Type 2 diabetes in morbidly obese subjects

Diagnosis, characteristics and effects of surgical and medical weight loss

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Tønsberg, February 2011

Dag Hofsø

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	The American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AGT	Abnormal Glucose Tolerance
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AUC	Area Under the Curve
BMI	Body Mass Index
CI	Confidence Interval
CV	Coefficient of Variation
DI	Disposition Index
HC	Hip Circumference
HOMA B	Homeostasis Model Assessment of β cell function
HOMA S	Homeostasis Model Assessment of insulin Sensitivity
HUNT	HelseUndersøkelsen i Nord-Trøndelag (The Nord-Trøndelag Health Study)
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
MOBIL	Morbid Obesity treatment, Bariatric Surgery versus Intensive Lifestyle Intervention
NC	Neck Circumference
NHANES	National Health and Nutrition Examination Survey
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PI/I	Proinsulin-to-Insulin
ROC	Receiver Operating Characteristics
SD	Standard Deviation
SOS	Swedish Obese Subjects
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
WC	Waist Circumference
WHO	The World Health Organisation
WHR	Waist-to-Hip Ratio

1. List of papers

Paper I

Fasting Plasma Glucose in the Screening for Type 2 Diabetes in Morbidly Obese Subjects

Dag Hofsø, Trond Jenssen, Helle Hager, Jo Røislien and Jøran Hjelmesæth

Obesity Surgery 2010; 20: 302-307

Paper II

Anthropometric characteristics and type 2 diabetes in extremely obese Caucasian subjects: a cross-sectional study

Dag Hofsø, Trond Jenssen, Jens Bollerslev, Jo Røislien, Helle Hager and Jøran Hjelmesæth

Diabetes Research & Clinical Practice 2009; 86: e9-e11

Paper III

Obesity-related cardiovascular risk factors after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention

Dag Hofsø, Njord Nordstrand, Line Kristin Johnson, Tor-Ivar Karlsen, Helle Hager, Trond Jenssen, Jens Bollerslev, Kristin Godang, Rune Sandbu, Jo Røislien and Jøran Hjelmesæth

European Journal Endocrinology 2010; 163:735–745

Paper IV

Beta cell function after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention

Dag Hofsø, Trond Jenssen, Jens Bollerslev, Thor Ueland, Kristin Godang, Michael Stumvoll, Rune Sandbu, Jo Røislien and Jøran Hjelmesæth

European Journal Endocrinology, e-pub ahead of print November 2010

2. Introduction

To say that obesity is caused by merely consuming too many calories is like saying that the only cause of the American Revolution was the Boston Tea Party.

Adelle Davis (1904 - 1974), American author and a pioneer in the field of nutrition

With this statement Adelle Davis highlighted obesity's complex chain of causation. Equally complex are the consequences of obesity, of which one, type 2 diabetes, is the focus of this thesis. Firstly, the effectiveness of fasting glucose in the screening for type 2 diabetes is addressed; secondly, the associations between several anthropometric characteristics and type 2 diabetes are explored; and finally, the effects of gastric bypass surgery and intensive lifestyle intervention on obesity-related cardiovascular risk factors and beta cell function are compared. The participants of the studies included in this thesis were either morbidly [body mass index (BMI) $\geq$ 40 or $\geq$ 35 kg/m^2 with a weight-related comorbidity] or extremely (BMI $\geq$ 40 kg/m^2) obese, and were all recruited from the Morbid Obesity Centre at Vestfold Hospital Trust in Tønsberg. The first study used receiver operating characteristics (ROC) curve analyses to examine the diagnostic accuracy of fasting glucose to predict type 2 diabetes in 1 253 morbidly obese patients. Although obesity is known to influence the sensitivity and specificity of fasting glucose for the detection of type 2 diabetes, this had not been previously examined in morbidly obese subjects. The second study in this thesis had a cross-sectional design and addressed the association between measures of central and general obesity and type 2 diabetes in extremely obese patients (n = 1 003). The third and fourth studies used data from the one-year non-randomised clinical MOBIL (Morbid Obesity treatment, Bariatric surgery versus Intensive Lifestyle intervention) study. In this study 80 patients were treated with Roux-en-Y gastric bypass surgery and 66 patients received intensive lifestyle intervention at a rehabilitation centre. The third study addressed changes in

type 2 diabetes and other obesity-related cardiovascular risk factors, whereas the fourth study explored changes in beta cell function estimated by indices including glucose, insulin and proinsulin obtained during an oral glucose tolerance test (OGTT). Although changes in metabolic parameters after both bariatric surgery and lifestyle interventions programmes have been reported previously, few have compared such treatments in head-to-head studies.

2.1. Obesity

Throughout most of human history, securing an adequate energy intake to meet daily requirements has been a major nutritional problem. However, today, along with rising standards of living, obesity, the result of over-nutrition, has become a major threat to the health of populations in countries all over the world (1). In fact, "globesity" has become more of a problem than under-nutrition and infectious diseases and, paradoxically, co-exists with problems related to under-nutrition in many developing countries (1).

2.1.1. Definition of obesity

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may impair health (1). The degree of obesity is most commonly classified according to the BMI [defined as the weight divided by the square of the height (kg/m^2)] (Table 1). In addition, other anthropometric measures, and especially measures of abdominal obesity, have been used to identify subjects at risk of obesity related metabolic conditions. Due to different patterns of fat accumulation in men and women sex-specific cut-off values exist. In Caucasians, waist-to-hip ratio (WHR) > 1.0 in men and > 0.85 in women indicates abdominal fat accumulation (2). Furthermore, cut-off point for waist circumference (WC), which may provide a more practical correlate of abdominal fat distribution than WHR, has been suggested (Table 2).

Table 1. The World Health Organisation`s (WHO) classification of obesity (1).

	BMI (kg/m^2)	**Risk of comorbidities**
Underweight	< 18.5	Low
Normal	18.5 – 24.9	Average
Overweight	≥ 25.0	
Preobese	25.0 – 29.9	Increased
Obese class I	30.0 – 34.9	Moderate
Obese class II	35.0 – 39.9	Severe
Obese class III*	≥ 40.0	Very severe

*Extreme obesity

Table 2. Sex-specific waist circumference and risk of metabolic complications associated with obesity in Caucasians (3).

	Waist circumference (cm)	
Risk of metabolic complications	**Men**	**Women**
Increased	≥ 94	≥ 80
Substantially increased	≥ 102	≥ 88

2.1.2. Obesity trends

Estimates indicate that more than 300 million people are obese worldwide (4). Data from the National Health and Nutrition Examination Survey (NHANES) show that the prevalence of obesity in US adults has more than doubled from 15 % in the late seventies up to 31 % in the year 2000 (5). Results from large telephone surveys in the US show that from 1986 to 2005 the increase in self-reported obesity has been greatest amongst those with the severest degree of obesity (6). During this period the prevalence of BMI ≥ 30, 40 and 50 kg/m^2 increased by

approximately 200, 500 and 1000 %, respectively (6). Interestingly, data from 2008 indicate that the obesity epidemic seems to be flattening out in the US, especially among women (7). Still, 32 % of US adults are obese, with 4 % of men and 7 % of women being extremely obese (7). Correspondingly, the prevalence of obesity among women and men aged 40-44 years has increased in Norway the last three to four decades (Figure 1) (8). Three major health surveys in the county of Nord-Trøndelag in Norway, The Nord-Trøndelag Health Study (HUNT 1, 2 and 3), have shown that the prevalence of obesity has increased from 7.8 to 14.4 to 22.1 % in men and from 13.6 to 18.6 to 23.2 % in women from 1984-86 to 1995-97 to 2006-08, respectively (9). The greatest increase was seen in those less than 40 years of age (9). Results from other health surveys performed in five Norwegian counties in 2000-03 showed that the prevalence of BMI $\geq$ 35 and $\geq$ 40 kg/m^2 were approximately 3 and 0.5 % in men and 5 and 1 % in women, respectively (10). Based on these figures, we can assume that the overall prevalence of morbid obesity in Norway is around 2 %.

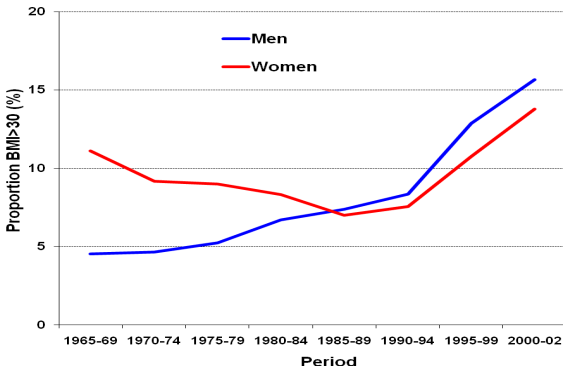

Figure 1. Proportion of Norwegian women and men aged 40-44 years with BMI $\geq$ 30 kg/m^2 from 1965 to 2002. Modified figure from The Norwegian Institute of Public Health with permission from A. Engeland (8).

2.1.3. The burden of obesity

Recently, the WHO estimated that obesity and two of its most common metabolic consequences, hyperglycaemia (11-21) and high blood pressure (19-22), alongside tobacco usage and physical inactivity, represent the five leading global risks to mortality (23). The positive association between BMI and all-cause and cardiovascular mortality is documented in numerous studies (24-32). One large study, including almost 900 000 subjects with a mean age of 46 years, showed that during a mean follow-up period of 8 years the median survival was reduced by 8 to 10 years for subjects with a BMI of 40 to 45 kg/m^2 compared to subjects with a BMI of 22.5 to 25 kg/m^2 (29). Importantly, higher mortality rates among obese subjects seem to be mainly explained by obesity related co-morbidities such as hypertension and type 2 diabetes rather than by obesity alone (33).

Several other cardiovascular risk factors, such as metabolic syndrome, albuminuria, left ventricular hypertrophy and low grade inflammation, are all closely associated with obesity (34-37). Furthermore, obesity is a risk factor for cancer (38), urinary incontinence (39), gastro-oesophageal reflux (40), obstructive sleep apnoea (41), osteoarthritis (42), depression (43) and reduced quality of life (44).

Several lines of evidence indicate that it is not only the total amount of fat but the distribution of fat that determines the risk associated with obesity. Excess intra-abdominal fat, which can be assessed using imaging techniques, seems to be an independent predictor of metabolic risk factors (45-48). Due to the strong correlation between anthropometric measures of abdominal obesity and visceral adipose tissue deposition (46,49), these measures have been widely used as surrogate measures of intra-abdominal fat mass in order to identify subjects at risk. Indeed, several large cross-sectional and longitudinal population studies indicate that WC and/or

WHR are more strongly associated with type 2 diabetes and other obesity related disorders than BMI (11-19). Furthermore, one large case-control study including 27 000 participants showed that WHR and WC, but not BMI, were independently associated with the risk of myocardial infarction (50). Finally, some studies indicate that WHR is a better predictor of death than BMI (19,51,52).

2.2. Type 2 diabetes

Hand in hand with the rising obesity rate is the substantial increase of diabetes worldwide (53-55). Due to the strong association between diabetes and obesity the coexistence of these conditions has been referred to as "diabesity" (56). The term reflects both the etiological and clinical presentation of this phenomenon. Women and men with BMI $\geq$ 35 kg/m^2 have 93 and 42 times higher risk of type 2 diabetes than those with the lowest risk (57,58).

2.2.1. Definition of type 2 diabetes

The diagnosis of type 2 diabetes and its intermediate forms has been debated for decades, and the diagnostic criteria have been changed several times: In the late nineties the fasting glucose cut-off level was lowered from 7.8 to 7.0 mmol/l (59,60); in 2003 the American Diabetes Association (ADA) lowered the threshold for impaired fasting glucose (IFG) from 6.1 to 5.6 mmol/l (61); and finally in 2010 ADA included the use of HbA1c to diagnose diabetes (HbA1c $\geq$ 6.5 %) and to identify subjects at "increased risk for future diabetes" (HbA1c 5.7 – 6.4 %) (62). The current diagnostic criteria for diabetes and intermediate hyperglycaemia according to the WHO and ADA are shown in Table 3.

Table 3. Diagnostic criteria for diabetes and intermediate hyperglycaemia according to serum/plasma glucose levels.

	WHO 2006 (63)	ADA 2010 (62)
Diabetes mellitus		
Fasting glucose	≥ 7.0 mmol/l	≥ 7.0 mmol/l
	Or	or
2-hour glucose	≥ 11.1 mmol/l	≥ 11.1 mmol/l[1]
		or
HbA1c		≥ 6.5 %
Increased risk for future diabetes		
Fasting glucose[2]	6.1 – 6.9 mmol/l	5.6 – 6.9 mmol/l
	and/or	and/or
2-hour glucose[3]	7.8 – 11.0 mmol/l	7.8 – 11.0 mmol/l[1]
		and/or
HbA1c		5.7 – 6.4 %

[1]Corresponding values for capillary plasma are ≥ 12.2 mmol/l for diabetes mellitus and 8.9 – 12.2 mmol/l for pre-diabetes. [2]Impaired fasting glucose. [3]Impaired glucose tolerance.

2.2.2. Type 2 diabetes and cardiovascular risk

The scientific evidence for the current thresholds is mainly based upon an increased risk of retinopathy above these cut-off levels (Figure 2) (59,64). However, these cut-off points are still arbitrarily chosen, and some publications indicate that there exists no consistent glycaemic threshold when the risk of retinopathy increases (65,66). The latter findings are consistent with observations indicating that no glucose cut-off value exists in which the risk of macrovascular complications and death increases (67-69). This is analogous to end-organ

damage found with other cardiovascular risk factors such as blood pressure and serum cholesterol levels, where the associations are continuous (70,71). Despite the limitations with the data from which the diagnostic criteria for diabetes are derived, the current criteria distinguish a group with significantly increased premature mortality and increased risk of microvascular and macrovascular complications (64-68,72-77).

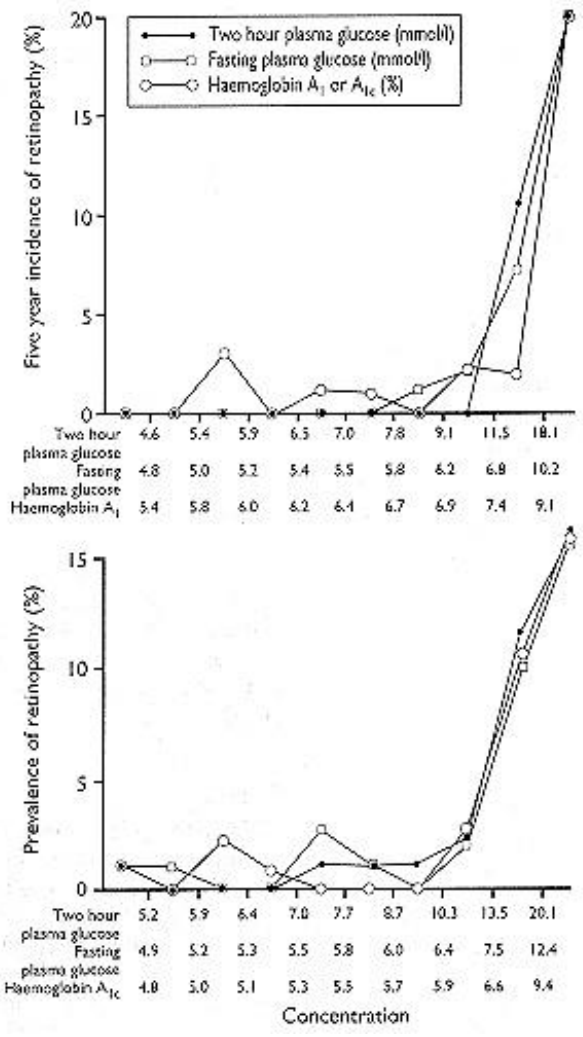

Figure 2. Five year cumulative incidence (top) and prevalence (bottom) of retinopathy by deciles of the distribution of fasting plasma glucose, two hour plasma glucose and glycated haemoglobin A1 and A1c in Pima Indians. Reproduced from McCane et al. (64) with permission.

2.2.3. Diabetes trends

During a 15 year period from 1985 to 2000, the estimated number of people with diabetes worldwide increased from 30 to 171 million, and the prevalence is likely to increase to at least 366 million by 2030 (55). Norway is no exception: Data from the HUNT surveys indicate an increase in the prevalence of diabetes during the last two decades (9,78), with 3.8 % of women and 4.9 % of men having diagnosed diabetes in 2006-08 (9). Including subjects with unknown diabetes would probably double these figures (79). There is an increase in the prevalence of diabetes within each obesity category, and among the extremely obese approximately one out of four has diabetes (21).

2.2.4. Screening for type 2 diabetes

Screening, the, search for undiagnosed conditions/diseases in asymptomatic subjects, is only appropriate under given circumstances. Some important criteria and their relevance to screening for type 2 diabetes are shown in Table 4 (80).

Table 4. Screening for type 2 diabetes (80)

Criteria	**Met for diabetes**
Important health problem	Yes
Natural history of the disease is known	Yes
Asymptomatic period	Yes
Early treatment improves outcome	Probably
Available and reliable test	Yes
Reasonable costs/Available treatment	Unclear/Yes
Systematic and ongoing process	Unclear

Type 2 diabetes is undoubtedly an important health problem, the natural history of the disease is known, the disease has an asymptomatic period and reliable tests and treatments exist; all of which is supportive of screening for type 2 diabetes. However, the beneficial effects of early intervention (see below, 2.3.3) are unclear. Moreover, it is uncertain whether the costs of screening and treating type 2 diabetes are reasonable in relation to total health expenditures. In addition, it is also unclear how a screening programme should be organised and how often the tests should be repeated.

The screening test should ideally have high sensitivity (proportion of people with the disease who have a positive test) and high specificity (proportion of people without the disease who have a negative test). In addition, the test should be valid (reflect the true status of the individual), reliable (reflect the degree to which the results obtained by any given procedure can be replicated) and reproducible (reflect the test`s ability to obtain similar or identical results on repeated measurements on the same subject). The predictive value of a test (probability that a person has or does not have the disorder given the result of the test) depends both on the tests sensitivity and specificity but also on the prevalence of the disorder in the population being screened. Thus, in the case of diabetes screening, the positive predictive value of a positive test is higher in a population with a high prevalence of diabetes than in a population with a low prevalence. This explains why selective screening programmes for type 2 diabetes, for example in out-patient clinics and opportunistic screening (case finding) in high risk patients, may be more appropriate than population based screening programmes.

In general, despite lack of evidence, it is recommended that subjects with BMI $\geq$ 25 kg/m^2 and age $\geq$ 45 years should be tested every third year (81). Furthermore, it is recommended

that persons with additional risk factors, including severe obesity, should be tested independent of their age. In line with these recommendations, all patients attending the Morbid Obesity Centre for the first time are screened for type 2 diabetes.

2.2.5. The pathogenesis of type 2 diabetes

Insulin is a hormone produced by the pancreatic β-cells and is the key hormone for the regulation of blood glucose. The hormone stimulates uptake of glucose from the blood in the muscle and fat tissue, storage of glucose as glycogen in the liver and muscle cells (glycogenesis) and uptake and esterification (conversion into triglycerides) of fatty acids in adipocytes. Furthermore, insulin inhibits the breakdown of proteins (proteinolysis), the hydrolysis of triglycerides (lipolysis) and the production of glucose from amino acids, lactate and glycerol (gluconeogenesis). Glucagon, which is also secreted by the pancreas, has the opposite effects to that of insulin. The hormone causes the liver to convert stored glycogen into glucose and thereby increases blood glucose. In addition, glucagon stimulates insulin secretion so that glucose can be taken up by insulin dependent tissues. Thus, glucagon and insulin are part of a feedback system that keeps blood glucose at the right level.

Hyperglycaemia occurs when the balanced interplay between insulin`s action and release is disrupted. However, the causes for hyperglycaemia are complex and multi-factorial and include genetic and environmental factors that affect insulin secretion and insulin sensitivity. Firstly, older age is a major risk factor for diabetes (21,79). The prevalence of diabetes is approximately three times higher in subjects aged between 70-79 years than it is in those aged 50-59 years (79). Secondly, lack of exercise has been shown to be a independent risk factor for type 2 diabetes (82). Thirdly, a positive family history confers a 2.4 fold increased risk for type 2 diabetes (83). Fourthly, as mentioned, obesity is major risk factors for type 2 diabetes

(11-19). In recent years it has become clear that the adipose tissue is not only a passive storage depot for fat but rather an active endocrine organ expressing and secreting a variety of bioactive proteins with metabolic effects on distant cells and tissues (84,85). Non-esterified fatty acids, adipokines and inflammatory mediators released by adipocytes, especially from adipocytes located in the visceral adipose tissue, cause insulin resistance in the liver and skeletal muscle by adversely affecting the insulin signalling cascade (84-86). Consequently, gluconeogenesis and lipogenesis in the liver are stimulated and glucose uptake in the skeletal muscle inhibited, eventually resulting in hyperglycaemia and triglyceridaemia. In turn, these conditions will feedback and worsen both insulin sensitivity and β-cell function (gluco- and lipo-toxicity) (84,85,87,88).

The relationship between insulin sensitivity and insulin secretion displays a hyperbolic curve (Figure 3) (89,90). This denotes that the product of insulin secretion and insulin sensitivity, known as the disposition index (DI), is constant. Due to this feedback mechanism, normal blood glucose levels can be maintained in the presence of insulin resistance, as with obesity, if the insulin secretion is regulated adequately. As shown in Figure 3 (91), normoglycaemia is preserved when a reduction in insulin sensitivity is accompanied by an increase in insulin secretion. By contrast, impaired glucose tolerance (IGT) and type 2 diabetes occur when the insulin release is insufficient for a given degree of insulin sensitivity.

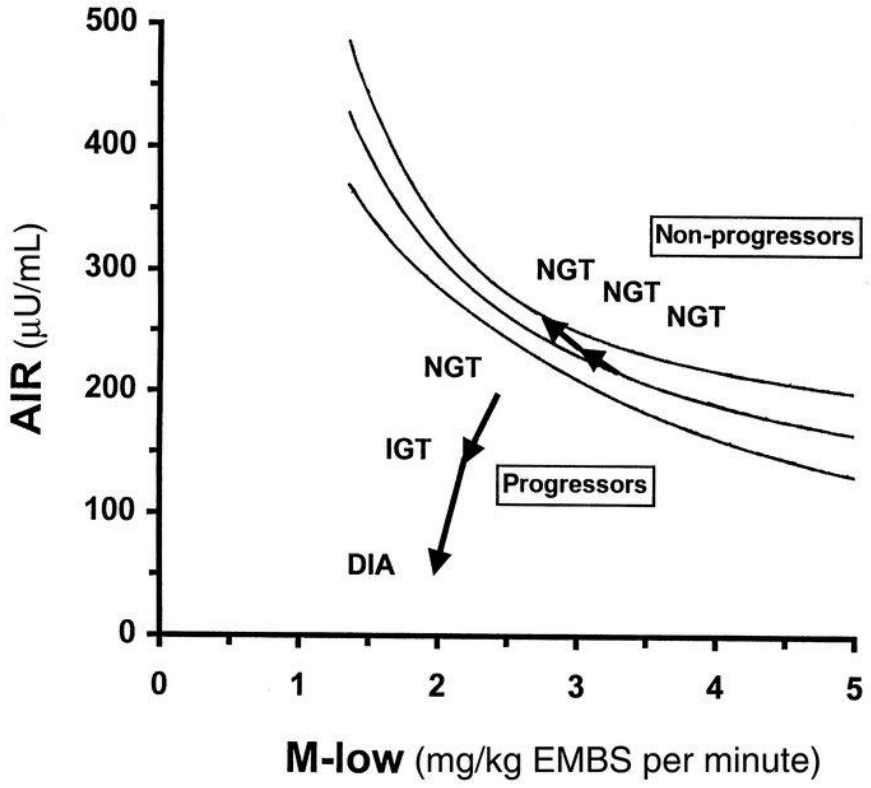

Figure 3. Changes in insulin secretion [acute insulin response (AIR) to intravenous glucose] relative to changes in insulin sensitivity [hyperinsulinaemic euglycaemic clamp (M-low)] in 11 Pima Indian subjects in whom glucose tolerance deteriorated from normal (NGT) to impaired (IGT) to diabetic (DIA) (Progressors), and in 23 subjects who retained NGT (Non-progressors). The lines represent the prediction line and the lower and upper limits of the 95% confidence interval of the regression between AIR and M-low as derived from a reference population of 277 Pima Indians with NGT. Reproduced from Weyer et al. (91) with permission.

2.3. Obesity treatment

The two main principles in the treatment of obesity are to reduce energy intake and to increase energy expenditure through lifelong behavioural changes. Medical management includes lifestyle intervention strategies compromising of dietary modifications, physical

activity, psychological interventions and anti-obesity drugs. Additionally, weight loss (bariatric) surgery can be used in those with the severest degree of obesity.

2.3.1. Medical management of obesity

The macronutrient composition of various weight loss diets is a topic of great interest, and several randomised controlled trials have addressed this question (92-102). Most studies indicate that low-carbohydrate diets yield greater short-term weight loss than low-fat diets (92-98). In a two-year trial that included 322 moderately obese subjects, mean weight loss was significantly greater after low-carbohydrate and Mediterranean diets than after a low-fat diet (5.5, 4.6 and 3.3 kg, respectively) (92). In line with these observations, a recent Cochrane review confirmed that low-carbohydrate diets were associated with a one kg greater weight loss than other diets (103). Moreover, two other recent Cochrane reports addressing obesity treatment have been published (104,105). In the first, exercise alone is shown to result in up to four kg weight loss, and when combined with a diet to result in approximately one kg greater weight reduction than diet alone (104). The second report shows that behavioural and cognitive-behavioural strategies alone result in three kg weight loss and that when combined with lifestyle interventions weight reduction is enhanced (105).

The use of orlistat, sibutramine and rimonabant in addition to lifestyle modifications have, in randomised placebo-controlled trials with a follow-up period of one year or longer, been shown to increase weight reductions in overweight and obese subjects (106-111). A recent meta-analysis showed that compared to placebo, orlistat, sibutramine and rimonabant reduced weight by 3, 4 and 5 kg, respectively (112). Anti-obesity drugs are also effective in preventing weight regain after an initial weight reduction (106-108,113), improving several metabolic conditions (106-116) and preventing the development of type 2 diabetes (117). Despite these

promising results the development of pharmacological therapies for the treatment of obesity has, due to serious side-effects, been a great disappointment. In 1997, fenfluramine, another weight-loss drug, was withdrawn from the U.S. market after reports of pulmonary hypertension and valvular heart disease (117). Later in 2008, rimonabant was withdrawn from the European market due to psychological side-effects (118), and the CRESCENDO study, which aimed to assess whether rimonabant could prevent cardiovascular event, was prematurely terminated (119). Finally, in 2010 the European Medicines Agency advisory committee recommended that sibutramine be withdrawn from the European market (120) due to increased risk for cardiovascular events reported among sibutramine-users in the SCOUT study (121).

The Finnish Diabetes Prevention Study, the Diabetes Prevention Program and the LookAhead trial, which all included overweight and obese subjects with IFG, IGT or type 2 diabetes, have all shown that dietary modifications and physical activity may result in 5 to 8 % weight loss after one year and 4 to 6 % weight loss after three to four years (122-126). Studies including solely morbidly obese subjects have shown that intensive lifestyle interventions, including low calorie-diets, physical activity and frequent meetings or institutionalisations, can result in 8 to 20 % weight reduction after 5 to 24 months (127-131). However, with no intervention in the follow-up period two thirds of the initial weight loss was regained two to four years after institutionalisation (128). Having a high physical activity level, sticking to a structured low-calorie diet and self-monitoring weight are important predictors of long-term weight loss maintenance (132). Additionally, regular personal contact in the weight maintenance follow-up period seems to help sustain weight loss (133).

2.3.2. Bariatric surgery

Due to the limited long term success of medical management of obesity, various surgical techniques have been developed during the last few decades (134-136). Along with the rising prevalence of severe obesity and the introduction of safer procedures and techniques, the number of bariatric operations performed worldwide has increased dramatically during the last decade; from 40 000 in 1998 to 340 000 in 2008 (137). Norway is no exception, with around 1 500 bariatric surgery operations performed in 2008 (137). To date, the annual number of operations is around 2000.

Surgical techniques

The procedures can be divided into three according to the mechanism by which they induce weight loss: Restrictive procedures reduce food intake by restricting gastric volume; malabsorptive procedures reduces energy uptake from the intestinal track by bypassing parts of the small intestine; whilst combined procedures do both. Such procedures began in the mid 1950s with the jejunoileal bypass, which is a purely malabsorptive procedure. Despite good weight loss this procedure was abandoned as many developed severe malnutrition, liver failure and diarrhea (138). In the 1980s and 1990s vertical banded gastroplasty and gastric banding with fixed band were commonly performed. However, these purely restrictive procedures often caused stenosis, persistent vomiting, acid reflux and ulcers, leading them to be replaced by other procedures.

The gastric bypass procedure is a combined restrictive and malabsorptive procedure and was initially developed by Mason and Ito in the 1960s (139). Over several decades the gastric bypass has been modified into its current form, and accounts today for almost 50 % of all bariatric operations performed worldwide (137) and for around 90 % of all procedures

performed in Norway (140). A Roux-en-Y gastric bypass first divides the stomach into a small upper pouch of about 30 ml and a much larger, lower "remnant" pouch. The small gastric pouch is then anastomosed to a Roux-en-Y proximal jejunal segment (Figure 4).

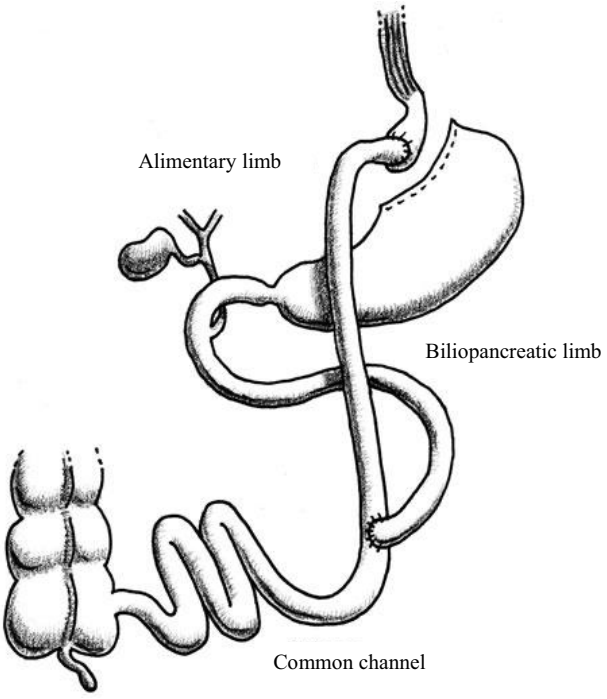

Figure 4. Illustration of the Roux-en-Y gastric bypass procedure. Illustration by Ole-Jacob Berge. Reproduced from Aasheim et al. (140) with permission.

The Roux-en-Y gastric bypass operations are often referred to as standard, long limb, or distal, depending on the length of the Roux (alimentary) limb. The long limb procedure which includes an alimentary limb of about 150 cm, a biliopancreatic limb of about 80 cm and a common channel of 2 to 5 meters (depending on the length of the small intestine), is most commonly used in Scandinavia (141,142).

Other bariatric procedures performed worldwide today include adjustable gastric banding (42 %), sleeve gastrectomy (5 %), and biliopancreatic diversion with or without duodenal switch (2 %) (137). Adjustable gastric banding uses an inflatable silicone device that is placed around the top portion of the stomach in order to reduce food intake. Although popular abroad, this operation is hardly performed in Norway. Sleeve gastrectomy reduces the stomach to a banana shaped tube by removing a large portion of the stomach. The operation can be used as a single procedure or as the first step in a two step procedure where the second is a conversion into duodenal switch. The biliopancreatic diversion includes either a horizontal gastrectomy with a gastro-jejunal anastomosis or a vertical gastrectomi with a duodenon-jejunal anastomosis. Both procedures include a short common limb (50-100 cm) and are highly malabsorptive.

The introduction of laparoscopic approaches during the last decade has reduced the time spent in hospital (143,144), post-operative pain (144), the number of incisional hernias (143,145) and mortality (146-148). For these reasons more than 90 % of bariatric procedures performed worldwide today are now performed laparoscopically (137).

Outcomes

Substantial and long term weight reduction and improvements in metabolic conditions after bariatric surgery are reported in a number of large case series (149-153), a few studies comparing bariatric surgery with lifestyle interventions (154-158) and in two meta-analyses (159,160). Especially worth noting is the large case-controlled Swedish Obese Subjects (SOS) study which prospectively included more than 2000 patients undergoing bariatric surgery and as many conservatively treated patients (154), and, in addition, the two randomised controlled trials by Dixon and O`Brian which compared the effect of adjustable gastric banding and

lifestyle intervention on weight and type 2 diabetes in adults (155,156). Weight loss is greatest after malabsorptive procedures and least after purely restrictive operations: One year weight reduction after banding, gastric bypass and biliopancreatic diversion is approximately 20, 30 and 40 %, respectively (154,156,159). Bariatric surgery seems especially effective in improving glycaemic control, with a remission rate of type 2 diabetes higher than 70 % two years after surgery reported in both the SOS study and the randomised controlled trial by Dixon and O`Brian (154,156). However, it should be noted that the criteria for remission type 2 diabetes in these studies varied, thereby making comparison difficult. In addition, the SOS study documented that bariatric surgery reduced blood pressure, triglycerides and total cholesterol and increased high density lipoprotein cholesterol (154). Moreover, surgical treatment of obesity has shown to ameliorate metabolic syndrome (152,155,156), albuminuria (161,162), left ventricular hypertrophy (163,164), low-grade inflammation (165,166) and obstructive sleep-apnoea (167,168). In addition, bariatric surgery improves psychosocial functioning and health related quality of life (169,170). Finally, both the SOS study and a retrospective cohort study by Adams et al. indicate that bariatric surgery is associated with reduced mortality (171,172).

Although the mortality rate after bariatric surgery has shown a downward trend since 1990 (173), no procedure is without risk. The longitudinal assessment of bariatric surgery consortium reported total mortality of 0.3 % within 30 days in 4 610 patients who had a first-time bariatric procedure (147). The mortality rate was 0 % after laparoscopic adjustable gastric banding and 0.2 and 2.1 % after laparoscopic and open Roux-en-Y gastric bypass, respectively (147). Correspondingly, total 30 days mortality rate was 0.28 % in a meta-analysis by Buchwald (173). Partly contrasting these findings, 2 % of the Medicare beneficiaries undergoing bariatric surgery died within 30 days (174). However, it should be

noted that the study population in the latter study had a higher men age and a higher proportion of men than other studies reporting mortality after bariatric procedures. Both high age and male gender are associated with increased risk of post-operative death and may explain some of these differences (146,173,174). Thromboembolic diseases, bleedings, small bowel obstruction and leakage are the most common causes of postoperative death and account for the majority of non-fatal complications (146-148,175). Long term complications after Roux-en-Y gastric bypass include gastrointestinal symptoms such as nausea, vomiting, postprandial regurgitation, dumping syndrome and diarrhea (176), micronutrient deficiencies (177-179), marginal ulcers (180,181), postprandial hypoglycaemia (182,183) and small bowel obstructions (184).

2.4. Treatment of type 2 diabetes

The main goal of type 2 diabetes treatment is to maintain a good quality of life and to minimize the risk of future microvascular and macrovascular complications. Lifestyle interventions have shown to improve glyceamic control in overweight and obese diabetic subjects (125,126). However, in the long-term, most diabetic subjects need glucose lowering drugs in order to prevent hyperglycaemia. Both the randomised controlled UK Prospective Diabetes Study (UKPDS) and the Kumamoto study have demonstrated that intensive blood glucose control with insulin, sulphonylureas and metformin reduce the risk of microvascular complications (185-187). In addition, the ten year post-trial follow-up of the UKPDS indicates that intensive glucose lowering treatment can reduce the risk of myocardial infarction and death of any cause (188). However, three recent major cardiovascular outcome trials [the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (189), the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (190) and Veterans Affairs Diabetes Trial (VADT) (191)] of intensive

diabetes therapies in patients with type 2 diabetes found no significant reduction in cardiovascular events. The ACCORD study actually reported a 22 % increase in total mortality in the intensive treated group. However, when the studies are combined, there is agreement both that non-fatal coronary episodes are reduced by intensive control and that the incidences of stroke, cardiovascular mortality and total mortality remain unaltered (192-194). Both national and international guidelines recommend that the goal of glucose lowering therapy should be HbA1c $\leq$ 7 % (81,195). Moreover, high blood pressure and dyslipidaemia should be treated aggressively in diabetic subjects in order to prevent cardiovascular complications (81). Norwegian data indicate that only a small number of type 2 diabetic subjects reach the combined targets for glucose, blood pressure and cholesterol control (196).

In recent years, new classes of glucose-lowering agents such as thiazolidinediones, glucagon-like peptide-1 agonists and dipeptidyl peptidase 4 inhibitors have become available and increased the number of treatment options for type 2 diabetes. In 2008 ADA and the European association for the study of diabetes jointly reviewed the current literature and based on the effectiveness, safety and cost of the different therapies published an algorithm for the medical management of hyperglycaemia in type 2 diabetes (197). The study group recommended that lifestyle modifications and metformin should be the initial therapy, with further treatment including either insulin or sulphonyureas. Alternatively, less validated treatments could be used. The statement also included, for the first time, bariatric surgery as an alternative for the treatment of type 2 diabetes in subjects with BMI $\geq$ 35 kg/m^2 (197).

3. Aims of the thesis

The aims of the studies in this thesis are:

Paper I

- To assess the effectiveness of fasting glucose in detecting undiagnosed diabetes in morbidly obese subjects

Paper II

- To explore in extremely obese subjects the relationship between various measurements of obesity and type 2 diabetes

Paper III

- To compare changes in obesity-related cardiovascular risk factors after gastric bypass surgery and intensive lifestyle intervention

Paper IV

- To compare changes in beta cell function after gastric bypass surgery and intensive lifestyle intervention

4. Research design and methods

4.1. Participants and study design

This thesis is based on both studies using cross-sectional data from The Morbid Obesity Biobank Registry and from the one year non-randomised controlled clinical MOBIL study (Table 5). All participants were referred from secondary health care clinics to the Morbid Obesity Centre at Vestfold Hospital Trust located in Tønsberg. The centre was established in September 2004 and had at first a temporary organisational form (Overvektsprosjektet i Helse Sør). Later, in 2007, it was established as a permanent centre and is today one of two tertiary health care centres in the South-Eastern Norway Regional Health Authority treating morbidly obese patients. The main tasks of the centre are to 1) evaluate, assess and treat morbidly obese subjects, 2) conduct research in the field of obesity and 3) educate and support other health care centres treating obese patients.

Table 5. Study design, population and sample size of the studies.

Paper	Study design	Population	Participants
I	Cross-sectional	Morbidly obese	1 253
II	Cross-sectional	Extremely obese	1 003
III	One year non-randomised	Morbidly obese	80 gastric bypass
			66 lifestyle
IV	One year non-randomised	Morbidly obese	64 gastric bypass
			55 lifestyle
			29 normal weight controls

4.1.1. The Morbid Obesity Biobank Registry

Paper I and II had cross-sectional designs and included patients registered in The Morbid Obesity Biobank Registry. Since December 2005, all patients who attend the Morbid Obesity Centre and give informed consent are consecutively included in the Registry. Clinical data from the patients' first visit, along with the results of the laboratory analyses performed the same day, are recorded on standardised forms and included in the Registry. In addition, results of OGTTs performed one year before or after the first visit were, until November 2008, included.

Paper I included all the morbidly obese patients registered in the Morbid Obesity Biobank Registry as of November 2008 (n = 1 329). After the exclusion of 76 subjects due to; type 1 diabetes mellitus (n = 11), prior non-reversed bariatric surgery (n = 10), usage of oral corticosteroids (n = 21) or BMI < 35 kg/m^2, a total of 1 253 subjects were included in the analyses.

Paper II included extremely obese patients registered in the Registry by January 2009 (n = 1 068). In this study 65 subjects were excluded due to; prior non-reversed bariatric surgery (n = 6), missing glucose measurements (n = 5), type 1 diabetes (n = 6), usage of oral corticosteroids (n = 16) and non-Caucasian ethnicity (n = 32). Consequently, a total of 1 003 subjects were included in the analyses.

4.1.2. The MOBIL study

Paper III and IV included patients from the MOBIL study. The flow of the study participants is shown in Figure 5. Firstly, during a six month period, between December 2005 and May 2006, 228 consecutive patients attending the Morbid Obesity Centre for the first time were

pre-screened for participation in the study. Secondly, 181 patients who satisfied the criteria for bariatric surgery (198) and wanted either gastric bypass surgery or intensive lifestyle intervention were referred to a screening examination which included an oral glucose tolerance test, 24-hour ambulatory blood pressure monitoring, a somnography, pulmonary function tests, quality of life questionnaires and a structured dietary interview. The elapsed period of time between the pre-screening examination and the screening examination was 18 (11) weeks. Finally, 146 subjects were accepted for either gastric bypass surgery (n = 80) or intensive lifestyle intervention (n = 66) and were enrolled in the study.

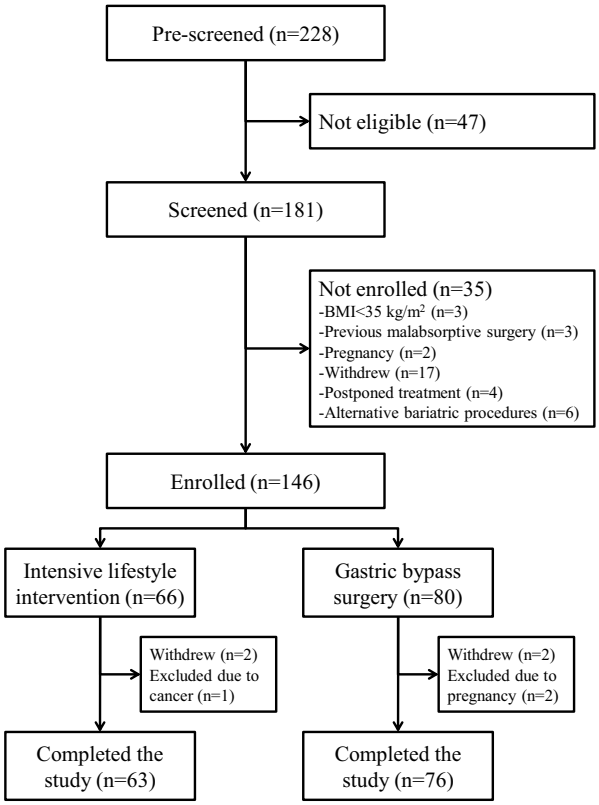

Figure 5. Flow of participants throughout the MOBIL study. Reproduced from Hofsø et al (199), no permission required.

The time between the screening examination and either the date of surgery or the start of lifestyle intervention was, due to a waiting list for surgery, significantly longer in the surgery group than in the lifestyle group, 65 (14) versus 19 (15) weeks ($P < 0.001$). One year follow-up was completed by June 2009. The completion rate within both groups was 95 % (76 in the surgery group and 63 in the lifestyle group).

Allocation to treatment was made as a joint decision between the patient and the physician. All patients underwent a thorough assessment conducted by a multidisciplinary team consisting of an internist, a dietician and, in cases of surgery, a surgeon prior to treatment. These health professionals provided complete information about the possible risks and benefits of an operation and encouraged patients to incorporate their own values and preferences into the decision-making process.

Patients in the surgical group completed a low calorie diet (800 to 900 kcal/day) in the three to six weeks preceding surgery. A Roux-en-Y gastric bypass was performed laparoscopically in 74 of the 76 surgically treated patients. The gastric pouch was about 25 ml, whilst the intestinal limb lengths were measured as follows: alimentary limb, median 120 (range 80 to 250) cm; biliopancreatic limb, median 100 (range 50 to 170) cm; and common channel, variable length. To optimise the result of the procedure patients were encouraged, both before and after the surgery, to normalise their eating behaviour and to increase their physical activity level.

The majority (59 out of 63) of patients in the lifestyle group were referred to a rehabilitation centre specialising in the care of morbidly obese patients (Evjeklinikken). Using a cognitive approach the programme at this centre aimed to induce a weight loss of at least 10 %. Each

patient was motivated to increase their physical activity and to normalise their eating habits. The one year lifestyle programme comprised four stays at the rehabilitation centre lasting for either one week or four weeks (Figure 6).

Figure 6. Schedule of stays during the one year lifestyle programme at Evjeklinikken. Reproduced from Hofsø et al (199), no permission required.

The daily programme was divided between organised physical activity (3 to 4 hours) and different psychosocially oriented interventions. The interventions involved individual consultations with a medical doctor, nutritionist, physiotherapist and a trained nurse. The patients also took part in group sessions focusing on the emotional aspects of sedentary behaviour as well as classroom lessons on topics related to nutrition, physical activity and co-morbidities. No special diet or weight loss drugs were prescribed, but patients were encouraged to follow the guidelines of the Norwegian National Council of Nutrition (200) which recommend that the daily intake of protein, fat, carbohydrate and alcohol should account respectively for 10 to 20, < 30, 50 to 60 and < 5 % of energy consumed. Outside of these stays patients were contacted by phone once every two weeks. They were encouraged to self-monitor their eating habits and physical activity, as well as to visit their general practitioner for a consultation and weight control check once every four weeks. The remaining four participants were allocated to two rehabilitation centres with comparable intervention programmes.

Paper III included all 146 of the patients who took part in the MOBIL study. Results are reported for the 139 completers.

Paper IV included a subset of 119 participants from the MOBIL study who did not use glucose lowering agents at baseline and who underwent an OGTT both before and after the interventions. Additionally, a control group of 29 normal weight (18 kg/m^2 < BMI < 25 kg/m^2) persons with NGT were recruited from healthy employees at Vestfold Hospital Trust in Tønsberg. The controls were examined in August 2007.

4.2. Clinical characteristics and definitions

Demographic and clinical data were recorded on standardised forms. All anthropometric measures were made with patients in an upright position wearing light clothing and no shoes. Height was measured using wall mounted stadiometers; WC was measured at the level midway between the lowest rib margin and the iliac crest; hip circumference (HC) was measured at the widest level over the greater trochanters; and neck circumference (NC) was measured at a point just below the larynx and perpendicular to the long axis of the neck. Weight was measured to the nearest 0.1 kg, height to the nearest 0.5 cm and circumferences to the nearest 1 cm. After at least five minutes of rest, blood pressure was measured three times using a sphygmomanometer. The average of the second and third measurements was registered.

In all of the papers presented in this thesis, participants have been classified into categories of glucose tolerance according to the WHO criteria (Table 3). Patients who used glucose lowering agents were classified as having type 2 diabetes. In Paper IV subjects with IFG, IGT and type 2 diabetes were pooled into an abnormal glucose tolerance (AGT) group. Remission of diabetes was defined as either partial (serum glucose levels below the diagnostic cut-off values and HbA1c < 6.5 %) or complete (fasting serum glucose < 5.6 mmol/l, 2 hour glucose < 7.8 mmol/l and HbA1c < 6.2 %) in the absence of glucose lowering agents (201).

In Paper III the below summarised endpoints were defined as follows; hypertension, the usage of anti-hypertensive drugs, systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg (202); metabolic syndrome, at least three of the following five characteristics (modified ATP III criteria): waist circumference ≥ 102 cm in men and ≥ 88 cm in women, fasting triglycerides ≥ 1.7 mmol/l, systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg or on anti-hypertensive drugs, fasting glucose ≥ 5.6 mmol/l or on glucose lowering agents, or high density lipoprotein cholesterol < 1.0 mmol/l in men and <1.3 mmol/l in women (203); albuminuria, albumin to creatinine ratio in urine ≥ 2.5 mg/mmol in men and ≥ 3.5 mg/mmol in women (204); and left ventricular hypertrophy, Cornell voltage-QRS duration product ($R_{aVL} + S_{V3}$, with 6 mm added in women) ≥ 2440 mm x ms (205,206).

Dietary intake and physical activity during the preceding year were assessed through structured interviews performed by registered dieticians (Paper III and IV). Data were recorded on an optically readable food frequency questionnaire (Department of Nutrition, University of Oslo, Norway). Similar questionnaires have been validated using weighted records (207). Questionnaire data were scanned using Teleform 10.0 (Cambridge, UK). Dietary intake was calculated using a database assembled from official food composition tables (Norwegian Nutrition Council, 1995). Calculations were computer driven (Kostberegningssystem 6.0; University of Oslo, Norway). Time spent performing light (e.g. casual walking), moderate (e.g. brisk walking) and vigorous (e.g. jogging) intensity aerobic physical activities in periods of 10 minutes or more were recorded. Participants who performed 150 minutes or more per week of moderately intense aerobic physical activity were considered to be physically active, as were those participants who performed 60 minutes or more per week of vigorously intense aerobic physical activity (208).

Perioperative (first 30 days) and late (after 30 days) complications were recorded in each patient's record file (Paper III). In addition, all medical emergencies, hospitalisations and gastrointestinal side-effects were reported on standardised self-report questionnaires. Reported symptomatic postprandial hypoglycaemia was documented by blood glucose < 2.8 mmol/l (209,210). Complications and medical emergencies not recorded in each patient's record file at our hospital were verified by reports from other institutions.

In Paper II and IV, the homeostasis model assessment of insulin sensitivity (HOMA S) and β-cell function (HOMA B) were calculated using the computer program HOMA calculator (211). OGTT-derived estimates of insulin sensitivity and insulin secretion were calculated in Paper IV: Insulin sensitivity was calculated using indices of Belfiore (212) and Stumvoll (213), and insulin secretion was estimated using the insulinogenic index ($\Delta Ins_{30}/\Delta Gluc_{30,}$), the ratio of the total area under the insulin curve to the total area under the glucose curve (total $AUC_{Ins/Gluc}$) and the Stumvoll first phase index (fist $phase_{est}$: 1283 + 1.829 x Ins_{30} -138.7 x $Gluc_{30}$ + 3.772 x Ins_0) (213). Furthermore, the DI, which yields a better measure of β-cell function (90), was calculated by multiplying HOMA S and first $phase_{est}$. Finally, proinsulin-to-insulin (PI/I) ratios in a fasting and stimulated state (30 minutes after glucose ingestion) were calculated. Elevated PI/I ratios have been associated with IGT (214) and reduced insulin secretion (215), and these indexes may therefore indicate another aspect of beta cell function.

4.3. Laboratory analyses

4.3.1. Sampling

Blood was collected by vein puncture either in a fasting state or during an OGTT. Standard 75 g OGTTs with blood samples taken before and 120 minutes after the glucose load were used. In addition, the OGTTs performed in the MOBIL study included blood sampling 30 minutes after the ingestion of glucose. Paper II-IV included blood samples taken solely at the Department of Clinical Chemistry at Vestfold Hospital Trust. Paper I included, in addition, glucose measurements from 348 OGTTs performed at seven other laboratories in the health region (Drammen, Kongsberg, Ringerike, Skien, Notodden, Arendal and Kristiansand). At Vestfold Hospital Trust samples clotted at room temperature and serum was separated from cells within either 30 minutes (OGTTs) or 2 hours (fasting samples). At the other laboratories in the health region glucose was analysed in serum (n = 210) or plasma (n = 64), both centrifuged within 60 minutes, or in capillary full blood (n = 74). All the samples at these laboratories were analysed at the day of the sampling. Serum samples collected at Vestfold Hospital Trust were either stored at -80^{o}C (analyses performed at the Endocrine Laboratory, Oslo University Hospital Rikshospitalet, Paper III-IV) or -20^{o}C (analyses performed at the Hormone Laboratory, Oslo University Hospital Aker, Paper II) or analysed the same day (analyses performed at the Department of Clinical Chemistry, Vestfold Hospital Trust, all Papers). Spot morning urine samples were collected and analysed the same day (Paper III).

4.3.2. Biochemical assays

At the Department of Clinical Chemistry at Vestfold Hospital Trust analyses of serum blood lipids and serum glucose were performed using dry reagent slide technology on the Vitros 950 Analyzer until November 2006 and the Vitros FS 5.1 Analyzer (Ortho-Clinical Diagnostics, New York, NY) thereafter. Furthermore, HbA1c was analysed using high performance liquid

chromatography on Tosoh HLC-723 G7 (Tosoh Corporation, Tokyo, Japan), and albumin and creatinine in urine were analysed using Konelab 60i (Thermo Electron Corporation, Helsinki, Finland) until August 2008 and Vitros FS 5.1 Chemistry System thereafter.

At the Endocrine Laboratory at Oslo University Hospital Rikshospitalet serum levels of insulin, c-peptide, pro-insulin were measured by radio immunoassay (Insulin Coat-A-Count, DPC, Los Angeles, CA), whilst serum levels of C-reactive protein (R&D systems, Minneapolis, MN, USA) and adiponectin (R&D systems) were measured using enzyme immunoassays on stored samples. All samples were measured in duplicate and serial samples from a given individual were run at the same time (insulin, C-peptide and proinsulin). Intra- and inter-assay coefficients of variation (CV) were < 10 % for all assays.

For measurements of glucose in serum or plasma (during OGTT) at the other laboratories in the health region automated instruments using either a hexokinase or a glucose oxidase method were used [Vitros 950 and Vitros FS 5.1 (Ortho-Clinical Diagnostics), Aeroset and Architect (Abbott Diagnostics), Advia 1650 and Advia 1800 (Siemens), Cobas Integra 800 and Cobas 6000 (Roche)]. Furthermore, plasma calibrated capillary whole blood glucose concentrations were analyzed with portable instruments [Precision PCx (Abbott Diagnostics) or Accu-Check Sensor (Roche Diagnostics)].

At the Hormone Laboratory at Oslo University Hospital Aker insulin was analysed in serum by radioimmunoassay (Linco Research Inc, St. Charles, MO, and DiaSorin, Stillwater, MN) within 1 week of blood sampling. The inter-assay CV for insulin was 8 %.

4.4. Statistics

4.4.1. Sample size calculation for The MOBIL study

The sample size of the MOBIL study was calculated (80 % statistical power, α-level of 0.05, and equal distribution to the treatment groups) based on anticipated remission rates of type 2 diabetes and obstructive sleep apnoea. Given remission rates of type 2 diabetes of 70 % in the surgery group and 20 % in the lifestyle group, at least 30 subjects with type 2 diabetes were required. Expecting a prevalence of type 2 diabetes of 25 % and a dropout rate of 30 % from the screening examinations, a minimum of 172 subjects were required for screening.

4.4.2. Statistical analyses

Data are presented as mean [standard deviation (SD)], median (25th and 75th percentiles) or number (%) unless otherwise specified. Skewed data were transformed using natural logarithms to approximate normality. Unadjusted between groups differences were analysed using independent samples t-test, one- and two-way analysis of variance (ANOVA) or Mann-Whitney U test for continuous variables and Chi-square or Fisher`s exact test for categorical data. Within-group comparisons were performed using paired samples t-test or Wilcoxon signed-rank test for continuous variables and McNemar test for dichotomised variables. Post-hoc testing was done with least significant difference tests. Correlations were calculated with Pearson's correlation coefficients. For all analyses a two-tailed $P < 0.05$ was considered significant. The analyses were implemented using SPSS 16.0 (SPSS, Chicago, IL).

In Paper I, ROC curve analysis was employed to determine the diagnostic accuracy of fasting glucose to predict a 2-hour glucose concentration ≥ 11.1 mmol/L. The diagnostic accuracy of the test is presented as an area under the curve (AUC) [95 % confidence interval (CI)], where AUC equal to 1 is the optimal value. The optimal cut off value of fasting glucose was

obtained using the Youden index, maximising sensitivity and specificity (sensitivity + specificity – 1) (216).

In Paper II, logistic regression analyses were performed to study the association of anthropometric characteristics (continuous and standardized variables) with prevalent type 2 diabetes. Odds ratios (ORs) per one SD increase in the anthropometric variable for type 2 diabetes were calculated in both unadjusted and adjusted models.

In Paper III and IV, adjusted between-group changes in outcome variables were assessed using analysis of covariance (ANCOVA). Furthermore, regression analyses were used to identify the effect of treatment choice and predictors of changes in outcome variables.

In Paper IV, linear regression analyses were used to 1) explore a potential hyperbolic relationship between HOMA S and measures of insulin secretion [95% CI of the specialised regression coefficient (β) in the equation ln (insulin secretion) = constant + β x ln (insulin sensitivity) must include -1 and exclude 0].

4.5. Ethics

4.5.1. Approvals

Written informed consent was provided by all participants. The Morbid Obesity Biobank Registry has been approved by the regional ethics committee of what was formerly the Southern Norway Regional Health Authority (Reference number S-05175), the Norwegian Social Science Data Service (Reference number 14029) and the former The Directorate for Health and Social Affairs (Reference number 06/530). The MOBIL study was approved by the regional ethics committee of what was formerly the Southern Norway Regional Health

Authority and was registered in the ClinicalTrials.gov-registry under the unique trial number NCT00273104.

4.5.2. Funding

This work has been supported by unrestricted grants from Novo Nordisk A/S, Vestfold Hospital Trust and South-Eastern Norway Regional Health Authority to DH. One of the co-authors of Paper III (TIK) is one of the founders of Evjeklinikken A/S and is a former board member (until November 2008) and stockholder (until August 2009). He is now a PhD-student at the Morbid Obesity Centre and is supported financially by Evjeklinikken A/S. All the other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

5. Results

Paper I

The primary objective of this study was to assess the effectiveness of fasting glucose to detect undiagnosed diabetes in morbidly obese subjects. Among the 1 253 participants 46 % had NGT, 8 % had isolated IFG, 16 % had IGT and 31 % had type 2 diabetes of which those with screen-detected diabetes accounted for 8 percentage points. The ROC curve analysis showed that fasting glucose was highly accurate in predicting a diabetic 2-hour glucose concentration in subjects with unknown glucose tolerance status (n = 670); AUC (95 % CI) 0.93 (0.89-0.98). The optimal fasting glucose cut off value was 6.5 mmol/l with corresponding sensitivity and specificity values of 88 % and 89 %, respectively.

Among patients with screen-detected diabetes 80 % (53 out of 66) had elevated fasting glucose whereas only 20 % (13 out of 66) had isolated elevated 2-hour glucose. Performing an OGTT in subjects with fasting glucose between 6.1 and 6.9 mmol/l would identify 77 % (10 out of 13) of those with isolated elevated 2-hour glucose. Taken together, 95 % [80 % (53 out of 66) by fasting glucose and 15 % (10 out of 66) by 2-hour glucose] of all subjects with unknown type 2 diabetes would be identified if subjects with a fasting glucose level between 6.1 and 6.9 mmol/l underwent a confirmatory OGTT.

Paper II

This paper reports the relationship between various measurements of obesity and type 2 diabetes in subjects with BMI $\geq$ 40 kg/m^2. Out of 1 003 subjects 267 (27 %) had type 2 diabetes. The regression analyses showed that WC, WHR and NC were independently and positively associated with type 2 diabetes. By contrast, HC was negatively associated with type 2 diabetes, and no association between BMI and type 2 diabetes was found.

Paper III

In this paper we compared the effect of bariatric surgery (n = 80) and intensive lifestyle intervention (n = 66) on type 2 diabetes and obesity-related cardiovascular risk factors. Among the 76 completers in the surgery group and the 63 completers in the lifestyle group mean (SD) one year weight loss was 30 (8) % and 8 (9) %, respectively. Although both treatment groups experienced improvements in nearly all measures of obesity, blood pressures, lipids, glucose metabolism and inflammatory markers, the improvements were significantly greater after surgical treatment than after lifestyle intervention. Multi-adjusted regression analyses showed that weight loss, but not treatment choice, was significantly associated with reduction in HbA1c ($P = 0.008$) and systolic blood pressure ($P = 0.001$).

Remission rates of type 2 diabetes and hypertension were significantly higher in the surgery group than the lifestyle intervention group; 70 % versus 33 %, $P = 0.027$; and 49 % versus 23 %, $P = 0.016$. No usage of glucose lowering agents and anti-hypertensive drugs at baseline were, independent of percentage weight change and treatment choice, associated with remission of type 2 diabetes ($P = 0.023$) and hypertension ($P < 0.001$).

The surgery group experienced a significantly greater reduction in the prevalence of metabolic syndrome (76 % to 18 % versus 70 % to 48 %, $P < 0.001$), albuminuria (15 % to 6 % versus 13 % to 19 %, $P = 0.012$) and electrocardiographic left ventricular hypertrophy (17 % to 4 % versus 11 % to 8 %, $P = 0.046$) than the lifestyle group. There was a greater increase in the physical activity level of the lifestyle group than the surgery group ($P = 0.022$).

Overall, complications occurred more often after gastric bypass than after lifestyle intervention. Gastrointestinal symptoms developed more frequently after gastric bypass than

lifestyle intervention, 48 % versus 7 %, $P < 0.001$. Five surgically treated patients reported symptomatic postprandial hypoglycaemia. There were no deaths.

Paper IV

In this paper we compared the effect of intensive lifestyle intervention (n = 55) and Roux-en-Y gastric bypass surgery (n = 64) on beta cell function. The patients were classified as having either NGT or AGT. In addition, 29 normal weight subjects with NGT served as controls. Insulin secretion relative to insulin sensitivity (DI) increased more after surgical treatment than after lifestyle intervention ($P < 0.001$), with no effect of glucose tolerance status at baseline ($P = 0.323$). The reduction in stimulated PI/I ratio was greatest after surgical treatment ($P < 0.001$) and was most pronounced among those with AGT ($P < 0.001$). Notably, at one year DI was higher and stimulated PI/I ratio lower in surgically treated patients with NGT at baseline than in the NGT controls ($P < 0.001$ and $P = 0.027$, respectively).

Multiple linear regression analyses showed that both surgical treatment and weight reduction independently predicted increase in DI ($\beta = 0.337$, $P = 0.008$, and $\beta = -0.329$, $P = 0.008$, respectively). By contrast, only surgical treatment independently predicted reduction in stimulated PI/I ratio ($\beta = -0.339$, $P = 0.022$).

6. Discussion

The main results of the papers included in this thesis are: 1) Fasting glucose identifies four out of five morbidly obese subjects with unknown type 2 diabetes. 2) Measures of central obesity, and not BMI, are associated with type 2 diabetes in extremely obese patients. 3) Gastric bypass surgery improves obesity-related cardiovascular risk factors and beta cell function to a significantly greater extent than intensive lifestyle intervention. This section of the thesis will discuss methodological aspects, compare the results with other studies, state possible implications and suggest topics for future research.

6.1. Methodological considerations

The main limitations and strengths of the studies are summarised in Table 6.

Table 6. Main limitations and strengths of the studies

Paper	Limitations	Strengths
Paper I	Missing OGTTs	Clinically relevant
	Few patients with screen-detected diabetes	
Paper II	Cross-sectional design	Large study sample
Paper III-IV	Non-randomised design	Controlled study
		Few drop-outs
Paper IV	Non-validated indices of beta cell function	Frequent samples OGTTs

6.1.1. Study designs and statistics

Patients included in the studies presented in this thesis were recruited from a tertiary health care centre exclusively treating morbidly obese patients. Therefore, it is possible that the referral of patients to our centre might have introduced a sampling selection bias (tendency of

a sample to exclude or include some members of the sampling universe). Moreover, as the definition of morbid obesity is not solely dependent upon BMI but also takes into account obesity related co-morbidities, the prevalence of obesity related co-morbidities among patients with BMI between 35 and 40 kg/m^2 may have be especially high and differ from the general population. This may have reduced the external validity of the results of the studies reported in this thesis. Caution should therefore be used when generalising the results to all grade II and III obese subjects.

No adjustments for multiple comparisons were made in any of the studies. However, most of the between group differences were highly significant and adjustments for multiple comparisons would probably not have influenced the main conclusions of the studies.

Paper I

The high proportion of missing OGTTs in Paper I may have resulted in a systematic difference (selection bias) between subjects who did and did not perform the OGTT. Despite similar fasting glucose values in the two groups, we cannot exclude that important differences between these groups may have influenced the results. This may have reduced the internal validity of this paper.

The sample size was relatively large (n = 1 253). However, only 66 subjects had screen-detected diabetes and only a very few (n = 13) had an isolated diabetic 2 hour glucose concentration. Accordingly, the glucose values of the subjects with screen-detected diabetes had a major impact on the results. Small changes in glucose values could potentially have resulted in relatively large changes in the percentages reported. This should be kept in mind when evaluating the accuracy of the results of the ROC curve analysis in this subgroup.

Paper II

As mentioned, the prevalence of obesity-related conditions may, due to the definition of morbid obesity, be artificially high in subjects with BMI between 35 and 40 kg/m^2. To avoid sampling selection bias, only subjects with BMI ≥ 40 kg/m^2 were considered for inclusion in this study. As this study had a cross-sectional design it cannot be used to identify causal relationships. Therefore, we cannot, based upon the results in this study, determine whether central obesity causes type 2 diabetes or vice versa.

The sample size was relatively large (n = 1 003). Still, we cannot exclude the possibility that the lack of association between BMI and waist-to-height ratio and type 2 diabetes may be due to limited power (type 2 errors).

Paper III and IV

Random allocation of different treatment strategies to study participants is preferable when conducting clinical trials. The most important advantage of this design is that it enhances the internal validity (difference in outcomes is related to the intervention) of the study by minimising selection bias and confounders. According to Norwegian guidelines, treatment seeking morbidly obese subjects should be offered either conservative or surgical therapy (217). For this reason we considered it unethical to assign patients to surgery if they qualified for a lifestyle intervention programme and preferred this course of treatment to surgery. This stance also held vice-versa. The MOBIL study therefore had a non-randomised design. Although not randomised, the MOBIL study is one of a few studies that actually compare the effects of bariatric surgery and lifestyle intervention on obesity-related health outcomes. Importantly, some baseline differences were observed (the surgery group was younger and heavier). These factors could influence the outcomes and are therefore potential confounding

factors. In an attempt to cope with these differences, adjustments for baseline differences and changes in relevant medications were made when the effects of treatment choice were calculated. Still, we cannot exclude the possibility that factors not included in the statistical analyses could have influenced the results.

Drop-outs can also result in selection biases. However, due to the low drop-out rate in the MOBIL study, it is not likely that this has influenced the result significantly. This is supported by the last observation carried forward analyses in Paper III which showed that the main conclusions of the study were not altered by these analyses.

All patients in the MOBIL study followed routine care pathways and were given the same priority for treatment as other patients. Due to a waiting list for bariatric surgery at our institution, the time from inclusion to intervention was significantly longer for the surgery group than the lifestyle group. Since no re-registrations were made immediately before the start of treatment, we cannot exclude the possibility that changes in weight, medications and metabolic variables occurred prior to, and not after, the interventions.

The sample size of the MOBIL study was calculated based on expected remission rates of type 2 diabetes (and obstructive sleep apnoea). Despite a higher remission rate of type 2 diabetes in the lifestyle group than expected, significant differences between the groups were observed due to a higher number of diabetic subjects than originally anticipated.

6.1.2. Data quality

All the anthropometric measures were performed in a standard manner. Despite standardised measuring techniques, we cannot exclude the possibility that inter-individual differences may

have affected the results. It should also be noted that measuring body circumferences in morbidly obese subjects is challenging and may limit, due to inaccurate measures, their usage in predicting cardiovascular risk (218).

Blood glucose measurements may, due to biological and analytic variability, vary considerably from day-to-day (219). For these reasons, the diagnoses of type 2 diabetes should be based on repeated measurements (63). In the studies included in this thesis serum glucose was measured at one occasion, and this may have overestimated the number of diabetic patients not using hypoglycaemic drugs. However, in epidemiological studies one glucose measurement is sufficient for the diagnosis of type 2 diabetes (220). Similarly, in Paper III blood pressure and albumin and creatinine in urine were measured only once.

Paper I included glucose measurements from OGTTs performed in eight laboratories using different analysing methods. In addition, glucose was measured in plasma, serum and capillary blood, and the time from sampling to analysing differed slightly (30 to 60 minutes) between the laboratories. Glucose concentration in uncentrifuged blood declines approximately 0.3 to 0.6 mmol/l per hour due to glycolysis (221,222). This could potentially have resulted in a selection bias. However, the fact that there was no significant ($P = 0.109$) difference in fasting glucose between the laboratories indicates that the impact of including glucose measurements from different laboratories was minor.

In Paper III left ventricular hypertrophy was identified based on electrocardiographic characteristics. The Cornell voltage criteria was used since this index is less influenced by the presence of obesity (223) and weight reduction (224) than other more commonly used indices. Moreover, regression of electrocardiographic left ventricular hypertrophy identified by the

Cornell voltage criteria is known to predict regression of echocardiographic left ventricular hypertrophy (225). However, the Cornell voltage criteria only has a 54 % sensitivity for detecting left ventricular hypertrophy (226) and imaging techniques for the estimation of ventricle mass would therefore have been preferable. Nevertheless, electrocardiographic left ventricular hypertrophy is a strong predictor of cardiovascular mortality in both subjects with hypertension and those without (227).

In Paper III dietary intake and physical activity were assessed through structured interviews performed by registered dieticians. Obese subjects are known to under-report food intake (228). Consequently, the actual energy intake is likely to be slightly higher than reported. Furthermore, based on self-reported physical activity levels patients were categorised as being either physically active or inactive. Similarly, the use of self-reported data may have reduced the internal validity of the results. The use of use accelerometers (229) or physical tests would have been preferable, but also more demanding, and were therefore not performed.

In Paper IV OGTT-derived indices were used for the estimation of beta cell function. The insulin secretion index included in the disposition index (first $phase_{est}$) has been validated against hyperglycaemic clamp (213). The usage of a disposition index requires a hyperbolic association between insulin secretion and insulin sensitivity (89). The combination of HOMA S and first $phase_{est}$ showed a non-linear relationship in subjects with NGT but did not fully satisfy the criteria for a hyperbolic relationship (Figure 7A). This is a limitation of the study and should be kept in mind when interpreting the results. In addition, none of the indices have been validated in post-bypass patients. The rearrangement of the intestinal tract seems to result in relatively enhanced glucose absorption with a prompter increase in serum glucose levels (Figure 7B). This may in turn affect serum insulin and proinsulin levels which are all

used for the calculation of these indices. It is therefore possible that changes in glucose absorption post-surgery may result in changes in insulin and proinsulin secretion that are not solely related to improved beta cell function. Indeed, one study has shown that the DI from OGTT data increased more than the intravenous glucose tolerance test derived DI after bariatric surgery (230).

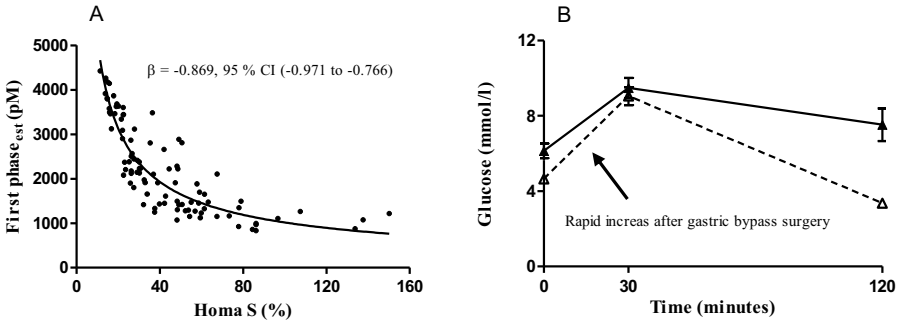

Figure 7. A The association between insulin secretion (first phase$_{est}$) and Homa S in 94 subjects with normal glucose tolerance showed a non-linear relationship that was close to hyperbolic (ideally the 95 % CI of β should have included -1). **B** Mean (95 % CI) serum glucose levels during the OGTT before (straight line) and after (dashed line) gastric bypass surgery in 64 morbidly obese subjects. Post surgery there was a prompter rise in glucose 30 minutes after the glucose load. Figures are based on data from Paper IV (231).

6.1.3. Ethnicity

The great majority of the study population was of Europoid origin, meaning that the results of this study cannot be generalised to include other ethnic groups.

6.2. In context with other studies

6.2.1. Screening for type 2 diabetes in morbidly obese subjects

Paper I showed that in morbidly obese patients fasting glucose ≥ 7.0 mmol/l identified 80 % of all subjects with unknown diabetes. In addition, we verified an extremely high prevalence of type 2 diabetes (31 %) in morbidly obese subjects (21).

A two step screening strategy was explored using fasting plasma glucose as a screening variable followed by an OGTT in subjects with fasting plasma glucose below the diagnostic level for type 2 diabetes. The results showed that fasting plasma glucose ≥ 7.0 mmol/l identified 80 % of all subjects with unknown diabetes (Figure 9). This is to some extent higher than reported in several lager population based studies (45 to 76 %) (232-236). However, previous reports have shown that obese and young people are more likely to be diagnosed by fasting plasma glucose than 2 hour plasma glucose (233,235,236). The relatively low age and the extreme obesity of participants in this study are probably the main reasons for the high proportion diagnosed by fasting plasma glucose. Indeed, two studies including surveys from southern hemisphere islands and from European populations reported the sensitivity of fasting plasma glucose to detect diabetes in obese subjects to be comparable with our findings, 78 % and 84 %, respectively (233,237). Moreover, increasing fasting plasma glucose levels up to the WHOs recommended cut-off value of 6.1 mmol/l only slightly reduced the sensitivity of fasting plasma glucose for detecting subjects with a diabetic 2 hour plasma glucose concentration. However, the proportion of subjects needing an OGTT was reduced substantially. If a confirmatory OGTT was used only if fasting plasma glucose was between 6.1and 6.9 mmol/l, 21 % of the population with unknown glucose tolerance would need an OGTT, and this strategy would identify 95 % of all subjects with unknown diabetes.

The same approach in a European population identified 82 % of the people with diabetes after testing 12 % of the population.

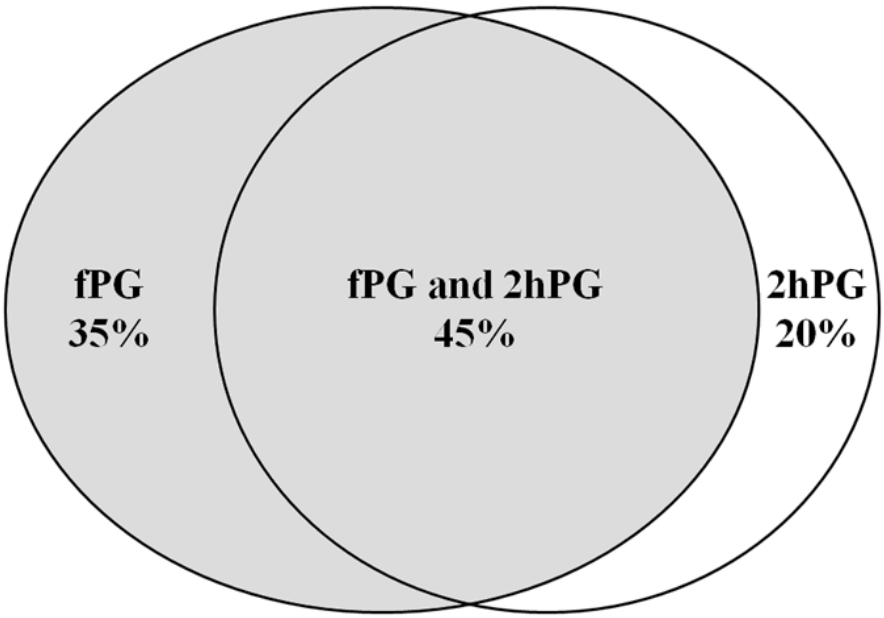

Figure 9. Overlap between screen-detected diabetic subjects (n = 66) diagnosed by a fasting plasma glucose (fPG) ≥ 7.0 mmol/L or a 2 hour plasma glucose (2hPG) ≥ 11.1 mmol/L. Reproduced from Hofsø et al. (238) with permission.

The results of Paper I indicate that fasting glucose followed by an OGTT in subjects at risk is an effective strategy for detecting undiagnosed type 2 diabetes. However, it is still not clear how diabetes screening should be performed and what the benefits of pro-active screening strategies would be. Interestingly, unpublished data from the ADDITION trial show that in patients with screen-detected diabetes intensive multifactorial treatment was not significantly better than routine care in preventing cardiovascular events (239). Partly in contrast with these findings, poor long-term glycaemic control during 20 years follow-up was associated with an

increased risk of death by ischemic heart disease in subjects with newly diagnosed diabetes (240).

6.2.2. Anthropometric measures and type 2 diabetes in extremely obese subjects

Paper II suggests that central, but not overall obesity is associated with prevalent type 2 diabetes in extremely obese individuals (Figure 8).

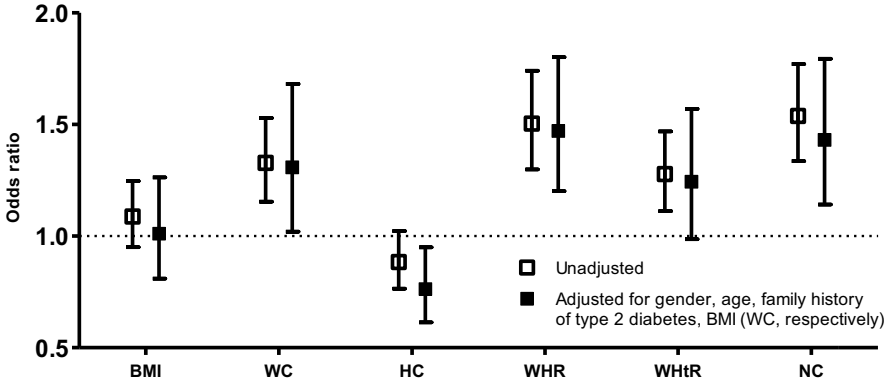

Figure 8. Odds ratios (vertical bars, 95% CIs) for having type 2 diabetes per one standard deviation (SD) increase in the anthropometric variable 1 003 extremely obese subjects. One SD: BMI, 5.5 kg/m2; waist circumference (WC), 13.7 cm; hip circumference (HC), 11.5 cm; waist-to-hip ratio (WHR), 0.10; waist-to-height ratio (WHtR), 0.07 and neck circumference (NC), 4.5 cm. Reproduced from Hofsø et al. (241) with permission.

The lack of association between BMI and type 2 diabetes is in contrast with several previous reports in normal weight to moderately obese patients (13-19,242,243). This may indicate that increasing BMI levels above 40 kg/m^2 do not necessarily translate into higher odds of having type 2 diabetes. Furthermore, our findings suggest that measures of central obesity may be useful predictors for type 2 diabetes in extremely obese subjects, as has been previously reported in less obese subjects (13-19,242). A 1 SD increase in WHR (0.10) and WC (14 cm) was associated with about 50 % and 30 % increased odds of having type 2 diabetes. In line

with some (13,18,242), but not all (14-17,19) reports, our data suggest that WHR may be a better predictor of type 2 diabetes than WC. In addition, the inverse association between HC and type 2 diabetes was strengthened after adjusting for confounding factors, as shown previously (13,18,242). Finally, previous reports have shown an association between NC and type 2 diabetes in white women from Canada and the US (13). Moreover, NC has been shown to correlate with both glucose and insulin in severely obese subjects (244). Our results extend these observations, showing an independent association between NC and type 2 diabetes in extremely obese individuals. The inclusion of HOMA S in the regression analyses attenuated the associations between the anthropometric characteristics and type 2 diabetes. This finding corresponds with results reported by Haffner et al. (243), suggesting that these associations might be mediated by insulin resistance.

6.2.3. Obesity-related cardiovascular risk factor after weight loss

The one year non-randomised controlled MOBIL study (Paper III) showed that obesity-related cardiovascular risk factors improved after both gastric bypass surgery and intensive lifestyle intervention. Importantly, the improvements were greater after surgical treatment.

This study was planned and initiated in 2005. By that time the beneficial effect of weight loss on obesity-associated medical complications was well known (122,124,245). Furthermore, two drugs available on the European market had proven effective in inducing and maintaining weight loss and in improving metabolic conditions (106-109). Similarly, bariatric surgery had demonstrated substantial weight loss and positive effects on numerous obesity related comorbidities (149-152,154,157,159,160,246). However, with the exception of the case-controlled SOS study (154), none of the studies included medically treated controls. The aim

of the MOBIL study was therefore to compare the effect of gastric bypass surgery and a comprehensive lifestyle intervention programme on several obesity related health conditions.

Several reports with great relevance to the field of obesity treatment have been published since the MOBIL study was initiated:

Bariatric surgery versus lifestyle intervention

- Three randomised controlled clinical trials from an Australian group comparing laparoscopic adjustable gastric banding and conventional therapy have shown that gastric banding results in greater weight loss and resolves type 2 diabetes and metabolic syndrome more effectively than conventional therapy (155,156,158).
- One non-randomised controlled Norwegian study showed that gastric bypass surgery resulted in greater weight loss than comprehensive lifestyle intervention programmes. However, the improvements in metabolic risk factors did not differ between the study groups (127).

Bariatric surgery

- Mortality data from the SOS study and a large retrospective cohort study indicate that bariatric surgery reduces mortality (171,172).
- A systematic review and meta-analysis by Henry Buchwald clearly demonstrates reduced 30-days mortality after bariatric surgery (173).

Medical treatment of obesity

- The randomised LookAHEAD trial has shown that in overweight and obese subjects with type 2 diabetes a mean weight loss of 6 % can be sustained for four years by combining diet modification and physical activity (125,126).

- Two US studies including extremely obese subjects reported 15 to 20 % weight loss after six months (129,131) and 10 % weight loss after 2 year by including low calorie diets in a lifestyle intervention programme (131).
- Due to their serious side-effects, sibutramine and rimonabant have been withdrawn from the European market (118,120).

In light of what was known when the MOBIL study was planned and new knowledge published the last five years, our results confirm that gastric bypass surgery results in greater weight reduction (30 % versus 8 %) and higher remission rates of type 2 diabetes and hypertension than intensive lifestyle intervention (Figure 10). Furthermore, we verify that modest weight reduction after intensive lifestyle intervention also improved several obesity-related cardiovascular risk factors. Lower mortality rates after bariatric surgery, as reported by Sjöström et al. and Adams et al., indicate that weight reduction may translate into increased survival (171,172). In the study by Adams et al. mortality caused by coronary artery disease was decreased significantly. Due to the lack of clinical data in this study it is impossible to estimate the potential effect of improvements in obesity-related cardiovascular risk factors on cardiovascular mortality. However, meta-analyses of intervention trials have shown that 1 mmol/l reduction in low density lipoprotein cholesterol, 10/5 mmHg reduction in blood pressure and 0.9 % reduction in HbA1c is associated with a reduction in fatal and non-fatal myocardial infarction and sudden death of 23, 22 and 9.7 %, respectively (247). Based on these figures and our own results (reduction in low density lipoprotein cholesterol, blood pressure and HbA1c after surgery: 1.0 mmol/l, 14/12 mmHg and 0.4 %, respectively) we might speculate that the reduction in death caused by coronary artery disease after bariatric surgery is most likely mediated by the improvements in cholesterol and blood pressure and to a lesser extent by the improved glycaemic control.

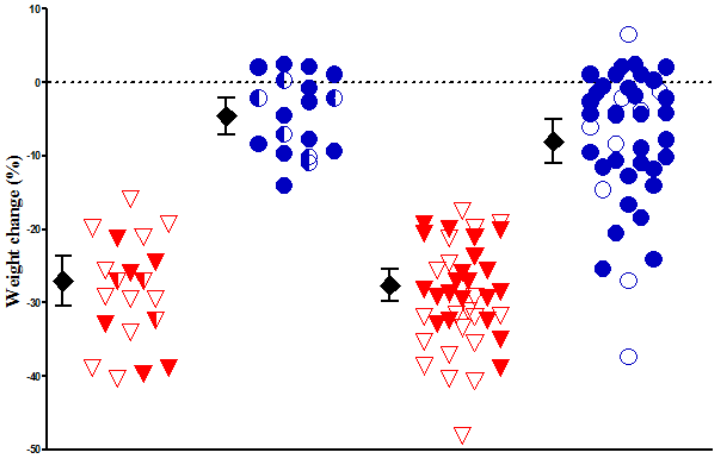

Figure 10. Remission of type 2 diabetes and hypertension at one year correlated to percentage weight change in individuals treated with gastric bypass surgery or intensive lifestyle intervention. Red triangles represent patients treated with gastric bypass, whilst blue circles represent subjects who chose lifestyle intervention. Open triangles/circles denote complete remission of type 2 diabetes and remission of hypertension, half filled triangles/circles denotes partial remission of type 2 diabetes, and filled triangles/circles denote no remission. Mean percentage weight changes (black diamonds) within the groups are shown with bars extending from the diamonds representing 95% CI. Odds ratios (OR) were calculated using logistic regression analyses. Combined (partial and complete) remission of type 2 diabetes was used in the analysis. Reproduced from Hofsø et al (199), no permission required.

Physical activity level increased slightly more in the lifestyle group than in the surgery group. Increase in physical fitness has been shown to reduce mortality (248,249). If increased physical activity translates into improved physical fitness, this could potentially have a positive effect on mortality rates.

Lower mean weight reduction in the MOBIL study than in two Scandinavian studies (127,128) also using specialised rehabilitation centres may be due to the short duration of stay (7 weeks versus 16 to 21 weeks) at the centre in the present study. These findings may indicate that weight loss is related to the intensity and duration of the lifestyle intervention programme. The programme at Evjeklinikken focused mainly on physical activity and no special diet or weight loss drugs were prescribed routinely. However, the patients were encouraged to follow the guidelines of the Norwegian National Council of Nutrition (200). Systematic use of low calorie diets and weight loss drugs could potentially have increased the weight loss.

6.2.4. Beta cell function after weight loss

Gastric bypass surgery improved beta cell function to a significantly greater extent than intensive lifestyle intervention.

As is reported in most intervention studies, our data indicate improved beta cell function after lifestyle intervention (250-252) and bariatric surgery (230,253,254). Figure 11 shows that the first $phase_{est}$ in relation to HOMA S shifted to the right after treatment in both the surgery and lifestyle groups. These findings are consistent with increased insulin secretion relative to insulin sensitivity after both interventions. However, the DI increased significantly more after surgical treatment than lifestyle intervention in both glucose tolerance groups

In contrast, insulin secretory capacity to intravenous glucose in subjects with NGT or IGT did not change one year after gastric bypass when accounting for prevailing insulin sensitivity (255). This discrepancy may illustrate the impact of different techniques for calculating DI (intra venous versus per oral) as discussed previously (230). Since improvement in DI was

independently associated with weight reduction, a greater weight loss in the surgery groups than in the lifestyle groups could explain some of the differences. However, it should be noted that surgical treatment also independently predicted improvements in DI and that improvements in stimulated PI/I ratio was associated with surgical treatment and not with weight reduction. The latter findings indicate that the improvements in beta cell function may be partly related to the surgical procedure *per se* and not only to weight reduction.

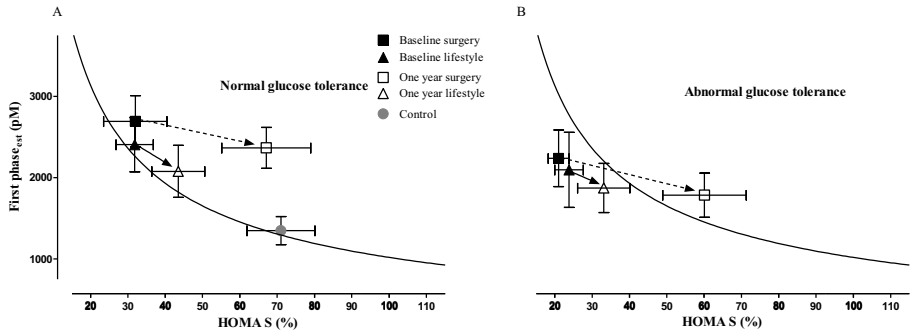

Figure 2. Mean HOMA-S plotted against first phase$_{est}$ in controls and morbidly obese subjects with normal glucose tolerance (A) and abnormal glucose tolerance (B) before and one year after gastric bypass and lifestyle intervention. The curve represents the regression line of the natural logarithm of estimated insulin secretion as a linear function of the natural logarithm of estimated insulin sensitivity for all participants with normal glucose tolerance at baseline. Based on data from Paper IV (231).

One year after surgery, there was a high prevalence (7 %) of post-challenge hypoglycaemia. As demonstrated in this and previous studies, excessive insulin secretion may occur after gastric bypass (183,254). Rapid absorption of glucose after bypass surgery may, as discussed previously, in turn stimulate insulin secretion and thereby contribute to the observed hyperinsulinaemia. However, it is also very likely that other factors are involved, and a few publications have recently addressed this phenomenon (182,183). Some researchers argue that

post-gastric bypass hyperinsulinaemia may be explained by the increase in gut hormones such as glucagon-like peptide 1 and gastric inhibitory peptide which follow the rearrangement of the intestine (183,254). Alternatively, but not mutually exclusive, pathologic overgrowth of pancreatic beta cells after bypass surgery, possibly stimulated by glucagon-like peptide 1 may result in hypersecretion of insulin (182). Interestingly, a large Swedish nationwide cohort study showed that patients who had undergone gastric bypass had an increased risk of hospitalisation for hypoglycaemia and related diagnoses (256). This underscores the clinical relevance of this phenomenon. Compared to the Swedish study, we report a much higher incidence of symptomatic post-challenge hypoglycaemia. This may indicate that the problems associated with post-gastric bypass hypoglycaemia are under-diagnosed.

6.3. Clinical implications

A two-step screening approach including fasting glucose followed by an OGTT in subjects with IFG is an effective screening strategy and identifies 95 % of all morbidly obese subjects with unknown type 2 diabetes. This screening strategy could be used at institutions treating morbidly obese patients.

Measures of central obesity seem to be more strongly associated with type 2 diabetes than general obesity in extremely obese subjects. These findings highlight the impact of abdominal fat accumulation on type 2 diabetes. However, due to the high prevalence of type 2 diabetes in this population, all subjects should, independent of body composition, be tested for type 2 diabetes.

Although gastric bypass surgery is more effective than lifestyle intervention in terms of improving obesity-related cardiovascular risk factors and beta cell function, both treatments

should, due to the safety concerns associated with the surgical treatment, be offered to all treatment seeking morbidly obese subjects. The MOBIL study also demonstrates the limitations of both the surgical and medical treatment of obesity. From a societal perspective the prevention of obesity is probably just as important as the treatment of obesity. It is therefore of paramount importance that changes are made within society that promote healthy living (1,257).

6.4. Topics for future research

The beneficial effects of screening for type 2 diabetes are not fully known. The effects of early detection and treatment of diabetes on micro- and macro-vascular outcomes and mortality are therefore relevant topics for future studies. In addition, the validation of alternative screening strategies (questionnaires and HbA1c) for the detection of type 2 diabetes is also a potential research avenue.

Positive effects on type 2 diabetes and obesity-related cardiovascular risk factors after bariatric surgery and lifestyle intervention have been documented. However, several questions remain unanswered: 1) Are the improvements after gastric bypass surgery related only to weight reduction or is there an independent effect of the gastrointestinal rearrangement? 2) Can bariatric procedures other than gastric bypass surgery yield similar or better results with lower complication rates and fewer side-effects? 3) How can lifestyle interventions be optimised? 4) How can the subjects who will benefit the most from the different treatments be identified? These are all relevant questions that should be addressed in future mechanistic and clinical studies.

The mechanism by which weight-loss after gastric bypass surgery and lifestyle intervention improves beta cell function is not fully understood. Future studies addressing this question should be longitudinal, use both intravenous and oral techniques for the estimation of beta cell function and include gut hormones.

7. Conclusions

When screening for type 2 diabetes in morbidly obese subjects a two-step screening approach, fasting glucose followed by a supplemental OGTT in selected subjects, identified the great majority of subjects with undiagnosed type 2 diabetes.

Measures of central obesity, and not BMI, were independently associated with type 2 diabetes in extremely obese subjects.

Type 2 diabetes and obesity-related cardiovascular risk factors improved after both gastric bypass surgery and intensive lifestyle intervention. However, the improvements were greatest in those patients treated with gastric bypass.

Gastric bypass surgery improved beta cell function to a significantly greater extent than intensive lifestyle intervention. Supra-physiological insulin secretion and proinsulin processing may indicate excessive beta cell function after gastric bypass surgery.

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III

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CLINICAL STUDY

Obesity-related cardiovascular risk factors after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention

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Abstract

Objective: Weight reduction improves several obesity-related health conditions. We aimed to compare the effect of bariatric surgery and comprehensive lifestyle intervention on type 2 diabetes and obesity-related cardiovascular risk factors.

Design: One-year controlled clinical trial (ClinicalTrials.gov identifier NCT00273104).

Methods: Morbidly obese subjects (19–66 years, mean (S.D.) body mass index 45.1 kg/m^2 (5.6), 103 women) were treated with either Roux-en-Y gastric bypass surgery ($n=80$) or intensive lifestyle intervention at a rehabilitation centre ($n=66$). The dropout rate within both groups was 5%.

Results: Among the 76 completers in the surgery group and the 63 completers in the lifestyle group, mean (S.D.) 1-year weight loss was 30% (8) and 8% (9) respectively. Beneficial effects on glucose metabolism, blood pressure, lipids and low-grade inflammation were observed in both groups. Remission rates of type 2 diabetes and hypertension were significantly higher in the surgery group than the lifestyle intervention group; 70 vs 33%, $P=0.027$, and 49 vs 23%, $P=0.016$. The improvements in glycaemic control and blood pressure were mediated by weight reduction. The surgery group experienced a significantly greater reduction in the prevalence of metabolic syndrome, albuminuria and electrocardiographic left ventricular hypertrophy than the lifestyle group. Gastrointestinal symptoms and symptomatic postprandial hypoglycaemia developed more frequently after gastric bypass surgery than after lifestyle intervention. There were no deaths.

Conclusions: Type 2 diabetes and obesity-related cardiovascular risk factors were improved after both treatment strategies. However, the improvements were greatest in those patients treated with gastric bypass surgery.

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Introduction

Obesity (body mass index (BMI) ≥ 30 kg/m^2) and its metabolic consequences, hyperglycaemia and high blood pressure, are major risk factors of cardiovascular morbidity and mortality (1, 2). Alongside tobacco usage and physical inactivity they represent the five leading global risks to mortality (3). In addition, several other cardiovascular risk factors, such as metabolic syndrome, albuminuria, left ventricular hypertrophy and low-grade inflammation, are all closely associated with obesity (4–7).

As the prevalence of obesity, and especially extreme obesity, has dramatically increased in the last few decades (8), so too has the usage of bariatric surgery to treat morbid obesity (BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with at least one obesity-related comorbidity) (9). Currently, the most commonly performed bariatric procedure worldwide is the Roux-en-Y gastric bypass surgery (9). Several studies have documented how obesity surgery allows for large weight reduction and improvements in obesity-related conditions (10–15). Furthermore, comprehensive lifestyle intervention programmes have also demonstrated, although to a lesser extent, significant short-term weight reduction and improvements in cardiovascular risk factors in moderate to severely obese subjects (16–19). Importantly, increased physical activity, a pivotal component of all lifestyle intervention programmes, has been shown to have positive metabolic effects beyond weight reduction (20). However, only two controlled clinical trials have compared the effect of

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bariatric surgery and conventional therapy on the resolution of diabetes and cardiovascular risk factors (10, 11). In these studies, the average weight loss in the non-surgically treated groups was negligible. Not all morbidly obese subjects are suitable for bariatric surgery and therefore non-surgical treatment alternatives are needed.

The objective of this 1-year non-randomised controlled clinical trial was to compare the effect of Roux-en-Y gastric bypass surgery and a comprehensive lifestyle intervention programme on type 2 diabetes and obesity-related cardiovascular risk factors.

Subjects and methods

Study design and participants

This study was conducted at a public tertiary care centre at Vestfold Hospital Trust, Tønsberg, Norway.

Although preferable when conducting a clinical trial, we did not find randomisation to be appropriate. According to Norwegian guidelines, treatment seeking morbidly obese subjects should be offered either conservative or surgical therapy (21). We therefore considered it unethical to assign patients to surgery if they qualified for a lifestyle intervention programme and preferred this course of treatment to surgery. This stance also held vice versa.

In order to participate in the non-randomised controlled morbid obesity treatment, bariatric surgery versus intensive lifestyle intervention (MOBIL) study consecutive patients were pre-screened between December 2005 and May 2006 (Fig. 1). The MOBIL study aimed to address changes in several health outcomes related to obesity. Clinical and laboratory examinations were performed during pre-screening. Furthermore, patients who satisfied the criteria for bariatric surgery (22) and wanted either gastric bypass surgery or intensive lifestyle intervention were referred to a screening examination which included an oral glucose tolerance test, a somnography, pulmonary function tests, quality of life questionnaires and a structured dietary interview. All patients underwent a thorough assessment conducted by a multidisciplinary team consisting of an internist, a dietician and, in cases of surgery, a surgeon before treatment. These health professionals provided complete information about the possible risks and benefits of an operation and encouraged patients to incorporate their own values and preferences into the decision-making process. Each patient and their physician agreed together upon the most appropriate choice of therapy. The elapsed period of time between the pre-screening examination and the screening examination was 18 weeks (11); this did not differ significantly between the study groups ($P=0.063$). By contrast, the time between the screening examination and either the date of surgery or the start of lifestyle intervention was significantly longer in the surgery group than in the lifestyle group, 65 weeks (14) versus 19 weeks (15) ($P<0.001$). One-year follow-up was completed by June 2009. This article reports changes in weight, glucose- and lipid metabolisms, blood pressure, albuminuria, left ventricular hypertrophy, low-grade inflammation, energy intake and physical activity.

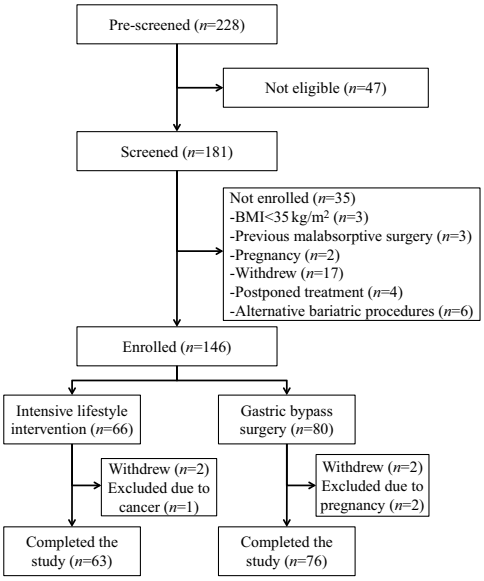

Figure 1 Flow of participants throughout the study.

The study was approved by the regional ethics committee of what was formerly known as the Southern Norway Regional Health Authority. The study is registered in the ClinicalTrials.gov-registry under the unique trial number NCT00273104. Written informed consent was provided by all the participants.

Intervention

Both treatment groups were seen by an internist half yearly and by a dietician when required. Changes in medications were made on an individual basis by both the patients' general practitioner and by hospital physicians.

Patients in the surgical group completed a low-calorie diet (3.3–3.8 MJ/day) in 3–6 weeks preceding surgery. A Roux-en-Y gastric bypass surgery was performed laparoscopically in 74 of the 76 surgically treated patients. The gastric pouch was about 25 ml, while the intestinal limb lengths were measured as follows: alimentary limb, median 120 (range 80–250) cm; biliopancreatic limb, median 100 (range 50–170) cm; and common channel, variable length. The bariatric

surgeons tended to choose longer limbs in the heaviest patients. After surgery, a standardised regimen of dietary supplements (23) and a proton pump inhibitor were prescribed to all patients. Patients with a high risk of venous embolism were prescribed low-molecular weight heparin. During follow-up, patients allocated to surgery were examined by a bariatric surgeon 6 weeks post surgery, while groups of patients were seen by a dietician quarterly. To optimise the result of the procedure patients were encouraged, both before and after the surgery, to normalise their eating behaviour and to increase their physical activity level.

The majority (59/63) of patients in the lifestyle group were referred to a rehabilitation centre specialising in the care of morbidly obese patients (Evjeklinikken). Using a cognitive approach the programme at this centre aimed to induce a weight loss of at least 10%. Each patient was motivated to increase their physical activity and to normalise their eating habits. The 1-year lifestyle programme comprises four stays at the rehabilitation centre lasting for either 1 week or 4 weeks (Fig. 2). The daily programme was divided between organised physical activity (3–4 h) and different psychosocially oriented interventions. The interventions involved individual consultations with a medical doctor, a nutritionist, a physiotherapist and a trained nurse. Those leading the counselling interviews were trained in motivational interviewing, a client-centred counselling style that aims to invoke behaviour change. The patients also took part in group sessions focusing on emotional aspects of sedentary behaviour as well as classroom lessons on topics related to nutrition, physical activity and co-morbidities. No special diet or weight-loss drugs were prescribed, but patients were encouraged to follow the guidelines of the Norwegian National Council of Nutrition (24), which recommend that the daily intake of protein, fat, carbohydrate and alcohol should account respectively for 10–20, <30, 50–60 and $<5\%$ of energy consumed. Outside of these stays, patients were contacted by phone once every 2 weeks. They were encouraged to self-monitor their eating habits and physical activities, as well as to visit their general practitioner for a consultation and weight control check once every 4 weeks. The remaining four participants were allocated to two rehabilitation centres with comparable intervention programmes. Fifty-four patients (86%) attended all scheduled centre visits.

Outcome variables

Demographic and clinical data were recorded on standardised forms. Height, weight and waist and hip circumferences were measured with patients in an upright position wearing light clothing and no shoes.

A 75 g oral glucose tolerance test was performed at 0800 h after an overnight fast. Type 2 diabetes was diagnosed in patients who used glucose-lowering agents or had fasting serum glucose ≥ 7.0 mmol/l and/or 2 h serum glucose ≥ 11.1 mmol/l (25). Remission of diabetes was defined as either partial (serum glucose levels below the diagnostic cut-off values and HbA1c $<6.5\%$) or complete (fasting serum glucose <5.6 mmol/l, 2 h glucose <7.8 mmol/l and HbA1c $<6.2\%$) in the absence of glucose-lowering agents (26). Combined remission rates (partial and complete) are presented unless otherwise specified.

Blood pressure was measured three times after at least 5 min rest. The average of the second and third measurements was registered. Patients using anti-hypertensive drugs, as well as those with systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg (27) were categorised as having hypertension. Remission of hypertension was defined as blood pressure below the diagnostic cut-off values in the absence of anti-hypertensive drugs.

Metabolic syndrome was defined according to the modified ATP III criteria (28). Albuminuria was defined as present if the albumin to creatinine ratio was ≥ 2.5 mg/mmol in men and ≥ 3.5 mg/mmol in women (29). The product of QRS complex duration times Cornell voltage combination ($R_{aVL}+S_{V3}$, with 6 mm added in women) was used with a threshold value of 2440 mm$\times$ms to identify electrocardiographic left ventricular hypertrophy (30). Regression of electrocardiographic left ventricular hypertrophy estimated by the Cornell voltage-duration product is known to predict regression of echocardiographic left ventricular hypertrophy (31).

Dietary intake and physical activity during the preceding year were assessed through structured interviews performed by registered dieticians. Data were recorded on an optically readable food frequency questionnaire (Department of Nutrition, University of Oslo, Norway). Similar questionnaires have been validated using weighted records (32). Questionnaire data were scanned using Teleform 10.0 (Cambridge, UK). Dietary intake was calculated using a database assembled from official food composition tables (Norwegian Nutrition Council, 1995). Calculations were computer driven (Kostberegningssystem 6.0; University of Oslo, Norway). Time spent performing light (e.g. casual walking), moderate (e.g. brisk walking) and vigorous (e.g. jogging) intensity aerobic physical activities in periods of 10 min or more was recorded. Participants who performed 150 min or more per week of moderately intense aerobic physical activities were considered to be physically active, as

Figure 2 Schedule of stays during the 1-year lifestyle programme at Evjeklinikken.

were those participants who performed 60 min or more per week of vigorously intense aerobic physical activities (33).

Perioperative (first 30 days) and late (after 30 days) complications were recorded in each patient's record file. In addition, all medical emergencies, hospitalisations and gastrointestinal side effects were reported on standardised self-report questionnaires. Reported symptomatic postprandial hypoglycaemia was documented by blood glucose <2.8 mmol/l (34). Complications and medical emergencies not recorded in each patient's record file at our hospital were verified by reports from other institutions.

Laboratory analyses

Blood samples were collected either in the fasting state or during the oral glucose tolerance test. Samples clotted 30 min at room temperature, and serum was separated by centrifugation. Analyses of blood lipids and glucose were performed by dry reagent slide technology on the Vitros 950 Analyzer until November 2006 and the Vitros FS 5.1 Analyzer (Ortho-Clinical Diagnostics, New York, NY, USA) thereafter. HbA1c was analysed using HPLC on Tosoh HLC-723 G7 (Tosoh Corporation, Tokyo, Japan).

Serum samples collected during the oral glucose tolerance test were either stored at -80 °C or analysed on the day of collection (glucose). Insulin, C-reactive protein and adiponectin were measured in stored serum obtained before the glucose ingestion. Insulin was analysed using an RIA (Millipore Corporation, Billerica, MA, USA), whereas C-reactive protein and adiponectin were analysed using enzyme immunoassays (R&D systems, Minneapolis, MN, USA). All samples were measured in duplicate. The intra- and inter-assay coefficients of variation were $<10\%$ for all assays.

Albumin and creatinine in urine were analysed using Konelab 60i (Thermo Electron Corporation, Helsinki, Finland) until August 2008 and Vitros FS 5.1 Chemistry System thereafter.

Statistical analysis

The sample size of the MOBIL study was calculated (80% statistical power, α-level of 0.05 and equal distribution to the treatment groups) based on anticipated remission rates of type 2 diabetes and obstructive sleep apnoea. Given remission rates of type 2 diabetes of 70% in the surgery group and 20% in the lifestyle group, at least 30 subjects with type 2 diabetes were required. Expecting a prevalence of type 2 diabetes of 25% and a dropout rate of 30% from the screening examinations, a minimum of 172 subjects were required for screening.

Data are presented as mean (S.D.) or number (%) unless otherwise specified. Skewed data were transformed using natural logarithms to approximate normality. Between-group comparisons at baseline were analysed using independent samples *t*-test or Mann–Whitney *U* test for continuous variables and χ^2 or Fisher's exact test for categorical variables. Within-group comparisons were performed using paired samples *t*-test or repeated measures ANOVA for continuous variables and McNemar test for dichotomised variables. Between-group changes in outcome variables were assessed using logistic and linear regression analyses, analysis of covariance, repeated measures ANOVA and Fisher's exact test. Furthermore, changes in categorical and continuous variables were adjusted for baseline differences. In addition, continuous variables were, in the entire study population, adjusted for gender, age, BMI at baseline and changes in relevant medication. Regression analyses were used to identify predictors of remission of diabetes and hypertension and to explore the independent effects of several variables on changes in HbA1c and blood pressure. For each variable, only subjects who had values available at both baseline and follow-up are presented and included in the analyses. There were $<5\%$ missing and/or excluded data unless otherwise noted. The significance level was $P<0.05$. Statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of participants

Patient flow throughout the study is shown in Fig. 1. Of the 146 patients included, 80 chose to have surgery and 66 chose to participate in a lifestyle intervention programme. The completion rate was 95%. Baseline characteristics of the participants who completed the study are shown in Table 1. No significant differences were found between the two study groups in terms of sex, ethnicity, obesity-related comorbidities or the usage of weight-loss drugs or statins. However, patients who chose gastric bypass surgery were on average 4 years younger and 12 kg heavier than those in the lifestyle group.

Weight reduction

Weight changes in the two treatment groups during the study are shown in Fig. 3A. Mean (S.D.) percentage 1-year weight reduction was 30% (8) in the surgery group and 8% (9) in the lifestyle group (within-groups both $P<0.001$ and between-groups $P<0.001$). This corresponds to a mean (S.D.) loss of excess weight above 25 kg/m^2 of 67% (18) and 20% (23) ($P<0.001$) respectively.

The cumulative distribution of percentage weight change in the two treatment groups is shown in Fig. 3B. Within the lifestyle group, 62% lost $\geq 5\%$ of their initial

Table 1 Participant characteristics at baseline. Data are given as mean (S.D.), median (range), or *n* (%). Differences between categorical data were determined using either χ^2 or Fisher's exact test, whilst independent sample *t*-test or Mann–Whitney *U* test were used for continuous data.

	Surgery (*n*=76)	Lifestyle (*n*=63)	*P* value
Age (years)	42.8 (10.5)	47.0 (11.0)	0.023
Gender (female)	53 (70%)	44 (70%)	0.989
Caucasian	74 (97%)	61 (97%)	0.849
Type 2 diabetes	20 (26%)	18 (29%)	0.766
Duration of type 2 diabetes (years)	1 (0 to 31)	0 (0 to 16)	0.235
Hypertension	41 (54%)	40 (64%)	0.256
Metabolic syndrome	58 (76%)	44 (70%)	0.390
Albuminuria	11 (15%)[a]	7 (13%)[b]	0.745
Left ventricular hypertrophy	13 (17%)[c]	7 (11%)[d]	0.319
Coronary heart disease	5 (7%)	4 (7%)	1.000
Weight (kg)	137 (21)	125 (20)	0.001
Body mass index (kg/m^2)	46.7 (5.7)	43.3 (5.0)	<0.001
Waist circumference (cm)	135 (13)	129 (12)	0.009
Waist-to-hip ratio	0.99 (0.09)	0.97 (0.09)	0.447
Glucose, fasting (mmol/l)	6.8 (2.3)	6.4 (1.7)	0.520
Glucose, 2 h (mmol/l)	7.5 (3.4)[e]	7.6 (3.1)[f]	0.877
Insulin, fasting (pmol/l)	247 (106)	228 (111)	0.254
HbA1c (%)	5.9 (1.1)	5.7 (0.8)	0.520
Systolic BP (mmHg)	133 (18)	135 (16)	0.510
Diastolic BP (mmHg)	83 (11)	83 (10)	0.857
Pulse pressure (mmHg)	51 (13)	52 (14)	0.476
Total cholesterol (mmol/l)	5.1 (1.1)	5.2 (1.0)	0.724
LDL cholesterol (mmol/l)	3.1 (0.9)	3.3 (0.9)	0.226
HDL cholesterol (mmol/l)	1.2 (0.3)	1.2 (0.3)	0.457
Triglycerides (mmol/l)	1.8 (1.0)	1.5 (0.9)	0.013
C-reactive protein (mg/l)	2.9 (2.4)	3.2 (3.9)	0.408
Adiponectin (μg/ml)	5.7 (3.2)	5.8 (3.4)	0.721
Energy intake (MJ/day)	11.2 (4.5)[g]	12.0 (3.8)[h]	0.293
Physically active[i]	7 (10%)[g]	10 (18%)[h]	0.179
Currently smoking	21 (28%)	21 (33%)	0.466
Weight loss drugs	4 (5%)	2 (3%)	0.689
Statins	10 (13%)	7 (11%)	0.798

LDL, low density lipoprotein, HDL, high density lipoprotein.
[a]*n*=72; [b]*n*=53; [c]*n*=75; [d]*n*=62; [e]*n*=64; [f]*n*=55; [g]*n*=73; [h]*n*=55; [i]≥150 min of moderately intense or ≥60 min of vigorously intense aerobic physical activity per week.

weight, while 38% lost ≥10% of their initial weight. Within the surgery group, all subjects experienced a weight reduction >10% of their initial weight.

Changes in measures of obesity, glucose metabolism, blood pressure, lipids and inflammatory markers

With the exception of pulse pressure, changes in anthropometric measures, blood pressures and biochemical risk factors were significantly greater in the surgery group than in the intensive lifestyle group (Table 2). Both treatment groups experienced a significant reduction in all measures of obesity, glucose metabolism, blood pressure, total and low-density lipoprotein cholesterol, triglycerides and C-reactive protein during follow-up (all $P \leq 0.034$). Adiponectin increased significantly in both treatment groups (both $P<0.001$), whereas high-density lipoprotein cholesterol increased significantly only in the surgery group ($P<0.001$).

Subgroup analyses including subjects with ≥10% weight reduction showed that multi-adjusted (gender, age, BMI, baseline value and change in relevant medications) between-group changes in HbA1c and systolic and diastolic blood pressures did not differ significantly between the surgically and the conservatively treated groups (mean (95% CI) 0.0 (−0.2 to 0.2) %, $P=0.965$; −2 (−7 to 4) mmHg, $P=0.536$; and −3 (−7 to 1) mmHg, $P=0.115$, respectively).

Regression analyses, including percentage weight change, treatment choice, gender, age, BMI, baseline value and change in relevant medication as independent variables, showed that weight loss, but not treatment choice, was significantly associated with reduction in HbA1c and systolic blood pressure, but not diastolic blood pressure ($R^2=0.712$, $\beta=0.206$, $P=0.008$; $R^2=0.580$, $\beta=0.313$, $P=0.001$; and $R^2=0.423$, $\beta=0.140$, $P=0.210$).

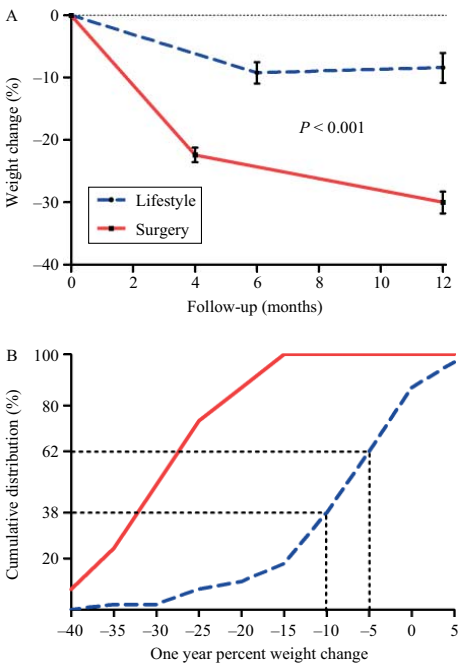

Figure 3 Mean (95% CI) percentage weight change during follow-up (A) and distribution of 1-year changes in weight (B) within the surgery and lifestyle groups. Repeated measures ANOVA was used to compare the change in weight between the two study groups.

Table 2 Changes from baseline in various continuous variables. Unadjusted within-group changes are given as mean (S.D.). Adjusted between-group differences and corresponding *P* value were calculated with the use of analysis of covariance and presented as mean (95% CI). All between-group differences were adjusted for gender, age, baseline body mass index, and baseline values. Furthermore, fasting and 2-h glucose, insulin and HbA1c were adjusted for change in the usage of glucose lowering agents; systolic and diastolic blood pressure and pulse pressure were adjusted for change in the usage of anti-hypertensive drugs; and total cholesterol, low and high density lipoprotein cholesterol, and triglycerides were adjusted for the change in the usage of statins.

	Surgery ($n=76$)	**Lifestyle** ($n=63$)	**Adjusted between-group difference, mean** (95% CI)	***P* value**
Weight (kg)[a]	−41.3 (13.1)	−10.7 (12.0)	−27.6 (−31.7 to −23.5)	<0.001
Body mass index (kg/m^2)	−14.0 (4.1)	−3.7 (4.2)	−9.4 (−10.8 to −8.0)	<0.001
Waist circumference (cm)[a]	−30.3 (10.5)	−10.3 (10.6)	−17.8 (−21.3 to −14.4)	<0.001
Waist-to-hip ratio	−0.06 (0.06)	−0.01 (0.07)	−0.05 (−0.07 to −0.03)	<0.001
Glucose, fasting (mmol/l)	−1.9 (2.0)	−0.8 (1.0)	−0.8 (−1.1 to −0.5)	<0.001
Glucose, 2 h (mmol/l)	−4.2 (3.2)	−1.6 (1.9)	−2.4 (−3.0 to −1.8)	<0.001
Insulin, fasting (pmol/l)	−142 (96)	−53 (84)	−77 (−100 to −54)	<0.001
HbA1c (%)	−0.4 (0.9)	−0.1 (0.5)	−0.2 (−0.3 to −0.0)	0.047
Systolic blood pressure (mmHg)	−14 (16)	−10 (15)	−4 (−8 to −0)	0.028
Diastolic blood pressure (mmHg)	−12 (10)	−6 (11)	−5 (−8 to −2)	0.002
Pulse pressure (mmHg)	−2 (14)	−4 (12)	1 (−3 to 4)	0.760
Total cholesterol (mmol/l)	−1.2 (1.1)	−0.7 (0.8)	−0.4 (−0.6 to −0.2)	<0.001
LDL cholesterol (mmol/l)	−1.0 (0.8)	−0.5 (0.7)	−0.5 (−0.7 to −0.4)	<0.001
HDL cholesterol (mmol/l)	0.2 (0.3)	0.0 (0.2)	0.2 (0.2 to 0.3)	<0.001
Triglycerides (mmol/l)	−0.9 (1.0)	−0.4 (0.8)	−0.2 (−0.3 to −0.0)	0.014
C-reactive protein (mg/l)	−2.1 (2.2)	−1.4 (3.6)	−1.0 (−1.5 to −0.6)	<0.001
Adiponectin (μg/ml)	3.9 (3.8)	1.8 (3.2)	2.0 (1.0 to 3.0)	<0.001
Energy intake (MJ/day)	−4.7 (4.5)	−3.5 (3.5)	−1.7 (−2.3 to −1.0)	<0.001

LDL, low density lipoprotein, HDL, high density lipoprotein.
[a]Not adjusted for body mass index.

All participants had 2 h glucose >2.8 mmol/l at baseline. In contrast, 2 (4%) patients in the lifestyle group and 15 (23%) patients in the surgery group had 2 h glucose <2.8 mmol/l after the intervention ($P=0.003$).

Type 2 diabetes and hypertension

Among participants with type 2 diabetes, HbA1c was reduced from 6.6% (1.0) to 6.3% (0.9) in the lifestyle group and from 7.1% (1.5) to 5.8% (0.5) in the surgery group (adjusted between-group difference, $P=0.003$). Moreover, the hypertensive subgroups' systolic blood pressure declined from 144 mmHg (16) to 125 mmHg (12) after the surgical procedure and from 143 mmHg (15) to 130 mmHg (14) after the lifestyle intervention (adjusted between-group differences, $P=0.061$). Furthermore, the number of diabetic subjects using glucose-lowering agents dropped (from 11 to 6) in the surgery group and increased (from 6 to 10) in the lifestyle group (between-group difference, $P=0.017$). In contrast, the reduction in the number of hypertensive participants using anti-hypertensive drugs did not differ significantly between the surgery group (from 24 to 21) and the lifestyle group (from 30 to 25) (between-group difference, $P=1.00$).

The remission rates of type 2 diabetes and hypertension related to weight change after gastric bypass surgery and lifestyle intervention are shown in Fig. 4. The remission rates of both conditions were significantly higher after surgical treatment than after lifestyle intervention. Complete remission of type 2 diabetes was significantly more frequent in the surgery group than in the lifestyle group (11/14 vs 0/6, $P=0.002$).

Multiple regression analyses demonstrated that no usage of glucose-lowering agents and anti-hypertensive drugs at baseline were, independent of percentage weight change and treatment choice, associated with remission of type 2 diabetes ($P=0.023$) and hypertension ($P<0.001$). In addition, univariate linear regression analyses showed that greater reductions in HbA1c and systolic blood pressure were associated with surgical treatment ($\beta=-0.408$, $P=0.011$ and $\beta=-0.187$, $P=0.096$ respectively). Inclusion of percentage weight change in the regression analyses showed that weight loss mediated the effects of treatment choice on these outcomes ($\beta=0.406$, $P=0.160$ and $\beta=0.142$, $P=0.410$ respectively). Furthermore, weight loss was significantly associated with reductions in HbA1c and systolic blood pressure ($\beta=0.926$, $P=0.002$ and $\beta=0.423$, $P=0.016$ respectively).

Metabolic syndrome, albuminuria and left ventricular hypertrophy

The changes in the number of individuals with metabolic syndrome (−44 vs −14), albuminuria (−7 vs 3) and left ventricular hypertrophy (−10 vs −2) were significantly greater in the surgery group than in the lifestyle group (Fig. 5). The prevalence of metabolic syndrome reduced significantly in both treatment groups (both $P\leq0.001$), while the

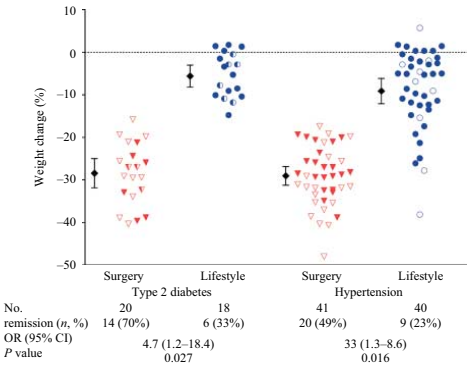

Figure 4 Remission of type 2 diabetes and hypertension at 1 year correlated to percentage weight change in individuals treated with gastric bypass surgery or intensive lifestyle intervention. Red triangles represent patients treated with gastric bypass surgery, while blue circles represent subjects who chose lifestyle intervention. Open triangles/circles denote complete remission of type 2 diabetes and remission of hypertension, half filled triangles/circles denote partial remission of type 2 diabetes and filled triangles/circles denote no remission. For definitions of partial and complete remission of type 2 diabetes, see 'Subjects and methods' section. Mean percentage weight changes (black diamonds) within the groups are shown with bars extending from the diamonds representing 95% CI. Odds ratios (OR) were calculated using logistic regression analyses. Combined (partial and complete) remission of type 2 diabetes was used in the analysis.

prevalence of left ventricular hypertrophy was significantly reduced in only the surgery group ($P=0.002$). In contrast, the prevalence of albuminuria did not change significantly within either treatment group.

Lifestyle and medications

Although both treatment groups reported significantly lower energy intake at 1 year than at baseline (both $P<0.001$), the reduction was significantly greater in the surgery group than in the lifestyle group (Table 2). The number of subjects in the surgery group and lifestyle group which either moved from being inactive to active (12 vs 18), stayed inactive or active (57 vs 32) or moved from being active to inactive (4 vs 5) differed significantly between the groups (Fig. 6). Overall, there was a greater increase in the physical activity level of the lifestyle group than the surgery group. However, the median (range) time spent performing physical activities with moderate or vigorous intensity after the interventions did not differ significantly between the surgery and lifestyle groups, 20 (0–510 min) versus 65 (0–660 min), $P=0.148$.

Usage of weight-loss medications was stopped in all surgically treated patients and started in only one patient in the lifestyle group. The change in the number of individuals using statins did not differ significantly between the surgery and the lifestyle (10 vs 3, $P=0.114$).

Last observation carried forward

In additional calculations, missing values were replaced by the last observed value of the respective variable (data not shown). These results did not alter the conclusions of the study.

Adverse events

Median (range) post-operative stay was 2 (1–9) days. Perioperative complications in the surgery group included one gastrojejunal anastomotic leakage, which was successfully re-operated on during the first post-operative day, one major bleeding at the site of the trocar insertion, which needed a blood transfusion, and two pneumonias treated effectively with antibiotics.

Late complications in the surgery group included four patients with symptomatic cholelithiasis (imaging verified), two patients with marginal ulcers, five patients with postprandial hypoglycaemia, one patient with a fracture of the fifth right proximal phalange and one patient with myocardial infarction. In the lifestyle group, one patient was diagnosed with breast cancer, one patient suffered a right ankle fracture that was treated with a stabilising cast and complicated by a deep venous thrombosis and one patient developed cholelithiasis. There were no deaths.

In total, 48% (33/69) of patients in the surgery group and 7% (4/59) of patients in the lifestyle group developed gastrointestinal symptoms, including abdominal pain, nausea, vomiting, diarrhoea and constipation ($P<0.001$).

Discussion

To our knowledge, this is the first controlled, clinical trial that has sought to evaluate the effects of gastric bypass surgery and intensive lifestyle intervention on cardiovascular risk factors. When compared with the lifestyle group, the surgery group had higher remission rates

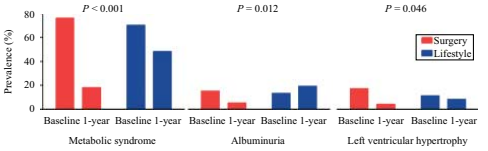

Figure 5 The prevalence of metabolic syndrome, albuminuria and left ventricular hypertrophy in the treatment groups at both baseline and 1-year follow-up. Between-group differences at 1 year were adjusted for differences in prevalence at baseline using logistic regression analyses. *P* values are for comparisons between surgery and lifestyle groups.

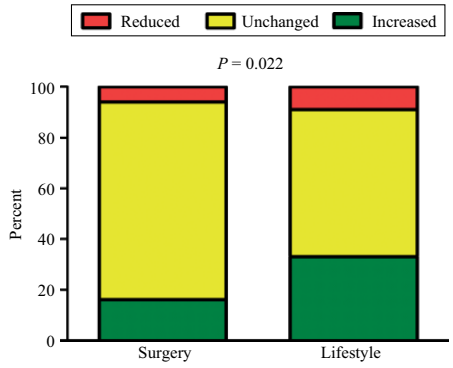

Figure 6 Change in physical activity during 1-year follow-up. The proportion of participants who went from being physically active (≥150 min of moderate or ≥60 min of vigorous aerobic physical activity per week) to inactive (reduced) were still physically active or inactive (unchanged) or went from being physically inactive to active (increased). The changes were adjusted for baseline activity level using linear regression analysis. *P* value is for comparisons between surgery and lifestyle groups.

of type 2 diabetes and hypertension, as well as greater reductions in the prevalence of metabolic syndrome, albuminuria and left ventricular hypertrophy. Notably, intensive lifestyle intervention was also associated with favourable changes in measures of glucose metabolism, blood pressure, lipids and low-grade inflammation.

Strengths and weaknesses of the study

The strengths of this study include the prospective design, the fact that the control group obtained a significant weight loss from lifestyle intervention and the high participant completion rate. Limitations of the study include the lack of randomisation (addressed in 'Subjects and methods' section), a larger intervention delay in the surgery group and the short-term follow-up. Furthermore, the diagnoses of type 2 diabetes and hypertension were, in the absence of hypoglycaemic or anti-hypertensive drugs, based on only one measurement and not repeated measurements as recommended (25, 27). Finally, the majority of the study population was of Europoid origin, meaning that the results of this study cannot be generalised to include other ethnic groups.

Type 2 diabetes and hypertension

Both the case controlled Swedish Obese Subjects (SOS) study (10) and the Australian randomised controlled clinical trial (11) demonstrated that 2 year remission rates of type 2 diabetes were significantly higher in patients treated with bariatric surgery than in conservatively treated controls. The SOS study also reported higher remission rates of hypertension in the surgery group. Our study extends these findings by showing that morbidly obese patients treated with gastric bypass surgery were more likely to achieve remission of type 2 diabetes and hypertension than those who participated in a comprehensive lifestyle intervention programme. In addition to a shorter intervention period, our study differs from these previous trials in several ways. First, in contrast with our standardised and comprehensive lifestyle programme, the above two studies are notable for the fact that non-surgical treatment varied considerably and that weight loss was negligible. Second, our surgical procedure was gastric bypass, whereas purely restrictive, bariatric procedures were mainly implemented in the two other studies. Accordingly, the average 1-year weight reduction was more pronounced in our surgical group. Third, our definition of remission of type 2 diabetes differed slightly from the previous studies. Finally, the Australian study differed in the sense that it only included those patients who had type 2 diabetes of <2 years duration and a BMI of between 30 and 40 kg/m^2. Nevertheless, despite these differences, the remission rate of diabetes in our surgical group was nearly identical with rates in these previous studies (70 vs 71 and 72%). Furthermore, while hypertension was resolved in approximately half the surgical patients in our study, it did so in only one-third of the patients in the SOS study.

Our study shows that weight reduction, and not treatment choice, predicted improvement in glycaemic control and systolic blood pressure. Furthermore, most of the beneficial metabolic effects were observed after a weight reduction of ≥10%. Accordingly, the metabolic effect of gastric bypass surgery seems to be mediated through weight reduction.

Despite extensive weight loss, type 2 diabetes and hypertension in a substantial number of surgically treated patients were not resolved. In contrast, remission of these conditions was observed in some lifestyle group patients despite only modest weight reduction. These findings might be explained by differences in the severity of the conditions and the possible beneficial effect of increased physical activity. Indeed, the absence of glucose-lowering drugs and anti-hypertensive medication independently predicted remission of both diabetes and hypertension. Furthermore, compared with subjects treated with surgery, a significantly higher proportion of the participants in the lifestyle group became physically active.

Both blood glucose and blood pressure are continuous risk factors for death and cardiovascular disease (35, 36). The observed decline in these measures in both intervention groups may therefore have positive health effects. Conversely, the five cases of symptomatic postprandial hypoglycaemia and the large proportion (23%) of patients with 2 h glucose <2.8 mmol/l in the gastric bypass group raise some concerns. Severe postprandial hypoglycaemia after Roux-en-Y gastric

bypass surgery has been reported previously and post-surgical nesidioblastosis may contribute to this complication (37). Furthermore, severe and symptomatic hypoglycaemia in type 2 diabetic subjects has been shown to be associated with increased mortality (38). Consequently, it cannot be excluded that the reduction in 2 h glucose observed after Roux-en-Y gastric bypass surgery may also have negative long-term health effects.

Other cardiovascular risk factors

Surgical therapy was superior to lifestyle intervention both in terms of the resolution of metabolic syndrome, left ventricular hypertrophy and microalbuminuria, as well as with respect to improvements in inflammatory markers. In line with previous studies, we report that weight reduction was associated with resolution of metabolic syndrome (11, 17), beneficial changes in C-reactive protein and adiponectin levels (16) and reduction in left ventricular mass (12). Improvement in all renal parameters, including albuminuria, has been reported after gastric bypass surgery (13). Similarly, weight reduction after lifestyle intervention has been reported to resolve albuminuria (17). In contrast to this finding and closer to our own results, modest weight reduction in the intensive lifestyle group of the Diabetes Prevention Program did not reduce albumin excretion significantly (39).

Clinical and research implications of the work

In sum, we have shown that gastric bypass surgery is more effective than intensive lifestyle intervention in terms of improving type 2 diabetes and obesity-related cardiovascular risk factors. However, morbidly obese patients treated with lifestyle intervention also experienced significant and meaningful improvements in most cardiovascular risk factors, and significantly more patients in the lifestyle group than the surgery group became physically active. Gastric bypass surgery was associated with a significantly higher risk of gastrointestinal symptoms and complications as reported previously (40). Furthermore, although a specified set of dietary supplements seems to prevent vitamin deficiencies after gastric bypass surgery (23), several deficiencies may occur if an inadequate supplementation is prescribed (41). Finally, even though reduced overall mortality after bariatric surgery has been reported (42), it is still unclear whether short-term improvement in obesity-related cardiovascular risk factors translates into long-term reduced cardiovascular morbidity and mortality. Our results indicate that when treating morbidly obese patients, gastric bypass surgery should not, despite its ability to improve risk factors, be considered the default course of treatment. Rather, both patient and physician should consider the possible side effects of this treatment, and, where appropriate, take up alternative conservative treatments. Indeed, intensive behavioural intervention has been shown to result in long-term weight reduction in some patients (43), while improved physical fitness is known to reduce all cause mortality (44). Moreover, it should be emphasised that if the success of bariatric surgery is to be optimised then behavioural changes are also necessary (45). Future studies comparing surgery and non-surgical treatment programmes should address the effect of these treatments on long-term cardiovascular morbidity and mortality.

Declaration of interest

T I Karlsen is one of the founders of Evjeklinikken A/S and is a former board member (until November 2008) and stockholder (until August 2009). He is now a PhD student at the Morbid Obesity Centre and is supported financially by Evjeklinikken A/S. All the other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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IV

Beta cell function after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention

Short running title: Beta cell function after weight loss

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Abstract

Objective: The effects of various weight loss strategies on pancreatic beta cell function remain unclear. We aimed to compare the effect of intensive lifestyle intervention (ILI) and Roux-en-Y gastric bypass surgery (RYGB) on beta cell function.

Design: One year controlled clinical trial (ClinicalTrials.gov identifier NCT00273104).

Methods: 119 morbidly obese participants without known diabetes from the MOBIL study [mean (SD) age 43.6 (10.8) years, BMI 45.5 (5.6) kg/m^2, 84 women] were allocated to RYGB (n=64) or ILI (n=55). The patients underwent repeated oral glucose tolerance tests (OGTTs) and were categorised as having either normal (NGT) or abnormal glucose tolerance (AGT). Twenty nine normal weight subjects with NGT [age 42.6 (8.7) years, BMI 22.6 (1.5) kg/m^2, 19 women] served as controls. OGTT-based indices of beta cell function were calculated.

Results: One year weight reduction was 30 (8) % after RYGB and 9 (10) % after ILI, ($P <$ 0.001). Disposition index (DI) increased in all treatment groups (all $P < 0.05$), although more in the surgery groups (both $P < 0.001$). Stimulated proinsulin-to-insulin (PI/I) ratio decreased in both surgery groups (both $P < 0.001$), but to a greater extent in the surgery group with AGT at baseline ($P < 0.001$). Post surgery, patients with NGT at baseline had higher DI and lower stimulated PI/I ratio than controls (both $P < 0.027$).

Conclusions: Gastric bypass surgery improved beta cell function to a significantly greater extent than intensive lifestyle intervention. Supra-physiological insulin secretion and proinsulin processing may indicate excessive beta cell function after gastric bypass surgery.

Introduction

Obesity is a major risk factor for type 2 diabetes, with approximately one out of three morbidly obese subjects (BMI $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 with at least one obesity related comorbidity) having type 2 diabetes (1). Reduced insulin sensitivity and beta cell dysfunction represent the core pathophysiologic defects in type 2 diabetes (2). It is well-known that weight reduction enhances insulin sensitivity in obese subjects (3), with this contributing to the improvement in glycaemic control reported after lifestyle intervention (4) and bariatric surgery (5). By contrast, the association between weight reduction and restoration of beta cell function is less clear. Modest weight loss induced by diet alone (6) or in combination with exercise (7) in older non-diabetic overweight and obese subjects has been shown to enhance beta cell function. Moreover, results from the Diabetes Prevention Program which predominantly included obese, middle-aged subjects with impaired glucose tolerance (IGT), indicate improved insulin secretion relative to insulin sensitivity after one year of intensive lifestyle intervention (8). By contrast, 24 months of diet and endurance exercise did not improve beta cell function in Japanese Americans with impaired glucose tolerance (9). Furthermore, recovery of beta cell function has been reported after bariatric surgery (10-12). Increased insulin secretion post surgery could contribute to high remission rates of type 2 diabetes after bariatric surgery (5) as well as to postprandial hypoglycaemia, a phenomenon which has drawn much attention recently (13, 14).

Given this background, we aimed to compare in morbidly obese patients without known diabetes the one year effect of intensive lifestyle intervention (diet and physical activity) and Roux-en-Y gastric bypass on beta cell function as assessed by oral glucose tolerance test (OGTT) derived indices.

Methods

Participants and study design

This is an ancillary study to the MOBIL study (Morbid Obesity treatment, Bariatric surgery versus Intensive Lifestyle intervention study, ClinicalTrials.gov identifier: NCT00273104) (15). It includes a subset of 119 morbidly obese participants without known diabetes who underwent an OGTT before and after intervention. In addition, 29 normal weight (BMI < 25 kg/m^2) subjects with normal glucose tolerance (NGT) served as a control group (data from 27 of these subjects has been published previously (16)).

The MOBIL study aimed to address changes in several health outcomes related to obesity, with details concerning the design and intervention published previously (15). In short, this one year controlled clinical trial included 146 consecutively recruited morbidly obese subjects predominantly of European descent and was conducted at a public tertiary care centre in Norway between December 2005 and June 2009. Patients in the surgery group were allocated to laparoscopic Roux-en-Y gastric bypass, whereas patients who chose lifestyle intervention were referred to a rehabilitation centre specialising in the care of morbidly obese patients (Evjeklinikken A/S). The one year lifestyle programme aimed to induce a weight loss of at least 10% and comprised of four stays at the centre lasting for either one week or four weeks (total 7 week stay). The daily programme was divided between organised physical activity (3-4 hours) and different psychosocially oriented interventions. No special diet or weight loss drugs were prescribed, but patients were encouraged to follow the guidelines of the Norwegian National Council of Nutrition. Outside of these stays patients were contacted by phone once every two weeks. The patients were encouraged to self-monitor their eating habits and physical activity, as well as to visit their general practitioner regularly.

The regional ethics committee of the Southern Norway Regional Health Authority approved the study. Written informed consent was provided by all participants.

Oral glucose tolerance test

A 75 g OGTT was performed at 8:00 am after an overnight fast, with venous blood samples obtained at 0, 30, and 120 minutes for determination of serum glucose, insulin, c-peptide, and proinsulin. Treatment with hypoglycaemic agents was terminated two weeks prior to the OGTT for patients receiving such treatment. On the day of the OGTT no medications were taken prior to the test.

Glucose tolerance status was determined according to the criteria of the World Health Organization (17). NGT was defined as fasting glucose < 6.1 mmol/l and 2-h glucose < 7.8 mmol/l. The abnormal glucose tolerance (AGT, fasting glucose ≥ 6.1 mmol/l and/or 2-h glucose ≥ 7.8 mmol/l) groups included subjects with impaired fasting glucose (IFG), IGT, and new onset diabetes mellitus (NODM). Post challenge hypoglycemia was defined as 2-h glucose < 2.8 mmol/l.

Calculations

Several estimates of insulin secretion and insulin sensitivity were initially assessed using indices including the available glucose and insulin measurements from the OGTT (18-20). However, the insulin sensitivity indices of Belfiore (19) and Stumvoll (20), comprising of glucose and insulin concentrations at 120 minutes, seemed to overestimate post surgery insulin sensitivity (significantly higher median values than NGT controls, both $P \leq 0.001$) and were therefore not included in the analyses. Consequently, the computer based homeostasis model assessment of insulin sensitivity (HOMA-S) was preferred as the insulin sensitivity index (18).

Insulin secretion was estimated using the insulinogenic index ($\Delta Ins_{30}/\Delta Gluc_{30,}$), the ratio of the total area under the insulin curve to the total area under the glucose curve (total

$AUC_{Ins/Gluc}$), and the Stumvoll first phase index (fist $phase_{est}$: 1283 + 1.829 x Ins_{30} -138.7 x $Gluc_{30}$ + 3.772 x Ins_0) (20). Because insulin secretion is determined in part by the prevailing insulin sensitivity, the disposition index (DI), which is the product of insulin sensitivity and insulin secretion, yields a better measure of beta cell function (21). Based on the above mentioned indices of insulin secretion, three alternative DI`s were calculated.

Circulating proinsulin-to-insulin (PI/I) ratio, especially stimulated PI/I ratio (22), has previously been used as an estimate of the beta cell`s ability to transform proinsulin to insulin. Indeed, elevated PI/I ratio has been associated with IGT (22) and reduced insulin secretion (23). PI/I ratios in a fasting and stimulated state (30 minutes after glucose ingestion) were therefore calculated.

Laboratory analyses

HbA1c was analysed using high performance liquid chromatography on Tosoh HLC-723 G7 (Tosoh Corporation, Tokyo, Japan). Serum samples from the OGTT were separated after 30 minutes and either stored at -80^{o}C or analysed the same day (glucose). Analyses of glucose were performed using dry reagent slide technology on the Vitros 950 Analyser until November 2006 and the Vitros FS 5.1 Analyser (Ortho-Clinical Diagnostics, New York, NY) thereafter. Serum levels of insulin, c-peptide, and proinsulin (Millipore Corporatio, Billerica, MA, USA) were measured by radio immunoassay. All samples were measured in duplicate, with serial samples from a given individual run at the same time. Intra- and inter-assay CVs were less than 10 % for all assays.

Statistical analysis

Data are presented as mean (SD) or number (%) unless otherwise specified. Skewed data were either transformed using natural logarithms to approximate normality or analysed using non-

parametric tests. Between group comparisons were analysed using one-way analysis of variance (ANOVA) with post hoc comparisons (least significant difference, LSD), Mann-Whitney U test, χ^2, two-way ANOVA and analysis of covariance (ANCOVA) including gender, age and BMI at baseline and baseline value as covariates. Within group comparisons between baseline and follow-up variables were compared using paired samples t-test. Correlations were calculated with Pearson's correlation coefficients. Linear regression analyses were used to 1) explore a potential hyperbolic relationship between HOMA-S and measures of insulin secretion (95% CI of the specialised regression coefficient (β) in the equation ln (insulin secretion) = constant + β x ln (insulin sensitivity) must include -1 and exclude 0), and 2) identify possible predictors of change in DI and PI/I ratios (age, gender, change in smoking status (stopped/ unchanged/started), family history of type 2 diabetes (yes/no), glucose tolerance status (NGT/AGT), change in physical activity (became inactive/unchanged/became active) and treatment choice (surgery/lifestyle), and percent weight reduction). The significance level was $P < 0.05$. Statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics of participants

The 64 patients assigned to gastric bypass were on average 5 years younger and 13 kg heavier than the 55 patients in the lifestyle groups (both $P < 0.005$). Otherwise, within the normal and abnormal glucose tolerance groups, the surgery and lifestyle groups were comparable with respect to gender and measures of glucose homeostasis (Table 1). In both the surgery and lifestyle groups, patients with AGT had higher HbA1c, were less insulin sensitive and had lower insulin secretion than patients with NGT (Table 1). In the AGT surgery group 9 subjects had IFG, 12 had IGT and 11 had NODM, whilst in the AGT lifestyle group 1 had IFG, 10 had IGT and 11 had NODM.

Changes in weight, energy intake, medication and glucose tolerance

Mean (SD) weight reduction in the merged surgery and lifestyle groups was 30 (8) % and 9 (10) % respectively ($P < 0.001$). Self reported energy intake was significantly lower after surgical treatment than after lifestyle intervention (NGT and AGT groups combined: from 11.8 (5.1) to 6.9 (1.8) MJ/day and from 12.0 (3.6) to 8.6 (1.9) MJ/day, respectively, $P < 0.001$). At baseline, none of the participants used hypoglycaemic agents, whereas three patients who chose surgery and two patients who chose lifestyle intervention were taking weight loss medications. After surgery, neither hypoglycaemic nor weight loss medications were used. By contrast, after one year of lifestyle intervention five patients used hypoglycaemic agents (metformin) and three patients were taking weight loss medication. AGT was resolved in all gastric bypass surgery patients and in 41 % (9 out of 22) of lifestyle intervention patients ($P < 0.001$).

Glucose, insulin and c-peptide during the oral glucose tolerance test

With the exception of no change in glucose and an increase in insulin and c-peptide at 30 minutes after surgical treatment, both interventions resulted in a reduction in glucose, insulin, and c-peptide at all time points in both glucose tolerance groups (Figure 1). At one year, glucose, insulin and c-peptide in the surgery groups were lower at 0 and 120 minutes and higher at 30 minutes than in the lifestyle groups. Post challenge hypoglycaemia (< 2.8 mmol/l) was significantly more prevalent after surgical treatment than after lifestyle intervention (NGT and AGT groups combined: 23 % versus 4 %, P = 0.002), but did not differ significantly between the NGT and AGT groups (P = 0.768).

Insulin sensitivity and insulin secretion

HOMA-S increased after both interventions, though to a greater extent in the NGT and AGT surgery groups than in the corresponding lifestyle groups (Table 1). The changes in the three indices estimating insulin secretion during the OGTT yielded diverging results. While total $AUC_{Ins/Gluc}$ and fist $phase_{est}$ decreased or tended to decrease after both interventions in both glucose tolerance groups, the opposite was the case for $\Delta Ins_{30}/\Delta Gluc_{30}$ (Table 1).

Disposition index

Pairing HOMA-S with the indices of insulin secretion in subjects with NGT at baseline (n = 96) showed that the combination of HOMA-S and first $phase_{est}$ was closest to forming a hyperbola: HOMA-S and first $phase_{est}$ (β = -0.869, 95 % CI (-0.971 to -0.766), n = 94); HOMA-S and total $AUC_{Ins/gluc}$ (β = -0.796, 95 % CI (-0.922 to -0.671, n = 94); and HOMA-S and $\Delta Ins_{30}/\Delta Gluc_{30}$ (β = -0.515 95% CI (-0.697 to -0.334), n = 90). This combination was therefore used when calculating the DI presented.

Figure 2A and 2B depict the one year changes in first $phase_{est}$ and HOMA-S according to glucose tolerance status at baseline in the surgically and conservatively treated groups. The

first $phase_{est}$ in relation to HOMA-S shifted to the right after treatment in both the surgery and lifestyle groups. These findings are consistent with increased insulin secretion relative to insulin sensitivity after both interventions as verified by increased DI in subjects with NGT and AGT in the surgery and lifestyle groups (Figure 2C). However, the DI increased significantly more after surgical treatment than after lifestyle intervention in both glucose tolerance groups (Figure 2C). Notably, at one year the DI in the NGT surgery group was even higher than in NGT controls ($P < 0.001$).

Exchanging first $phase_{est}$ with total $AUC_{Ins/Gluc}$ when calculating the alternative DI yielded similar results to those described above (data not shown).

Proinsulin-to-insulin ratios

The reduction in stimulated PI/I ratio was greatest after surgical treatment and was most pronounced among those with AGT (Figure 3A). Fasting PI/I ratio was significantly reduced only in surgically treated patients with AGT (Figure 3B). By contrast, stimulated and fasting PI/I ratios did neither change significantly in the NGT group nor the AGT group after lifestyle intervention. At one year, stimulated PI/I ratio in the NGT surgery group was even lower than in the NGT control group ($P = 0.027$).

Predictors of improved beta cell function

In the whole study population, percentage weight change was correlated with both change in DI ($r = -0.56$, $P < 0.001$) and change in stimulated PI/I ratio ($r = 0.29$, $P = 0.001$). Furthermore, there was a significant correlation between change in DI and change in stimulated PI/I ratio ($r = -0.31$, $P = 0.001$). The changes in fasting and stimulated PI/I ratios were moderately correlated ($r = 0.41$, $P < 0.001$), whereas changes in fasting PI/I ratio correlated with neither weight nor DI changes.

The multiple linear regression analyses showed that 1) treatment choice remained associated with change in DI (β = 0.337, *P* = 0.008) and stimulated PI/I ratio (β = -0.339, *P* = 0.022); 2) glucose tolerance status at baseline remained associated with change in stimulated PI/I ratio (β = -0.297, *P* = 0.002); and 3) weight change remained associated with change in DI (β = -0.329, *P* = 0.008) but not with change in stimulated PI/I ratio (β = -0.027, *P* = 0.849).

Discussion

The aim of the present study was to compare the effects of Roux-en-Y gastric bypass and intensive lifestyle intervention on beta cell function in morbidly obese patients. Our results demonstrate that insulin sensitivity adjusted insulin secretion was significantly greater after gastric bypass than after lifestyle intervention. In addition, significant reductions in PI/I ratios in the surgery groups were observed.

Strengths and weaknesses of the study

The main strength of the study is the controlled design. The limitations are the use of OGTT-derived indices not validated in gastric bypass operated patients, the use of indices for the calculation of DI which did not fully satisfy the criteria for a hyperbolic relationship, the lack of gut hormone analyses, the non-randomised design and the inclusion of predominantly white subjects.

Comparison with other studies

In line with the Diabetes Prevention Program (8) and two smaller weight loss studies (6, 7) we confirm that lifestyle intervention is associated with improved insulin sensitivity adjusted insulin secretion. A positive effect of weight reduction on beta cell function has also been shown in a longitudinal study in Pima Indians (24). Contrasting previous results and the results of the present study, DI did not increase after 24 months of lifestyle intervention in a study of Japanese Americans with IGT (9). Since the improvement in insulin secretion may be proportional to the amount of weight loss (24), these differences may partly be explained by a modest weight reduction (2.6 %) in the latter study (9). This notion is further supported by our own results, which demonstrate that improvement in DI is partly explained by weight reduction. Furthermore, increased DI after gastric bypass is in line with some previous studies

addressing insulin secretion after bariatic surgery in subjects with various degrees of glucose tolerance (11, 12). However, in contrast with our findings, Morínigo *et al.* (10) failed to demonstrate an increase in insulin secretory capacity to intravenous glucose in subjects with NGT or IGT one year after gastric bypass when accounting for prevailing insulin sensitivity. This discrepancy might have several explanations. First, we included a higher number of patients than Morínigo *et al.*, and, second, our use of an OGTT derived DI may have yielded a greater increase in the DI (11).

The pattern of change in the DI calculated by total $AUC_{Ins/Gluc}$ and HOMA-S resembled that of the DI based on first $phase_{est}$ and HOMA-S in all groups. This may indicate that both early and late phase insulin section increased after both treatments.

A decrease in both fasting and stimulated PI/I ratios in the AGT surgery group further supports improved beta cell function after gastric bypass. The results are also partly in line with some (12, 25), but not all (26), previous studies reporting reduced fasting PI/I ratio after bariatric surgery in morbidly obese subjects with normal and abnormal glucose tolerance. To the best of our knowledge, the possible effect of gastric bypass on stimulated PI/I ratio has not been reported previously. Our finding of a greater reduction in the PI/I ratios in subjects with AGT than in those with NGT may indicate that the improvement in insulin processing after gastric bypass is greatest in those who need it the most. By contrast, no significant reductions in the PI/I ratios were neither observed in the NGT group nor the AGT group after lifestyle intervention. However, the results correspond with those of a study reporting no reduction in fasting PI/I ratio in obese women with type 2 diabetes after diet induced weight loss (25).

Overall beta cell function was ameliorated to a greater extent after gastric bypass surgery than after lifestyle intervention. Since improvement in DI was independently associated with weight reduction, greater weight loss in the surgery groups than in the lifestyle groups could clearly explain some of the differences. However, it should be noted

that surgical treatment also independently predicted improvements in DI and that improvements in stimulated PI/I ratio was associated with surgical treatment and not with weight reduction. The latter findings indicate that the improvements in beta cell function may be partly related to the surgical procedure *per se* and not only to weight reduction.

One year after surgery, post challenge glucose, insulin and c-peptide dropped sharply after an initial rise, with all values relatively high at 30 minutes and low at 120 minutes in both glucose tolerance groups. Specially worth noting is the high prevalence of post challenge hypoglycaemia. As demonstrated in this and previous studies, excessive insulin secretion may occur after gastric bypass (13, 25). Although the present study was not designed to explore the pathophysiological mechanisms for post bypass hyperinsulinaemia, it might be speculated that bypassing the gastric ventricle causes rapid absorption of glucose and consequently high glucose levels immediately after glucose ingestion. Indeed, we and others (13, 25) have reported elevated glucose levels 30 minutes after a glucose load in gastric bypass patients. Hyperglycaemia may in turn stimulate insulin secretion and thereby contribute to the observed hyperinsulinaemia. However, it is also very likely that other factors are involved, with a few publications recently addressing this phenomenon (13, 14). Some researchers argue that post-gastric bypass hyperinsulinaemia may be explained by the increase in gut hormones such as glucagon-like peptide 1 (GLP 1) and gastric inhibitory peptide which follows the rearrangement of the intestine (13, 25). Alternatively, but not mutually exclusive, pathologic overgrowth of pancreatic beta cells, possibly stimulated by GLP 1, after bypass surgery may result in hypersecretion of insulin (14).

Finally, improved glycaemic control caused by enhanced insulin sensitivity after weight loss may in turn reduce the toxic effect of glucose on the pancreatic beta cells and thereby increase insulin secretion. This would partly explain the improved beta cell function observed after lifestyle intervention in both the present study and others like it (6-8).

Conclusions

In summary, beta cell function improved in subjects with both normal and abnormal glucose tolerance after both interventions, although this was more pronounced after Roux-en-Y gastric bypass. Notably, supra-physiological insulin secretion and proinsulin processing may point towards excessive beta cell function after gastric bypass surgery. This may possibly contribute to improved glycaemic control in patients with abnormal glucose tolerance but also to postprandial hypoglycaemia observed after this procedure. Future studies addressing the same themes should be longitudinal, use both intravenous and oral techniques for the estimation of beta cell function, and include gut hormones.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Figure legends

Figure 1 Mean glucose, insulin, and c-peptide during the OGTT in controls and in morbidly obese subjects at baseline and one year after gastric bypass surgery and intensive lifestyle intervention according to glucose tolerance status at baseline. Error bars represent 95 % CIs. Independent samples t-tests were used for the comparison of means.

*$P < 0.05$, controls versus intervention groups.

†$P < 0.05$, surgery versus lifestyle group.

Figure 2 Mean HOMA-S plotted against first $phase_{est}$ in controls and morbidly obese subjects with normal glucose tolerance (A) and abnormal glucose tolerance (B) before and one year after gastric bypass and lifestyle intervention. The curve represents the regression line of the natural logarithm of estimated insulin secretion as a linear function of the natural logarithm of estimated insulin sensitivity for all participants with normal glucose tolerance at baseline. The bar graph (C) represents mean value of the corresponding disposition indices. Error bars represent 95 % CIs.

**P*-value for the effect of treatment choice and glucose tolerance status at baseline on change in disposition index, two-way ANOVA.

†$P < 0.05$, ††$P < 0.001$, one year versus baseline, paired samples t-test.

‡$P < 0.001$, between groups (surgery versus lifestyle) changes in disposition index within the same glucose tolerance group, ANCOVA with adjusting for gender, age and BMI at baseline and baseline value.

§$P < 0.001$, normal glucose tolerance versus abnormal glucose tolerance within the same intervention group at baseline, independent samples t-test.

Figure 3 Mean stimulated (A) and fasting (B) proinsulin-to-insulin ratios in controls and morbidly obese subjects with normal and abnormal glucose tolerance before and one year after gastric bypass and lifestyle intervention. Error bars represent 95 % CIs.

**P*-value for the effect of treatment choice and glucose tolerance status at baseline on change in disposition index, two-way ANOVA.

††$P < 0.001$, one year versus baseline, paired samples t-test.

‡$P < 0.001$, between groups (surgery versus lifestyle) changes in disposition index within the same glucose tolerance group, ANCOVA with adjusting for gender, age and BMI at baseline and baseline value.

§$P < 0.001$, normal glucose tolerance versus abnormal glucose tolerance within the same intervention group at baseline, independent samples t-test.

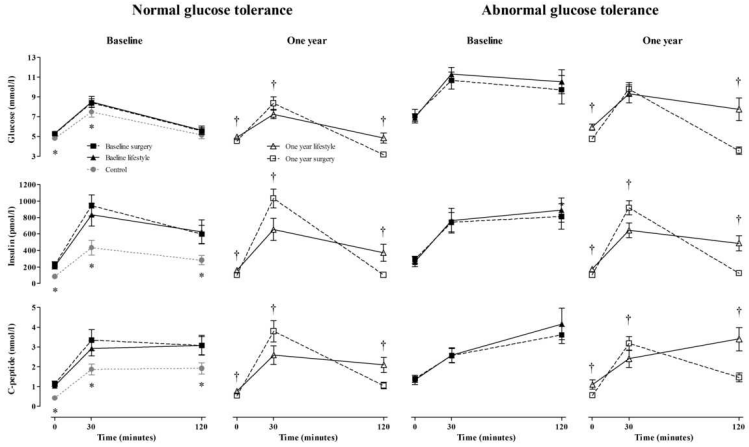
Table 1 Participant characteristics at baseline and at one year follow-up.

		Normal glucose tolerance (NGT)			Abnormal glucose tolerance (AGT)		*P* for change, effect of[a]	
		Control	Surgery	Lifestyle	Surgery	Lifestyle	treatment	glucose
		(n = 29)	(n = 34)	(n = 33)	(n = 30)	(n = 22)	choice	tolerance
Age (years)	Baseline	42.6 (8.7)	39.0 (9.6)	43.2 (11.6)	43.5 (10.3)	51.3 (8.1)[b,c]		
Gender (female, yes)	Baseline	19 (66 %)	23 (67 %)	24 (73 %)	22 (73 %)	15 (68 %)		
Body mass index (kg/m^2)	Baseline	22.6 (1.5)	47.2 (5.3)[b]	43.3 (5.2)[b,c]	47.3 (6.0)[b]	43.5 (4.5)[b,c]		
	One year		33.1 (5.1)[e]	39.6 (6.3)[e]	33.1 (5.4)[e]	39.4 (4.0)[e]	< 0.001	0.740
HbA1c (%)	Baseline	5.3 (0.3)	5.2 (0.3)	5.3 (0.3)	5.9 (0.6)[b,d]	5.9 (0.4)[b,d]		
	One year		5.2 (0.4)	5.3 (0.3)	5.4 (0.3)[e]	5.7 (0.5)[e]	0.103	< 0.001
HOMA S (%)	Baseline	71.0 (23.9)	32.0 (24.3)[b]	31.8 (14.0)[b]	21.0 (7.4)[b,d]	23.8 (8.6)[b,d]		
	One year		67.1 (33.6)[e]	43.5 (19.9)[e]	60.0 (29.9)[e]	33.1 (15.7)[e]	< 0.001	0.793
First phase$_{est}$ (pM)	Baseline	1348 (455)	2693 (906)[b]	2406 (942)[b]	2238 (931)[b]	2096 (1041)[b,d]		
	One year		2366 (710)[e]	2077 (903)[e]	1785 (728)[e]	1873 (683)	0.463	0.762
Total AUC$_{Ins/Gluc}$ (pmol/mmol)	Baseline	53.1 (22.4)	104.4 (36.6)[b]	96.5 (42.8)[b]	77.4 (34.6)[b,d]	72.9 (28.1)[b,d]		
	One year		97.2 (32.7)	78.7 (38.7)[e]	70.5 (30.6)	71.0 (26.3)	0.614	0.155
$\Delta Ins_{30}/\Delta Gluc_{30}$ (pmol/mmol)[f]	Baseline	147 (96)	230 (100)[b]	216 (123)[b]	144 (99)[d]	119 (62)[d]		
	One year		256 (139)	249 (167)	172 (153)	149 (111)	0.842	0.993

Data are given as mean (SD) or n (%). AGT is defined by fasting glucose ≥ 6.1 mmol/l and/or 2 hour glucose ≥ 11.1 mmol/l.

[a]*P*-value for the effect of treatment choice and glucose tolerance status at baseline on change in the variables, two-way ANOVA. Between group differences at baseline, one-way ANOVA with post hoc comparison (LSD): [b]$P < 0.05$ versus control group; [c]$P < 0.05$ versus surgery group in the same glucose tolerance group; and [d]$P < 0.05$ versus NGT group in the same treatment group. Within group differences, paired samples t-test: [e]$P < 0.05$. [f]Five subjects were excluded due negative or extremely high values.

Abbreviations: AUC, area under the curve; Ins, insulin; and Gluc, glucose.



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*P < 0.05, controls versus intervention groups.
†P < 0.05, surgery versus lifestyle group.

51x30mm (600 x 600 DPI)

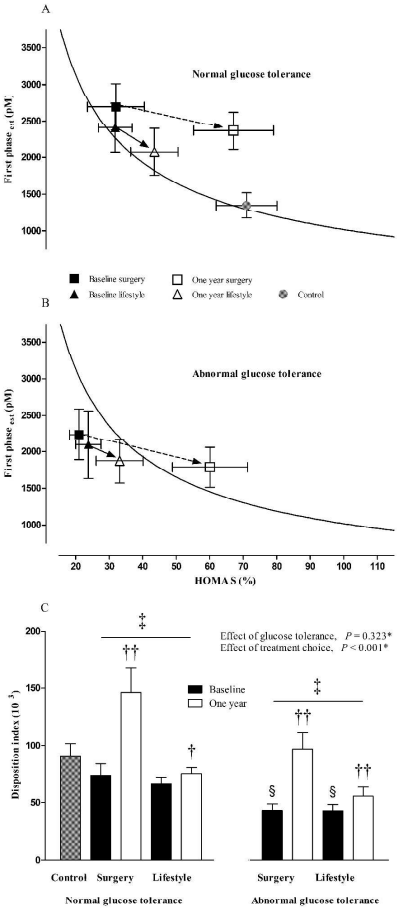

Figure 2 Mean HOMA-S plotted against first phaseest in controls and morbidly obese subjects with normal glucose tolerance (A) and abnormal glucose tolerance (B) before and one year after gastric bypass and lifestyle intervention. The curve represents the regression line of the natural logarithm of estimated insulin secretion as a linear function of the natural logarithm of estimated insulin sensitivity for all participants with normal glucose tolerance at baseline. The bar graph (C) represents mean value of the corresponding disposition indices. Error bars represent 95 % CIs.
*P-value for the effect of treatment choice and glucose tolerance status at baseline on change in disposition index, two-way ANOVA.
†P < 0.05, ††P <0.001, one year versus baseline, paired samples t-test.
‡P < 0.001, between groups (surgery versus lifestyle) changes in disposition index within the same glucose tolerance group, ANCOVA with adjusting for baseline value.
§P < 0.001, normal glucose tolerance versus abnormal glucose tolerance within the same

intervention group at baseline, independent samples t-test.

170x354mm (600 x 600 DPI)

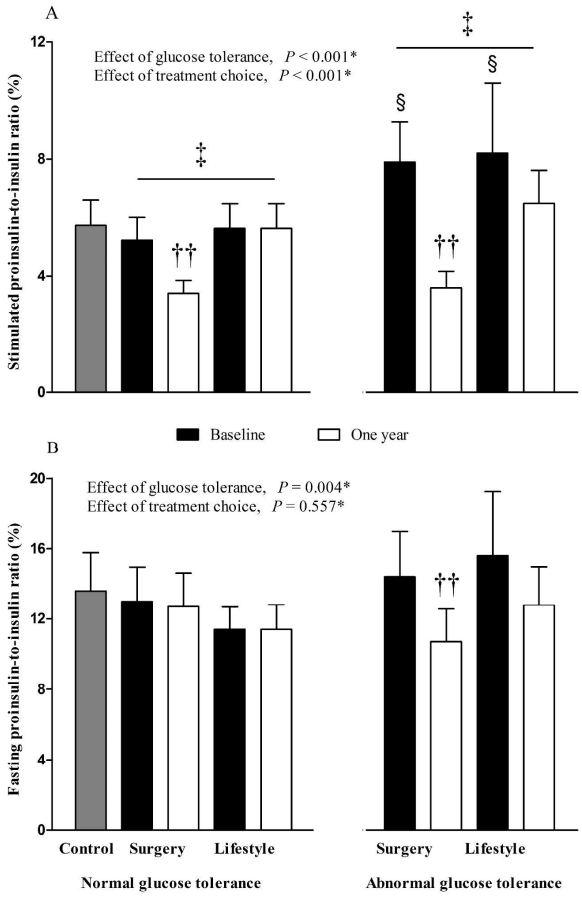

Figure 3 Mean stimulated (A) and fasting (B) proinsulin-to-insulin ratios in controls and morbidly obese subjects with normal and abnormal glucose tolerance before and one year after gastric bypass and lifestyle intervention. Error bars represent 95 % CIs.
*P-value for the effect of treatment choice and glucose tolerance status at baseline on change in disposition index, two-way ANOVA.
††P < 0.001, one year versus baseline, paired samples t-test.
‡P < 0.001, between groups (surgery versus lifestyle) changes in disposition index within the same glucose tolerance group, ANCOVA with adjusting for baseline value.
§P < 0.001, normal glucose tolerance versus abnormal glucose tolerance within the same intervention group at baseline, independent samples t-test.

122x181mm (600 x 600 DPI)