata version 11.1 (StataCorp, College Station, Texas), and StatXact 9 (Cytel, Cambridge, Massachusetts). Graphs were created with the R software, version 2.6.0 for Windows (R foundation for Statistical Computing, Vienna, Austria) and SigmaPlot 10.0 (Systat Software Inc, San Jose, California). A 2-sided *P* value <0.05 was considered statistically significant.

## 4.4 Ethics

The patient database used in paper I was approved and licensed by The Norwegian Data Protection Agency. A signed, informed consent was obtained from included patients.

The randomized trial was approved by the regional committees for medical and health research ethics in South-Eastern Norway and in Gothenburg, Sweden. All patients were carefully informed about the potential benefits and common complications following laparoscopic gastric bypass and laparoscopic duodenal switch. A signed, informed consent was obtained from all included patients. The trial was registered at ClinicalTrials.gov (registration number: NCT00327912) and supported by research grants from the South-Eastern Norway Regional Health Authority and Sahlgrenska University Hospital. The funding sources had no role in the design of the study; collection, analysis, and interpretation of the data; or drafting of the manuscripts.

# 5 Results

## 5.1 Paper I

### **Establishing laparoscopic Roux-en-Y gastric bypass: perioperative outcome and characteristics of the learning curve**

This study presents the 30-day outcome after laparoscopic gastric bypass and the learning curves for two surgeons while introducing laparoscopic bariatric surgery at Oslo University Hospital Aker. The morbidity rate in the series of 292 primary procedures was 15%, and there was no mortality. All primary procedures, and many reoperations, were completed by laparoscopy. A high patient age, but not a high BMI, was associated with an increased risk for complications. Only the lengths of surgery and hospital stay were suitable indicators of a learning curve, which comprised about 100 cases per surgeon.

## 5.2 Paper II

### **Randomized clinical trial of laparoscopic gastric bypass versus laparoscopic duodenal switch for superobesity**

In this report from a two-center randomized clinical trial, 60 superobese patients were randomized to either laparoscopic gastric bypass or duodenal switch, and followed for 1 year. The baseline patient characteristics were similar in the two groups. The changes in BMI and percent of excess BMI lost, and the numbers of complications and readmissions, were compared between groups. Duodenal switch was associated with significantly longer operating time and length of hospital stay. Early (30-day) complications occurred in 4 patients after gastric bypass and 7 after duodenal switch, and 4 and 9 patients, respectively, had late complications (no significant between-group differences). The mean BMI at 1 year decreased significantly more after duodenal switch (55.2 to 32.5 kg/m<sup>2</sup>) than after gastric bypass (54.8 to 38.5 kg/m<sup>2</sup>).

## 5.3 Paper III

### **Weight loss, cardiovascular risk factors, and quality of life after gastric bypass and duodenal switch: a randomized trial**

This paper reports 2-year weight loss and changes in cardiovascular risk factors and quality of life after gastric bypass and duodenal switch (the same patients as presented in paper II). The mean reduction in BMI (primary outcome) was significantly greater after duodenal switch than after gastric bypass (24.8 kg/m<sup>2</sup> versus 17.3 kg/m<sup>2</sup>). Duodenal switch was also associated with significantly greater reductions in total and LDL cholesterol concentrations, anthropometric measures, fat mass, and fat-free mass. The reductions in blood pressure and mean concentrations of glucose, insulin, and C-reactive protein were not significantly different between groups. Concentrations of vitamin A and 25-hydroxyvitamin D were reduced after duodenal switch, but not after gastric bypass. SF-36 scores improved in both groups, with greater improvement in 1 of 8 domains after gastric bypass. From surgery until 2 years, a significantly higher proportion of patients had adverse events after duodenal switch than after gastric bypass (62% versus 32%).

## 5.4 Paper IV

### **Gastrointestinal function and eating behavior after gastric bypass and duodenal switch**

In this report, 2-year changes in gastrointestinal symptoms, bowel function, eating behavior, dietary intake, and psychosocial functioning after gastric bypass and duodenal switch were evaluated. The same patients as described in papers II and III completed the GSRS, a bowel function questionnaire, the TFEQ-R21, a 4-day food record, and the OP scale. Compared with gastric bypass, duodenal switch patients had significantly more symptoms of diarrhea, a higher number of defecations at daytime, and more anal leakage of stool after surgery. Scores of uncontrolled and emotional eating were significantly and similarly reduced after both operations. The mean total caloric intake and intakes of fat and carbohydrates were significantly reduced in both groups. Protein intake was significantly reduced only after gastric bypass. Psychosocial function was significantly improved after both operations.

# 6 Discussion

## 6.1 Methodological considerations

### 6.1.1 Methods used in the randomized trial (papers II – IV)

#### Age and BMI criteria for inclusion

In the randomized trial, we included patients aged 20 – 50 years. Consequently, study participants were somewhat younger than generally reported in the bariatric literature (158). Also, inclusion was limited to patients with a BMI in the range of 50 – 60 kg/m<sup>2</sup>. The rationale for this was that a substantial proportion of gastric bypass patients with a preoperative BMI >50 kg/m<sup>2</sup> remain morbidly obese after peak weight loss (170). For patients with such BMIs, surgical treatments which are perceived to induce greater weight loss are sometimes preferred. However, for patients with a preoperative BMI >60 kg/m<sup>2</sup>, duodenal switch may be planned in two stages to reduce morbidity and mortality (143). For study purposes, we sought to compare gastric bypass with a one-stage duodenal switch. As a two-stage duodenal switch algorithm for patients with a BMI >60 kg/m<sup>2</sup> is advocated (134), we chose to only include participants with BMIs in the range of 50 – 60 kg/m<sup>2</sup>.

#### Two study centers

Single-center randomized controlled trials report substantially larger intervention effects than multicenter trials. Multicenter trials (i.e.  $\geq 2$  different study centers) possibly estimate true intervention effects more precisely (273). This may be explained by several factors, such as reporting bias (i.e. reports from single-center studies are harder to publish), as shown for drug trials (274). Some outcomes in our trial were measured at the two study sites with different equipment or techniques (e.g. blood pressure). However, as the study groups were well balanced with regard to baseline patient characteristics, and both operations were performed at both study sites, we assume that bias because of such differences in measurements is relatively small. We analyzed 2-year changes in all outcome variables by study site and surgeons (not published). The changes in outcomes differed significantly in 2 variables (hip circumference and blood pressure) between study centers. The mean values for both these



variables also differed between sites at baseline, which may possibly explain the differences in reductions between hospitals, i.e. a regression to the mean.

## **Surgical interventions**

At the upstart of the trial, 123 laparoscopic gastric bypass and 15 laparoscopic duodenal switch procedures had been performed at Oslo University Hospital Aker and 435 and 18 procedures, respectively, at Sahlgrenska. Consequently, surgeons at both hospitals were relatively less experienced in the surgical aspects of duodenal switch. We speculate that the number of laparoscopic duodenal switch operations needed to reach a plateau in operation time and a stable low frequency of complications is about the same as for laparoscopic gastric bypass. As indicated in Paper I, using operation time and hospital length of stay as indicators, a learning curve for laparoscopic duodenal switch might comprise about 100 cases. This implies a potential for a lower morbidity rate after duodenal switch than presented in our randomized trial. The mean operation time of laparoscopic duodenal switch of 206 minutes in our study is close to figures reported by others (275). We have observed a slight reduction in the length of duodenal switch surgery after the trial completed (138). The multidisciplinary team had relatively less experience with the follow-up of duodenal switch patients. These differences in experience with the two procedures should be taken into account when interpreting our findings.

The findings of the study may only be generalizable according to the specific surgical techniques described. There is no general agreement on standardization of these techniques. Worldwide, a gastric bypass with a small upper gastric pouch and a 150 cm alimentary limb length is widely performed. Applying a 150 cm versus a 75 cm alimentary limb might increase weight loss in superobese patients (276;277), but the effect of longer limb lengths may not be evident after >10 years of follow-up (168). A larger variation of surgical technique exists for the duodenal switch which makes direct comparison of results difficult. Some surgeons use bougie sizes up to 60 Fr for the sleeve gastrectomy (143). Although we constructed the sleeve gastrectomy with a smaller sized tube, the staple lines were not applied with tight proximity to the tube, but rather positioned at the border of the lesser curvature veins. Further variations of technique include a shorter alimentary limb length, sometimes calculated as a percentage of total small bowel length (278), and shorter common channel lengths (e.g. 50 or 75 cm) (143;226;275).

We did not perform a simultaneous cholecystectomy in any of the procedures. Ursodeoxycholic acid prescribed for 6 months after bariatric surgery is effective in reducing gallstone formation and routine cholecystectomy during laparoscopic duodenal switch is probably not indicated (279;280).

### **Power analysis**

As described earlier, sample size was based on expected changes in the primary endpoint (BMI) at 2 years after surgery. Results that are not related to the primary endpoint should therefore be interpreted cautiously. True differences in secondary outcomes might not have been identified because of type II statistical errors.

### **Adverse events**

Bariatric surgery is associated with a wide range of surgical, nutritional, and metabolic complications. We aimed to register all adverse events by asking patients open-ended questions about potential side effects, readmissions, and reoperations at every post-surgical visit, as previously suggested (281). This process included retrieving medical notes from other hospitals. We did not assess adverse events with a standardized instrument. Systems for classifying surgical complications have been proposed, e.g. the Clavien grading system (282), but the experience with and validation of such scoring systems in laparoscopic bariatric surgery is limited.

### **Ethical aspects of randomized studies in bariatric surgery**

Designing randomized trials in bariatric surgery might be considered ethically challenging. Comparing medical therapy to bariatric surgery, for example, can raise concern about lack of equipoise between treatments (283;284). Further, as patients become familiar with specific risks and benefits of surgical procedures, it might be difficult to agree to randomization between two different bariatric procedures.

In 2006, when the first patients were included in our trial, the surgeons involved in the study considered both gastric bypass and duodenal switch as acceptable therapeutic options for superobese patients. Preoperatively, patients were thoroughly informed about potential benefits and side effects of both procedures. Out of a total of 68 patients who received

information about the study, only 7 patients eventually declined to participate and 1 patient withdrew after randomization. Of interest, in a recently published Swedish randomized trial of open gastric bypass versus open duodenal switch, patients increasingly declined to participate, resulting in premature closure of inclusion (285). This might indicate that Scandinavian patients seeking treatment for morbid obesity have become more conscious about the differences in anti-obesity procedures over the last years, coinciding with a large increase in procedures performed and broad media coverage of such surgery.

## **6.2 Main findings**

### **6.2.1 Establishing laparoscopic gastric bypass**

We studied results after introducing a laparoscopic gastric bypass program in a hospital with no previous institutional experience in bariatric surgery. The surgeons who performed these primary operations were experienced in laparoscopy, but had no formal training in bariatric surgery. Baseline patient characteristics were comparable to most case series (158). We, and others (286;287), have found that a high patient age, but not a high BMI, is associated with an increased risk for complications. Thus, BMI might not be a good stratification criterion for gastric bypass surgery. In a later report from the Longitudinal Assessment of Bariatric Surgery (LABS) consortium, including 4776 primary bariatric operations, extreme BMI values, but not age or sex, were associated with an increased risk for complications (18). Other studies have suggested that male gender is a predictor of morbidity after gastric bypass (221) and that high age is a predictor of mortality (221;288;289).

There was no mortality in our series of almost 300 operations and the morbidity rate was comparable to published series at that time (211). However, it is difficult to evaluate outcome across bariatric surgery studies. For example, in large database registries administered by the ASMBS and the ACS, the classifications of adverse events and complications differ (17;19). In order to monitor the quality of bariatric surgery outcome in Norway, there is a need for a national bariatric surgery registry and a standardized collection of data, both in terms of which data to collect, and by whom and how data are collected.

## **What is a learning curve?**

There is no clear definition of a learning curve in surgery. Theoretically, the learning curve describes operative outcomes of a surgeon until a plateau is reached and further improvements are not detectable (290). Aspects such as operating time, risks for minor or major complications, rates of conversion to open surgery, and postoperative length of hospital stay are commonly evaluated (154;291). Some authors dismiss the concept of a learning curve in bariatric surgery all together, pointing out that surgeons are obliged to participate in adequate training to ensure that all patients are offered best possible care (292).

Our study demonstrated that lengths of surgery and hospital stay were indicators of a learning curve for laparoscopic gastric bypass, which comprised 100 cases. In a recent review, the learning curve was described to include 50 – 100 cases (293). Factors that may reduce the length of the learning curve include fellowship or training programs, a stepwise acquisition of surgical skills, and high surgical case volumes (212;217;293-296). At present, there is little evidence that introducing robotically assisted bariatric surgery confers advantages in terms of operation times or morbidity, although the length of the learning curve might be shorter (297;298).

Evidence suggests that patient outcome is improved in high-volume surgical centers (299). At Oslo University Hospital Aker today, the procedure volume of 300 cases per year may be regarded as high as evaluated by US standards (218). This allows new surgeons to be introduced to bariatric surgery by a stepwise learning of the procedures to ensure a low morbidity rate, as described by others (296).

### **6.2.2 Weight loss after gastric bypass and duodenal switch**

The main finding in papers II – IV is that laparoscopic duodenal switch induces greater weight loss than laparoscopic gastric bypass in superobese patients. Two years after surgery, 1 in 4 patients in the gastric bypass group had a BMI  $\geq 40$  kg/m<sup>2</sup>.

Some studies published within the last decade have suggested a greater weight loss effect of duodenal switch, but all have been limited by a retrospective design and a possible bias in treatment allocation (258;259). Recently, data from another randomized trial evaluating the two operations were published. In this study, procedures were performed by open surgery with some differences in surgical techniques compared to those described in our trial (285).

From a mean baseline BMI of 55 kg/m<sup>2</sup> in each group, reductions in BMIs in the groups after a mean follow-up of 4 years were very similar to our findings at 2 years.

Limited data exist on weight loss beyond 10 years after gastric bypass and duodenal switch. Available reports are often limited by low rates of follow-up. The patients in the gastric bypass group in our trial, with a mean BMI of 38 kg/m<sup>2</sup> at 2 years, may expect some regain of weight 2 to 10 years after surgery (166;168). In contrast, duodenal switch patients seem to experience sustained weight loss over time (300;301), in line with results after biliopancreatic diversion (302). Consequently, a relatively large proportion of superobese patients subjected to gastric bypass may still be morbidly obese after extended follow-up. Also, the difference in weight loss outcome might increase between the operations in favor of duodenal switch.

### **6.2.3 Cardiovascular risk factors**

Changes in risk factors for cardiovascular disease have been shown to be linked to the degree of weight loss after gastric bypass (303). Despite a large difference in weight reduction between the gastric bypass and duodenal switch groups in our trial, the reductions in outcomes such as blood pressure and concentrations of glucose, insulin, and CRP were similar. Our finding of a greater reduction in LDL cholesterol concentration after duodenal switch could mean that patients having this procedure have a greater reduction in long-term cardiovascular risk. In a meta-analysis of cholesterol-lowering trials, a 1 mmol/L reduction in LDL cholesterol concentration translated into a 12% reduction in total mortality and a 19% reduction in coronary mortality over 5 years (304).

Few participants in our trial had diabetes, possibly because of a relatively young study population. Although we found similar reductions in concentrations of glucose and insulin, other investigators have reported greater reductions in levels of glucose and HbA1c, and greater resolution rates of diabetes, after duodenal switch (285;305).

The literature contains several reports of high remission rates of hypertension and diabetes shortly after bariatric surgery (158;176;306). In three randomized trials, bariatric surgery was superior to medical treatment alone in controlling type 2 diabetes (178;307;308). However, hypertension and diabetes are progressive diseases that often require more intense treatment over time (309-311). The remission rate of diabetes in the SOS study was 72% after 2 years, but only 36% at 10 years based on a fasting plasma glucose <7.0 mmol/L and no antidiabetic

medication (166). The American Diabetes Association has recently published criteria for complete remission of diabetes, defined as a return to normal HbA1c levels and fasting glucose <5.6 mmol/L of at least 1 year's duration in the absence of medication (312). According to these criteria, remission rates of diabetes after bariatric surgery are lower than previously reported (313). This exemplifies that clinicians and patients must acknowledge that amelioration of conditions associated with increased cardiovascular risk might not persist after weight loss surgery and that lifelong follow-up is important to ensure adequate metabolic control.

At present, available data indicate that bariatric surgery is associated with clinically important long-term improvements in cardiovascular risk and metabolic disturbances (166;187;314;315). There is also evidence, albeit limited, of a survival benefit after bariatric surgery (195;196). However, the absolute reductions in mortality rates are relatively small. After 11 years of follow-up in the SOS study, the absolute difference in mortality was 1.3 percentage points between the surgically and nonsurgically treated groups (mortality rates of 5.0% versus 6.3%), yielding a number needed to treat of 76 patients for 1 patient to have a survival benefit (316). To investigate whether there is a difference in long-term mortality after gastric bypass and duodenal switch requires studies with larger patient groups and extended follow-up.

#### **6.2.4 Nutritional aspects and eating behavior**

Gastric bypass patients had stable or increased concentrations of vitamins after surgery. Duodenal switch was associated with a greater risk for deficiencies of vitamin A and 25-hydroxyvitamin D. Serious nutritional complications, e.g. protein-calorie malnutrition and night blindness, only occurred after duodenal switch. These results suggest that patients who undergo gastric bypass and duodenal switch probably require different vitamin supplementation regimens after surgery. Insufficiencies of fat-soluble vitamins after duodenal switch can be treated with high-dose supplementation (317). Dietary adjustment or hospitalization for parenteral nutrition is usually sufficient for treating malnutrition (226).

The results from our trial also indicate that patients should be followed more closely after duodenal switch to detect nutritional abnormalities. Compliance with outpatient follow-up and vitamin supplementation is particularly important after duodenal switch. Also, because of the possible risk for pregnancy-related nutritional deficiencies and adverse neonatal outcomes

after duodenal switch, this procedure should probably be used with caution in women of childbearing age (203;318).

Both groups had reductions in the intakes of fat and carbohydrates, but protein intake was reduced only after gastric bypass. The greater protein intake after duodenal switch suggests that these patients adhered to the recommended high-protein diet after surgery (>90 g/day) (319). Although our results showed that duodenal switch patients lost a mean of 5 kg more fat-free mass than did gastric bypass patients, the percentage of weight lost as fat-free mass did not differ between groups, indicating that duodenal switch patients did not lose disproportionately more fat-free mass than gastric bypass patients.

Our study also indicates that both gastric bypass and duodenal switch confer positive changes in eating behavior, with improved scores of uncontrolled and emotional eating. These findings are in line with those of others, which also demonstrate a reduced meal size and eating rate, and increased meal frequency after gastric bypass (241;320). However, some patients experience substantial weight regain after bariatric surgery. Strategies such as self-monitoring of food intake and increased physical activity are probably important for improved long-term outcome (321).

### **6.2.5 Gastrointestinal symptoms**

The rationale for developing the duodenal switch was to reduce the frequency of complications of the biliopancreatic diversion, such as marginal ulceration and dumping syndrome, by leaving in place the antrum, pylorus, a small segment of duodenum, and the lesser curvature of the stomach (130;275;322). Some patients in the duodenal switch group in our study reported vomiting, possibly because of a tight sleeve gastrectomy. However, our study did not indicate that reflux symptoms were aggravated after duodenal switch. Himpens et al have previously shown that a substantial proportion of patients reported de novo gastroesophageal reflux symptoms more than 6 years after stand-alone sleeve gastrectomy and after duodenal switch (323). Whether there is a difference in reflux symptoms after sleeve gastrectomy versus duodenal switch is not known. There is some evidence to suggest a beneficial effect of adding a hiatal hernia repair to sleeve gastrectomy in patients with gastroesophageal reflux disease (324;325).

Reflux symptoms improved after gastric bypass in our study, as also shown by others (326),

and this procedure may be used as a revisional procedure in sleeve gastrectomy patients with severe reflux symptoms (327). After duodenal switch, revisional surgery is most commonly performed to correct malnutrition, but also because of gastrointestinal side effects (226;231).

The effects of bariatric surgery on bowel habits are not clearly defined (328). After duodenal switch, several studies have reported an increased frequency of bowel movements in line with our results (229;278). Diarrhea after bariatric surgery is a risk factor for fecal incontinence (329), and half of duodenal switch patients in our study had anal leakage of stool 2 years after surgery. We suggest that duodenal switch should probably not be offered to patients suffering from moderate to severe irritable bowel-like symptoms, diarrhea, or fecal incontinence.

### **6.2.6 Quality of life**

We found significant and broadly similar improvements in generic health-related quality of life in the study groups. In one domain of the SF-36, bodily pain, improvement was greater in the duodenal switch group. Although the validity of this specific domain is probably acceptable, recent research suggests that physical and mental summary scales, which were not calculated in our study, might be preferred to the subscales (330). In other studies of different bariatric techniques, patients have reported low SF-36 scores before surgery and large improvements within few years after surgery (207;331-333). We found large and similar improvements in disease-specific quality of life as measured by the OP scale. In the SOS study, weight regain was associated with gradual deterioration of health-related quality of life (206). If weight loss is less sustained after gastric bypass than after duodenal switch in the long-term, the impact of the operations on quality of life aspects may also differ.

We did not find any evidence of a negative effect of changes in bowel habits on health-related quality of life or psychosocial functioning. However, whether potentially greater improvements in quality of life and psychosocial functioning after duodenal switch were obscured by negative effects of changes in bowel function is unknown.

## **6.3 Who should have bariatric surgery?**

There is no consensus on what constitutes a successful result after bariatric surgery. The literature contains a plethora of definitions. Results are often evaluated according to weight changes. In 1982, after analyzing outcome after 29 gastric bypass operations, Reinhold



defined an excellent result as having a final weight within 25% of ideal weight (334). Other definitions of success include a final BMI  $<35 \text{ kg/m}^2$  for morbidly obese patients and  $<40 \text{ kg/m}^2$  for superobese patients. A failed result may be defined as failure to achieve a certain percentage of weight loss or loss of excessive weight (335;336). The Bariatric Analysis and Reporting Outcome System (BAROS) incorporates changes in obesity-related comorbidities, complications or reoperations, and a quality of life questionnaire in the evaluation of results after surgery (337).

Without a clear concept of successful and failed therapeutic results after bariatric surgery, the indications for bariatric surgery are also not clear-cut. In both the United States and in Europe, the associations for bariatric surgeons have recently incorporated the term “metabolic” in the names of the organizations, indicating a shift of therapeutic focus from weight loss per se to metabolic normalization. Recently proposed obesity staging tools (e.g. the Edmonton Obesity Staging System and the King’s Obesity Staging Criteria) may help clinicians in selecting patients for surgery according to the severity of obesity-related disease (338;339).

The criteria for bariatric surgery as suggested by the NIH in 1991 should be updated to include available knowledge about the specific effects of different bariatric procedures.

## **6.4 Clinical implications**

The studies included in this thesis show that weight loss was greater after laparoscopic duodenal switch than after gastric bypass in superobese patients. Our findings suggest that a relatively large proportion of superobese patients submitted to gastric bypass can still expect to be classified as morbidly obese after such surgery.

Duodenal switch is a technically more challenging operation than gastric bypass. This is reflected by a longer operation time and a consistently higher morbidity rate reported in the literature. In our study, duodenal switch was associated with greater reductions in some fat-soluble vitamins, more gastrointestinal side effects, and more adverse events than gastric bypass. Both operations were associated with substantial improvements in cardiovascular risk factors, improved quality of life, and reduced uncontrolled and emotional eating.

The potential benefits of duodenal switch surgery with regard to weight loss must be balanced

against the higher risk for complications. Until a clear benefit of duodenal switch with regard to improved long-term metabolic control or lower mortality has been demonstrated, gastric bypass remains a safe surgical option for superobese patients.

In our opinion, duodenal switch may be offered to carefully selected superobese patients who are presumably adherent to follow-up. Duodenal switch should only be performed in specialist centers with support of a multidisciplinary team which is familiar with the procedure and procedure-specific complications. Currently, laparoscopic duodenal switch is performed as a two step procedure at Oslo University Hospital Aker. The aim of this approach is partly to ensure that patients are compliant with follow-up after sleeve gastrectomy before the malabsorptive component of the procedure (the duodenal switch) is introduced.

We also suggest that gastric bypass surgery should be limited to high-volume centers in Norway. Results included in this thesis have shown that the morbidity rate during the introduction of laparoscopic gastric bypass at Oslo University Hospital Aker was acceptable, but also that the procedure may result in potentially serious complications and has a long surgical learning curve. Our results support the existing literature suggesting that surgeons embarking on a career in laparoscopic bariatric surgery need extensive mentoring to acquire surgical skills.

## **6.5 Topics for further research**

Further follow-up of the randomized trial is warranted to elucidate long-term weight loss, metabolic control, and complications in the study groups. As mentioned earlier, gastric bypass patients often experience weight regain from a nadir at 1 to 2 years after surgery, and weight loss results may increasingly differ between gastric bypass and duodenal switch after longer follow-up.

Our study has shown that duodenal switch is a powerful tool for inducing weight loss. The data from our trial combined with other studies indicate that the potential benefit of an increased weight loss might be offset by a higher risk for complications and undesirable gastrointestinal side effects. Future studies should explore specific long-term effects of gastric bypass and duodenal switch, such as effects on vitamin concentrations and bone mineralization. Further, data on long-term patient satisfaction after the two surgical procedures are scarce.

We have initiated a new randomized trial in the surgical treatment of superobesity (ClinicalTrials.gov; registration number: NCT00821197). As an extension of the present trial, the idea behind this study is to compare potential benefits of a modified gastric bypass technique, i.e. the very, very long-limb gastric bypass (235), versus a standard long-limb gastric bypass in superobese patients. The aim is to achieve greater weight loss than standard gastric bypass in this group of patients, with a maintained low risk for surgical and nutritional complications.

# 7 Conclusions

I Laparoscopic gastric bypass was introduced at Oslo University Hospital Aker with a morbidity rate comparable to internationally published results. Lengths of surgery and hospital stay were indicators of a learning curve for surgeons, which comprised about 100 cases.

In the treatment of superobese patients:

II Duodenal switch induced a greater weight loss than gastric bypass within 2 years after surgery.

III Changes in other cardiovascular risk factors were similar after gastric bypass and duodenal switch, except for greater improvements in mean concentrations of blood lipids after duodenal switch.

IV Laparoscopic gastric bypass and laparoscopic duodenal switch were performed with comparable perioperative safety.

V Duodenal switch was associated with more adverse events at 2 years, more gastrointestinal side effects, and greater reductions in mean concentrations of fat-soluble vitamins.

VI Both gastric bypass and duodenal switch were associated with a more normalized eating pattern and improvements in generic health-related quality of life and psychosocial functioning.

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## 9 Papers I – IV

















