# Gastric bypass versus sleeve gastrectomy for type 2 diabetes (Oseberg): a single-centre, triple-blind, randomised controlled trial

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**Summary**

**Background:**

The comparative effectiveness of various bariatric procedures on remission of type 2 diabetes remains debated. We aimed to compare the two most commonly used procedures, hypothesising higher remission rates of diabetes after gastric bypass than after sleeve gastrectomy.

**Methods:**

The Oseberg study is an ongoing triple-blind, randomised, single-centre trial taking place at Vestfold Hospital Trust, Norway. Adult patients with type 2 diabetes and obesity were randomly assigned (1:1) to receive either gastric bypass or sleeve gastrectomy. Randomisation was performed with a computerised random number generator using block sizes of 10. Treatment allocation was concealed using sealed opaque envelopes, and was masked from participants, study personnel and outcome assessors. Primary outcomes were, first, the proportion of participants with complete remission of diabetes; glycated haemoglobin 6·0% (42 mmol/mol) or less with no diabetes medication, and, second, beta-cell function modelled from an intravenous glucose tolerance test at one year. Analyses were performed according to intention-to-treat and per-protocol principles. The trial is registered at ClinicalTrials.gov with identifier: NCT01778738.

**Findings:**

Between January 28, 2013 and February 4, 2018, 109 patients were randomly assigned to gastric bypass (n=54) or sleeve gastrectomy (n=55), with a total of 107 (98%) patients completing 1-year follow-up. Remission of diabetes occurred in 40/53 patients (75%) in the gastric bypass-group and 26/54 patients (48%) in the sleeve gastrectomy-group; risk ratio 1·57, 95% CI 1·14–2·15; p=0·0036. Beta-cell function increased 6- to 7-fold from baseline, with no differences between groups. The number of early and late complications after gastric bypass and sleeve gastrectomy were 10 versus 8 and 17 versus 22, respectively.

**Interpretation:**

Gastric bypass being found to be superior to sleeve gastrectomy for remission of type 2 diabetes might have important individual and societal implications, including the potential to improve diabetes care and reduce related societal costs.

**Funding:** No external funding.

# Introduction

Type 2 diabetes is strongly associated with obesity and is caused by insulin resistance and impaired insulin secretion from the pancreatic beta-cells.[1] For patients with obesity and diabetes, weight loss improves both insulin sensitivity and beta-cell function, and may even induce remission of diabetes.[2] Remission of diabetes improves health related quality of life, removes stigma of having diabetes, reduces costs, and may reduce diabetes-related microvascular complications.[3,4] In 2016, more than 100,000 people with diabetes underwent bariatric surgery worldwide, with the majority receiving either sleeve gastrectomy or gastric bypass.[5,6]

Before the initiation of the present study, no randomised trial had compared the efficacy of gastric bypass and sleeve gastrectomy on remission of diabetes as a primary outcome. However, the landmark open-label STAMPEDE randomised trial, which compared the effect of bariatric surgery and intensive lifestyle intervention on the primary outcome glycaemic control; HbA1c 6% (42 mmol/mol) or less, also reported 1-year remission rates of diabetes.[7] Importantly, the remission rate tended (non-significantly) to be more favourable after gastric bypass than after sleeve gastrectomy.[7] More recently, two open-label randomised controlled studies with remission of diabetes as primary endpoint, showed no significant difference between gastric bypass and sleeve gastrectomy.[8,9] However, these two studies had some methodological issues including small sample sizes, lack of allocation concealment, and no intention-to-treat analyses. In addition, a small open-label randomised controlled trial aiming to compare HbA1c level change at 1-year post surgery showed no significant differences between gastric bypass and sleeve gastrectomy.[10] Finally, two recently published randomised controlled trials including 25% and 42% patients with type 2 diabetes, reported remission of diabetes as secondary or exploratory outcomes, with no significant differences between groups.[11,12]

Some small mechanistic studies have suggested that gastric bypass and sleeve gastrectomy may improve pancreatic beta-cell function independent of weight loss, with no significant differences between the procedures.[13,14]

In view of the lack of sufficient evidence from previous studies, the randomised "*O*besity *s*urg*e*ry in Tøns*berg*" (*Oseberg*) trial was undertaken.[15] The primary objectives were to compare the effects of gastric bypass and sleeve gastrectomy on glycaemic control and β-cell function in subjects with severe obesity and type 2 diabetes. Specifically, we aimed to compare the effects of the two most commonly performed bariatric procedures worldwide, first, on remission of diabetes and, second, on beta-cell function. We hypothesised higher 1-year remission rates after gastric bypass than after sleeve gastrectomy, possibly explained by better β-cell function.

# Methods

## Study design

The Oseberg study is a randomised, triple-blind, single-centre superiority trial taking place at Vestfold Hospital Trust in Norway. Patients with severe obesity and type 2 diabetes were randomised and allocated to Roux-en-Y gastric bypass or sleeve gastrectomy. The study protocol was approved by the Regional Committees for Medical and Health Research Ethics in Norway (ref: 2012/1427/REK sør-øst B) and has been published previously,[15] the full protocol is also available in the appendix (pp 33-85).

## Participants

All patients scheduled for bariatric surgery at the centre were asked if they were willing to participate and thereafter were screened for study eligibility according to the following criteria: Age ≥18 years, current BMI ≥33·0 kg/$m^2$ with previously verified BMI ≥35·0 kg/$m^2$, and type 2 diabetes (glycated haemoglobin ≥6·5% [48 mmol/mol] or use of anti-diabetic medications with glycated haemoglobin ≥6·1% [43 mmol/mol]). Key exclusion criteria were previous major abdominal surgery, cancer, severe medical conditions associated with increased risk of complications, drug or alcohol addiction, pregnancy, and severe gastro-oesophageal reflux disease (Los Angeles classification grade>B or Barrett's oesophagus). Detailed exclusion criteria are shown in the appendix (p 6). Potentially eligible patients provided a written informed consent and underwent a screening examination to confirm eligibility.

## Randomisation and masking

Patients were randomised and allocated (1:1 ratio) to either gastric bypass or sleeve gastrectomy, using a computerised random number generator (randomization.com) with block sizes of 10. The surgeon generating the randomisation sequence (MS) was not involved with patient follow-up. Sequentially numbered, sealed opaque envelopes were used to conceal allocation, which was revealed in the operating theatre by the bariatric surgeon on the day of surgery. All study personnel, patients, and the primary outcome assessor (biostatistician, co-author MCS), were blinded to allocations. The surgeons used identical skin incisions during both surgeries, and did not participate

in patient follow-up. In case of emergency, a list linking name and study identification number with study procedure was available at the study office and in the emergency department.

## Procedures

The two intervention groups received identical pre- and post-operative treatment, including a low calorie diet (<1200 kcal/day) during the two weeks preceding surgery. Antidiabetic and antihypertensive medication, statin therapy, the management of reflux disease and vitamin and mineral supplementations, were adjusted according to specific predefined algorithms (appendix pp 7, 8). Patients were informed about healthy diets and physical activity, and the medical treatment was in accordance with international guidelines. [15]

The surgical procedures were performed laparoscopically.[15] Gastric bypass was performed with a 25 ml gastric pouch, an alimentary limb of 120 cm and a biliopancreatic limb of 60 cm. During sleeve gastrectomy, the greater curvature was dissected free starting 4 to 5 cm from the pylorus and up to the angle of His, with a tubular sleeve created using a 35 Fr bougie. All procedures were performed by at least one of four experienced bariatric surgeons, all of whom are certified specialists in gastrointestinal surgery.

After surgery, patients were assessed at 5 weeks, 16 weeks, 34 weeks and one year. The study is ongoing with annual visits at 2, 3, 4 and 5 years after the surgical procedure. Assessments at each time-point are shown in the appendix (p 9). Whole blood glycated haemoglobin (HbA1c) was analysed on a Tosoh high-performance liquid chromatography G8 analyser (Tosoh Corporation, Tokyo, Japan). An insulin-modified intravenous glucose tolerance test (IVGTT) was performed as previously described. [15,16] Measures of insulin sensitivity (SI) and first phase insulin secretion (acute insulin response to glucose, AIRg) were determined using the MINMOD Millennium Program version 6.02.[16] For the calculation of SI, a specific weighting algorithm formulated by the program developer was followed in order to better fit the model to the data (appendix pp 3-5). Disposition index (DI) was calculated as the product of SI and AIRg. Homeostasis model assessment (HOMA) insulin sensitivity and secretion indices based on fasting insulin and glucose were calculated using the

computer based HOMA 2 Calculator.[17] A complete list of method principles, sample matrix, units and analytical precision are shown in the appendix (pp 10, 11).

## Outcomes

This study has two primary outcomes; first, one clinical, the proportion of participants with complete remission of type 2 diabetes (glycated haemoglobin 6·0% [42 mmol/mol] or less without the use of glucose lowering medication); [18] and, second, one physiological, the DI, a measure of beta-cell function, both assessed 1 year after surgery. [15]

Secondary outcomes were assessed at baseline, 5 weeks, 16 weeks, 34 weeks and 1 year (appendix p 9). Key secondary outcomes addressed in the present article were 1-year changes in glucose homeostasis, body weight, body composition, cardiovascular risk factors and energy balance (appendix p 12). Adverse events were assessed and registered at each visit, including surgical and medical complications, hypoglycaemic episodes, dumping, and vitamin and mineral deficiencies. Early complications occurring within six weeks after the surgical procedure, were graded according to the Contracted Accordion Classification system (grade I-IV).

At each visit patients were examined for complications and side effects since the previous visit. [15] Medical records were obtained and reviewed to confirm possible complications. Symptomatic hypoglycaemia was defined as having symptoms of hypoglycaemia and a blood glucose level ≤ 3·9 mmol/l. Symptoms of early and late dumping were graded on a scale from zero to three. At baseline, symptoms of dumping and hypoglycaemia the preceding year were recorded.

## Statistical analysis

Before the study start (2013), based on data from the STAMPEDE trial, [7] a publication by Lee WJ et al., [20] and our own data, [19] we anticipated diabetes remission rates of 75 % and 50 % one year after gastric bypass and sleeve gastrectomy, respectively. Only one small study addressing changes in DI after RYGB was available, guiding us to assume mean (SD) DIs of 270 (160) and 180 (160), [21] after gastric bypass and sleeve gastrectomy, respectively.

Keeping significance level to 5% and power to 80%, a total study sample of either 110 (remission) or 100 (DI) subjects was required. To accommodate possible dropouts, [19] the study sample was set to 125 participants.

The primary outcomes were reported as counts and percentages of patients with remission and changes in DI in each group. Data were analysed according to the intention to treat principle and per-protocol. The binary outcomes were analysed using Chi-Square test and logistic regression for repeated measures. The results are presented as risk ratio (RR) and risk difference for remission, with 95 % confidence intervals (CI). Continuous outcomes were analysed using linear mixed effects models for repeated measures. Both repeated measures models were not adjusted for any confounders. The robustness of the results was assessed with sensitivity analyses using different glycated haemoglobin cut offs: below 6·5 % (48 mmol/mol) without use of anti-diabetic medications (combined complete and partial remission), and below 5·7 % (39 mmol/mol) without use of anti-diabetic medications (normoglycaemia). To assess a possible mediating effect of weight change on remission, we used the 2-stage regression method proposed by Baron and Kenny.[22] All tests were two-sided and significance level was set to 0·05. Since the study has two primary endpoints, the significance level for the main outcomes was adjusted using Bonferroni correction.

The primary statistical analyses were performed by MCS (biostatistician) with STATA software, version 15·0 and SPSS software, version 25·0. STATA was used to perform logistic regression for repeated measures, linear mixed effects models for repeated measures and the mediation analyses. All other statistical analyses were performed using SPSS. The complete statistical analysis plan is available in the appendix (pp 19-32).

The steering committee monitors the overall conduct of the ongoing clinical trial and meets face to face every sixth months.[15] This study is registered in ClinicalTrials.gov (NCT01778738).

## Role of the funding source

The study is organised and financed by the Morbid Obesity Centre, Vestfold Hospital Trust, Tønsberg, Norway. The funder of the study had no role in study design, data collection, data analysis, data

interpretation, or writing of the report. Seven authors (DH, FF, HB, JKH, LKJ, MSC and JH) had independent access to the data, with all authors vouching for data completeness, accuracy and for the fidelity of the trial to the protocol. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

# Results

A total of 1,305 patients preparing for bariatric surgery, including 319 consecutive patients with type 2 diabetes, were assessed for eligibility; 101 were found ineligible and 93 declined participation, leaving 125 patients who were initially enrolled and underwent a baseline examination between January 28, 2013 and February 4, 2018 (figure 1). The baseline examination revealed the presence of previously undetected exclusion criteria in the cases of 14 patients, and two patients withdrew their consent. After exclusion of these 16 patients, 109 patients were randomly assigned to gastric bypass (n=54) or sleeve gastrectomy (n=55) (figure 1). The 16 patients who were excluded or withdrew shortly after baseline examination did not differ significantly from the 109 randomised patients (appendix p 13). One patient in each group withdrew after surgery, leaving 107 patients (98%) to complete one year follow up.

At baseline, the 109 randomised patients had a mean age of 47·7 years (SD 9·6), mean BMI was 42·3 kg/$m^2$ (SD 5·3) median duration of diabetes was 5 years (IQR 2–10), median glycated haemoglobin level was 7·9 % (IQR 6·9–9·0), 63 mmol/mol (IQR 52-75), and 66% were women. The patient characteristics were similar in both groups (table 1). Mean operating time was significantly longer for gastric bypass than for sleeve gastrectomy; 65 minutes (SD 20) versus 49 minutes (SD 20); p<0·0001. Median (range) duration of hospital stay after the procedures was comparable between groups; 1 day (range 1-6) after sleeve gastrectomy and 1 day (range 1-4) after gastric bypass; p=0·34.

Complete remission of diabetes after one year follow-up occurred in 40 of 53 patients (75%) in the gastric bypass group and 26 of 54 patients (48%) in the sleeve gastrectomy group; RR 1·57, 95% CI 1·14–2·15; p=0·0036; risk difference 27%, 95% CI 10–45 (table 2). Intention to treat analyses showed that remission rates were comparable between groups at 5-week; risk difference -5%, 95% CI -20 to 10; p=0·49, and 16-week follow-up; risk difference 7%, 95% CI -11 to 26; p=0·44, but differed at 34-week; risk difference 26%, 95% CI 9 to 44; p=0·004, and 1-year follow-up; risk difference 27%, 95% CI 10 to 44; p=0·002 (figure 2A).

The IVGTT was performed in approximately 80% of the patients at baseline, 5-weeks and one-year follow-up (appendix p 14). Adjustments allowing for a better fit of the IVGTT minimal model were needed in approximately one fourth of the accepted tests, and were more often needed at baseline than at one year. From baseline to one year follow-up, DI increased 6- to 7-fold, with no significant difference between groups; between group difference 55, 95% CI -111 to 220; p=0·52 (table 2, figure 3). The per-protocol analyses, including only patients with measurements at all time-points, showed similar results (table 2).

Glycated haemoglobin decreased approximately 2 percent points in both groups during follow-up (table 2, figure 2B). The proportion of patients not using any diabetes medication after one year was higher after gastric bypass (85%) than after sleeve gastrectomy (63%), p<0·0001 (table 2, figure 2C). Detailed medication use at each visit point is listed on page 15 of the appendix.

AIRg and SI improved similarly within both groups (table 2, figure 3). HOMA2S% increased approximately 5-fold in the gastric bypass group and 3-fold in the sleeve gastrectomy group; the absolute between-group difference was 27 percentage points, 95% CI 14–39; p<0·0001, while HOMA2B% was stable in both groups during the study (table 2).

Estimated body weight loss and fat mass loss were significantly greater after gastric bypass than after sleeve gastrectomy (table 2, figure 2D), and the percentage total body weight loss was 29%, 95% CI 27–30; versus 23%, 95% CI 21–24; difference 6%, 95% CI 4–8; p<0·0001. Approximately one third (33%, 95% CI 9–93) of the effect of surgical group on remission was mediated by weight loss; indirect effect RR=1·16, 95% CI 1·04–1·41; p=0·0010. The direct effect of the type of operation; RR=1·37, 95% CI 1·01–1·97; p=0·0013, indicates that about two thirds of the effect was mediated by the type of operation.

During the one year follow-up, total daily energy intake declined similarly in both groups (table 2). Total daily energy expenditure declined more in the gastric bypass group than in the sleeve gastrectomy group, while energy expenditure per kg body weight per day increased similarly in both

groups (table 2). The number of daily steps increased similarly in both groups (table 2). Adherence to prescribed vitamin and mineral supplementations was high in both groups (appendix p 15). Total-cholesterol and LDL-cholesterol levels declined in the gastric bypass group only: estimated between-group differences 0·67 mmol/l, 95% CI 0·35-0·98; p<0.0001, and 0·63 mmol/l, 95% CI 0·35-0·92) mmol/l; p<0·0001, respectively (table 2), despite a lower proportion of patients using lipid lowering agents in the gastric bypass group (17% vs. 33%) after one year, p=0·042 (appendix p 15). Mean systolic blood pressure and the proportion of patients using any antihypertensive drugs declined similarly in both groups (table 2, appendix p 15). C-reactive protein decreased similarly in both groups (table 2).

The total number of adverse events is shown in table 3. One patient was reoperated for intra-abdominal bleeding after sleeve gastrectomy and one patient was readmitted 10 days after gastric bypass surgery due to a marginal ulcer requiring blood transfusions. Among patients with early complications, 5 out of 8 patients were readmitted after sleeve gastrectomy and 7 out of 10 patients after gastric bypass. There were no deaths. No clinically relevant changes in blood levels of haemoglobin, vitamins and minerals were observed after either surgery (appendix pp 16, 17). The number of patients reporting one or more episodes of symptomatic hypoglycaemia were 7 (13%) after sleeve gastrectomy and 9 (19%) after gastric bypass during the study period, p=0·60. The number of patients experiencing postprandial hypoglycaemia (one to four hours after a meal) tended to increase with time after gastric bypass in those patients not taking insulin or sulfonylurea drugs (appendix p 17). Five (9%) patients in the gastric bypass group not receiving insulin- or sulphonylurea-treatment had at least one episode of postprandial hypoglycaemia between week 34 and 52, compared with none in the sleeve gastrectomy group (p=0·027). However, the Arts' late dumping score[15] did not differ between the two groups at one year (appendix p 18). In contrast, the early dumping score was, although low, higher in the gastric bypass group than in the sleeve gastrectomy group at one year.

Sensitivity analyses confirmed the main finding with a similarly increased probability of combined complete and partial remission of diabetes among the patients in the gastric bypass group as compared with those in the sleeve gastrectomy group; RR 1·45, 95% CI 1·12-1·88; p=0·0038, while the proportion of patients with normoglycaemia did not differ significantly between groups; RR 1·56, 95% CI 0·92-2·65; p=0·091.

## Discussion

This randomised study of patients with type 2 diabetes and obesity showed that patients allocated to gastric bypass had a substantially higher likelihood of complete diabetes remission after one year than those allocated to sleeve gastrectomy, while beta-cell function improved similarly in both groups.

The main clinical finding of the present study is in accordance with our hypothesis, but in contrast with two randomised studies that showed similar effects of gastric bypass and sleeve gastrectomy.[8,9] However, these trials had some methodological limitations, and they differed from the present study by including different ethnic groups.

Our findings do, however, extend and support some secondary and exploratory outcomes from the STAMPEDE-trial which showed that both the proportion of patients achieving remission of diabetes and the proportion not using any antidiabetic medication at 1-year, tended to be higher after gastric bypass than after sleeve gastrectomy, 42% versus 27%, and 78% versus 51%, respectively. [7] Further, the STAMPEDE trial demonstrated that total weight loss was greater after gastric bypass than after sleeve gastrectomy, which is comparable with our results. Notably, the superior weight loss-effect of gastric bypass in STAMPEDE was sustained after 5 years. [23] However, as compared with STAMPEDE, the remission rates in the Oseberg trial were higher in both surgical groups, 42% vs 75%, and 27% vs 48%, respectively. This discrepancy is probably partly explained by less severe diabetes among participants in the Oseberg trial than those in STAMPEDE, as shown by lower HbA1c (mean 8·1% [65 mmol/mol] vs 9·4% [79 mmol/mol]), shorter duration of diabetes (mean 6·5 years vs mean 8·4 years) and less use of insulin (20% versus 44% of patient using insulin before surgery).

The SLEEVEPASS and the SM-BOSS open-label randomised clinical trials compared the long-term effects of gastric bypass and sleeve gastrectomy on weight loss (primary outcome), but 5-year remission rates of diabetes (secondary and exploratory outcomes) were also assessed in subgroups of participants with type 2 diabetes.[11,12] Although these studies were not powered to compare remission rates of diabetes, the crude proportions of patients achieving long-term diabetes remission

were numerically higher (not statistically significant) in the gastric bypass groups than in the sleeve gastrectomy groups, 10 of 40 patients (25%) versus 5 of 41 patients (12%), and 19 of 28 patients (68%) versus 16 of 26 patients (62%), respectively.[11,12] These studies were corroborated by two small open label randomised trials comparing gastric bypass and sleeve gastrectomy showing no significant differences in remission of diabetes between groups.[10,24]

The Diabetes Remission Clinical Trial (DiRECT) showed that 46% of participants allocated to a low energy formula diet had complete or partial remission of diabetes after a mean weight loss of 10 kg (10%) after 1 year, which is slightly lower than the 57% of patients achieving complete or partial remission in the sleeve gastrectomy group in the present study.[4] However, as compared with the Oseberg patients, the DiRECT participants had both less advanced diabetes and shorter duration of diabetes (mean 3·0 years vs mean 6·5 years), while none used insulin.

Although the present study focused on remission of diabetes, improved diabetes control might be equally important in terms of preventing future complications. All of the 3 long-term (5-year) studies comparing gastric bypass and sleeve-gastrectomy, [11,12,23] showed sustained improvement of diabetes control (HbA1c) in both groups, tending (non-significantly) to favour gastric bypass. In addition, a significantly higher proportion of patients in the STAMPEDE gastric bypass-group were off diabetes medication after 5 years compared with those who underwent sleeve gastrectomy (45% versus 25%). Although it has been argued that metformin should be continued even when HbA1c is less than 6% (42 mmol/mol), no patient in the present study stayed on metformin on this basis.

To our knowledge, the present study is the first to indicate that beta-cell function as assessed by IVGTT, improves similarly 1 year after gastric bypass and sleeve gastrectomy. Unexpectedly, beta-cell function did not improve more after gastric bypass than after sleeve-gastrectomy, which might mean that there is no true difference between procedures. However, this negative finding must be interpreted with caution. First, although the intravenous minimal model method is extensively validated and applied, [16,25] we cannot rule out that other measures of insulin sensitivity and insulin secretion, including the assessment of the incretin effect, would have given different results.

The IVGTT is, however, a dynamic test of beta-cell function, measuring the insulin secretion response to a standardised dose of intravenous glucose without the potential confounding effects caused by anatomical differences between the surgical procedures. Second, our findings of larger variations in DIs than anticipated reduced the power to detect any significant differences between groups. Our finding of a similar increase in early beta-cell function 5 weeks after gastric bypass and sleeve gastrectomy supports and extends the results from a recent study of subjects assessed 3 weeks after gastric bypass (n=10) and sleeve gastrectomy (n=10).[13]

The present study showed that gastric bypass was associated with a 6% larger 1-year weight loss than sleeve gastrectomy. This finding contrasts with those from a recent meta-analysis, in which few studies included patients with diabetes, [26] but supports both the findings of the STAMPEDE trial, [7,23] and an observational study including only patients with diabetes. [27] Further, the superior effect of gastric bypass on diabetes remission was partly mediated by weight loss, which confirms previous observational results.[27]

Given the strong association between body weight and insulin sensitivity,[1,2] it is somewhat surprising that insulin sensitivity measured by the IVGTT (SI) did not improve more after gastric bypass than after sleeve gastrectomy. Insulin sensitivity measured by this technique reflects whole body insulin sensitivity. In contrast, HOMA2S% is often considered a measure of hepatic insulin sensitivity.[1] HOMA2S% increased more after gastric bypass than after sleeve gastrectomy, and one might speculate that greater improvement in hepatic insulin sensitivity may have contributed to higher remission rates of type 2 diabetes after gastric bypass than after sleeve gastrectomy.

The measured changes in energy balance could not explain the observed weight loss differences between groups. However, the methods used to assess energy intake and expenditure have inherent limitations, and as such the results should be interpreted with caution. It might seem surprising that total daily energy expenditure decreased more in the gastric bypass group than in the sleeve gastrectomy group, but this was explained by the larger body weight loss in the former group, with

body weight adjusted energy expenditure (kcal/kg/day) increasing similarly in both groups. The latter results partly confirm previous studies which have shown increased weight corrected energy expenditure after bariatric surgery, particularly after gastric bypass. [28] Further, reductions in energy intake were comparable between groups (Table 4).

Almost half of the patients in each group reported at least one complication. However, only one severe complication occurred in each group, and many complications were not related to the treatment. Although the number of patients experiencing hypoglycaemia did not differ between the groups, post-prandial hypoglycaemia among patients not taking insulin or sulphonylureas was more common one year after gastric bypass than after sleeve gastrectomy. Moreover, dumping symptoms were more common after gastric bypass than after sleeve gastrectomy. Blood levels of haemoglobin, vitamins and minerals did not change significantly after surgery. Gastroesophagal reflux disease is a key secondary outcome in the Oseberg study, and will be fully addressed in a separate scientific paper.

The present study has some limitations. First, the generalisability of the results is limited by the single-centre design, the inclusion of less than half of the eligible patients, and a relatively short 1-year follow-up. Regarding the latter, although our definition of remission is in line with previous landmark trials,[4, 7] it does not satisfy the stricter criterion suggested by Buse et al. requiring at least 1 year's duration of remission.[18] Further, loss of remission may occur over time, and it is uncertain whether gastric bypass will remain superior to sleeve-gastrectomy longer term. However, we chose to assess this primary endpoint one year after surgery because maximum weight loss and remission rates were anticipated to appear 12-18 months after surgery, and we would be able to compare our 1-year results with those from STAMPEDE, the only contemporary high-quality study comparing the surgical methods.[7] In addition, we were able to calculate a reasonable sample size based on the contemporary trials addressing 1-year outcomes. [7,19,20] Importantly, participants in the Oseberg study will be followed for 5 years. [15] Second, most patient were white, and the results may not be generalisable to populations of other ethnicities. Third, the sample size calculations were performed

separately for each of the two primary end points, which reduced statistical power to detect differences between groups. Accordingly, Bonferroni correction was applied when interpreting the analyses to compensate for two outcomes. Fourth, it may be argued that the optimal technique for both procedures requires a variation of the skin incisions, and, accordingly, that our use of identical skin incisions may be considered a limitation. On the contrary, we would argue that the standardisation of procedures and port placement may have reduced operating time and overall complications, with the standardisation of port placement not limited to the present study, but also implemented as a part of our routine clinical practice.

The major strengths of the present study are the triple blind randomized design, an unbiased sample, a low attrition rate (1.8 %) and remission as a predefined primary endpoint, which all increase the generalisability of the results. Furthermore, changes in the prescription and dosage of glucose lowering medication were pre-specified in detail in the protocol.

The present study demonstrated a substantially greater 1-year glycaemic effect of gastric bypass (diabetes remission in 3 out of 4 patients) compared with sleeve gastrectomy (diabetes remission in 2 out of 4 patients) which challenges the common view that the surgical procedures yield comparable effects [26,29]. Reported complications and side effects were comparable. Our results might therefore have important individual and societal implications with the potential to improve patient care and clinical practice.[30]

**Contributors**

DH, NN and JH conceived the study and are the principal investigators. DH, FF, HB, KIB, HLG, JKH, LKJ, NN, MS, TGV, RS, and JH contributed to the design and overlooked the study conduct. DH, FF, HB, and JH wrote the manuscript. MCS was responsible for the statistical analyses. All authors critically participated in interpretation of the data, reviewed the manuscript for intellectual content and approved the final version of the manuscript.

**Declaration of interests**

FF declares an educational grant (PhD) from South-Eastern Norway Regional Health Authority during the conduct of the study. KIB declares grants from Novo Nordisk, Lilly, Merck, Astra Zeneca, Boehringer Ingelheim, and Roche Diagnostics, outside the submitted work. HLG declares other financial relationships from Novo Nordisk, GlaxoSmithKline, and Astra Zeneca, outside the submitted work. The other authors declare no conflicts of interest.

**Data sharing statement**

Access to data collected from this study, including de-identified individual participant data, will be made available following publication upon email request to the corresponding author. Data will be shared with investigators whose proposed use of the data has been approved by the Oseberg steering committee and is according to the consent given by the participants and Norwegian laws and legislations. The trial protocol and statistical analysis plan are available in the supplementary appendix.

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**Figure legends**

**Figure 1: Trial profile**

**Figure 2A: Remission of diabetes 5 weeks, 16 weeks, 34 weeks and 52 weeks after sleeve gastrectomy and gastric bypass.**

Intention to treat analyses showing proportions of patients with remission of diabetes on the y-axis during the follow-up period (x-axis). Bars indicate 95% confidence intervals.

**Figure 2B: Changes in glycated haemoglobin 5 weeks, 16 weeks, 34 weeks and 52 weeks after sleeve gastrectomy and gastric bypass.**

**Figure 2C: Changes in proportions of patients receiving antidiabetic drugs 1 year after sleeve gastrectomy and gastric bypass**

**Figure 2D: Changes in body mass index 5 weeks, 16 weeks, 34 weeks and 52 weeks after sleeve gastrectomy and gastric bypass.**

P-values for the comparisons of continuous data between the groups were derived from linear mixed effects models for repeated measures, and only presented when statistically significant ($p<0.05$).

**Figure 3: Changes in disposition index and its components from baseline to 5 weeks and 52 weeks after sleeve gastrectomy and gastric bypass.**

(A) Disposition index (AIRg*SI). (B) AIRg (acute insulin response to glucose, first phase insulin secretion). (C) SI (insulin sensitivity).

References


1. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia* 2003; **46**(1): 3-19.
2. Grams J, Garvey WT. Weight Loss and the Prevention and Treatment of Type 2 Diabetes Using Lifestyle Therapy, Pharmacotherapy, and Bariatric Surgery: Mechanisms of Action. *Curr Obes Rep* 2015; **4**(2): 287-302.
3. Coleman KJ, Haneuse S, Johnson E, et al. Long-term Microvascular Disease Outcomes in Patients With Type 2 Diabetes After Bariatric Surgery: Evidence for the Legacy Effect of Surgery. *Diabetes Care* 2016; **39**(8): 1400-7.
4. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018; **391**(10120): 541-51.
5. Welbourn R, Hollyman M, Kinsman R, et al. Bariatric Surgery Worldwide: Baseline Demographic Description and One-Year Outcomes from the Fourth IFSO Global Registry Report 2018. *Obesity surgery* 2019; **29**(3): 782-95.
6. Angrisani L, Santonicola A, Iovino P, et al. IFSO Worldwide Survey 2016: Primary, Endoluminal, and Revisional Procedures. *Obesity surgery* 2018; **28**(12): 3783-94.
7. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *New England Journal of Medicine* 2012; **366**(17): 1567-76.
8. Yang J, Wang C, Cao G, et al. Long-term effects of laparoscopic sleeve gastrectomy versus roux-en-Y gastric bypass for the treatment of Chinese type 2 diabetes mellitus patients with body mass index 28-35 kg/m(2). *BMC surgery* 2015; **15**: 88.
9. Tang Q, Sun Z, Zhang N, et al. Cost-Effectiveness of Bariatric Surgery for Type 2 Diabetes Mellitus: A Randomized Controlled Trial in China. *Medicine* 2016; **95**(20): e3522.
10. Keidar A, Hershkop KJ, Marko L, et al. Roux-en-Y gastric bypass vs sleeve gastrectomy for obese patients with type 2 diabetes: a randomised trial. *Diabetologia* 2013; **56**(9): 1914-8.
11. Salminen P, Helmio M, Ovaska J, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss at 5 Years Among Patients With Morbid Obesity: The SLEEVEPASS Randomized Clinical Trial. *Jama* 2018; **319**(3): 241-54.
12. Peterli R, Wolnerhanssen BK, Peters T, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: The SM-BOSS Randomized Clinical Trial. *Jama* 2018; **319**(3): 255-65.
13. Mullally JA, Febres GJ, Bessler M, Korner J. Sleeve Gastrectomy and Roux-en-Y Gastric Bypass Achieve Similar Early Improvements in Beta-cell Function in Obese Patients with Type 2 Diabetes. *Sci Rep* 2019; **9**(1): 1880.
14. Madsbad S, Dirksen C, Holst JJ. Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. *Lancet Diabetes Endocrinol* 2014; **2**(2): 152-64.
15. Borgeraas H, Hjelmesaeth J, Birkeland KI, et al. Single-centre, triple-blinded, randomised, 1-year, parallel-group, superiority study to compare the effects of Roux-en-Y gastric bypass and sleeve gastrectomy on remission of type 2 diabetes and beta-cell function in subjects with morbid obesity: a protocol for the Obesity surgery in Tonsberg (Oseberg) study. *BMJ Open* 2019; **9**(6): e024573.
16. Boston RC, Stefanovski D, Moate PJ, Sumner AE, Watanabe RM, Bergman RN. MINMOD Millennium: a computer program to calculate glucose effectiveness and insulin sensitivity from the frequently sampled intravenous glucose tolerance test. *Diabetes Technol Ther* 2003; **5**(6): 1003-15.
17. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004; **27**(6): 1487-95.
18. Buse JB, Caprio S, Cefalu WT, et al. How do we define cure of diabetes? *Diabetes Care* 2009; **32**(11): 2133-5.

19. Hofso D, Nordstrand N, Johnson LK, et al. Obesity-related cardiovascular risk factors after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. *Eur J Endocrinology* 2010; **163**(5): 735-45.
20. Lee WJ, Chong K, Ser KH, et al. Gastric bypass vs sleeve gastrectomy for type 2 diabetes mellitus: A randomized controlled trial. *Archives of Surgery* 2011; **146**(2): 143-8.
21. Plum L, Ahmed L, Febres G, et al. Comparison of glucostatic parameters after hypocaloric diet or bariatric surgery and equivalent weight loss. *Obesity (Silver Spring)* 2011; **19**(11): 2149-57.
22. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986; **51**(6): 1173-82.
23. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. *N Engl J Med* 2017; **376**(7): 641-51.
24. Kalinowski P, Paluszkiewicz R, Wroblewski T, et al. Ghrelin, leptin, and glycemic control after sleeve gastrectomy versus Roux-en-Y gastric bypass-results of a randomized clinical trial. *Surg Obes Relat Dis* 2017; **13**(2): 181-8.
25. Pacini G, Mari A. Methods for clinical assessment of insulin sensitivity and beta-cell function. *Best Pract Res Clin Endocrinol Metab* 2003; **17**(3): 305-22.
26. Yang P, Chen B, Xiang S, Lin XF, Luo F, Li W. Long-term outcomes of laparoscopic sleeve gastrectomy versus Roux-en-Y gastric bypass for morbid obesity: Results from a meta-analysis of randomized controlled trials. *Surg Obes Relat Dis* 2019.
27. Pucci A, Tymoszuk U, Cheung WH, et al. Type 2 diabetes remission 2 years post Roux-en-Y gastric bypass and sleeve gastrectomy: the role of the weight loss and comparison of DiaRem and DiaBetter scores. *Diabet Med* 2018; **35**(3): 360-7.
28. Munzberg H, Laque A, Yu S, Rezai-Zadeh K, Berthoud HR. Appetite and body weight regulation after bariatric surgery. *Obes Rev* 2015; **16 Suppl 1**: 77-90.
29. Osland E, Yunus RM, Khan S, Memon B, Memon MA. Diabetes improvement and resolution following laparoscopic vertical sleeve gastrectomy (LVSG) versus laparoscopic Roux-en-Y gastric bypass (LRYGB) procedures: a systematic review of randomized controlled trials. *Surgical endoscopy* 2017; **31**(4): 1952-63.
30. Jakobsen GS, Smastuen MC, Sandbu R, et al. Association of Bariatric Surgery vs Medical Obesity Treatment With Long-term Medical Complications and Obesity-Related Comorbidities. *Jama* 2018; **319**(3): 291-301.

**Table 1. Baseline characteristics**

| | Sleeve Gastrectomy (n=55) | Gastric Bypass (n=54) |
|---|---|---|
| **Sex** | ·· | ·· |
| Female | 32 (58%) | 40 (74%) |
| Male | 23 (42%) | 14 (26%) |
| **Age (years)** | 47·1 (10·2) | 48·2 (8·9) |
| **White ethnicity†** | 53 (96%) | 51 (94%) |
| **Employed** | 29 (53%) | 27 (50%) |
| **High school education** | 32 (59%) | 27 (50%) |
| **Current smoker** | 4 (7%) | 7 (13%) |
| **Body mass index (kg/m$^2$)** | 42·1 (5·3) | 42·4 (5·4) |
| **Body weight (kg)** | 126·7 (21·4) | 124·4 (23·2) |
| **Waist circumference (cm)** | 128 (12) | 127 (12) |
| **Duration of diabetes (years)** | ·· | ·· |
| Median (IQR) | 5·0 (2·0–9·0) | 4·0 (2·0–10·0) |
| Mean (SD) | 6·3 (5·5) | 6·6 (6·5) |
| **Glycated haemoglobin (%)** | ·· | ·· |
| Median (IQR) | 7·9 (6·9 –9·9) | 7·6 (6·8 –8·5) |
| **Glycated haemoglobin (mmol/mol)** | ·· | ·· |
| Median (IQR) | 63 (52-85) | 60 (51-70) |
| **Diabetes medication** | 50 (91%) | 46 (85%) |
| **Insulin** | 11 (20%) | 11 (20%) |
| **Diabetes complications†** | 6 (11%) | 7 (13%) |
| **History ischaemic heart disease†** | 2 (4%) | 6 (11%) |
| **Antihypertensive medication** | 36 (66%) | 37 (69%) |
| **Lipid lowering medication** | 28 (51%) | 21 (39%) |

Data are n (%), mean (SD), or median (IQR).

†Race, diabetes complications (retinopathy– neuropathy and nephropathy /albuminuria) and ischaemic heart disease were self-reported.

**Table 2. Primary and secondary outcomes**

| | Sleeve Gastrectomy | Gastric Bypass | Between group difference or risk ratio (95%CI) | p value |
|---|---|---|---|---|
| ***Diabetes remission*** | ·· | ·· | ·· | ·· |
| **Intention to treat analysis** | ·· | ·· | ·· | ·· |
| HbA1c ≤ 6·0 % with no diabetes medications | 26/55 (47%) | 40/54 (74%) | 1·57 (1·14–2·16) | 0·0054 |
| **Per-protocol analysis** | ·· | ·· | ·· | ·· |
| HbA1c ≤ 6·0 % with no diabetes medications | 26/54 (48%) | 40/53 (75%) | 1·57 (1·14–2·15) | 0·0036 |
| ***Disposition index†*** | ·· | ·· | ·· | ·· |
| **Intention to treat analysis** | ·· | ·· | ·· | ·· |
| Baseline | 64 (-32 to 159) | 67 (-28 to 161) | ·· | ·· |
| One year | 460 (363–556) | 518 (419–616) | 58 (-79 to 196) | 0·41 |
| Change from baseline | 396 (279–513) | 451 (334–568 ) | 55 (-111 to 220) | 0·52 |
| **Per-protocol analysis§** | ·· | ·· | ·· | ·· |
| Baseline | 73 (33–113) | 74 (42–106) | ·· | ·· |
| One year | 455 (290–620) | 520 (359–680) | 65 (-162 to 292) | 0·57 |
| Change from baseline | 450 (268–633) | 472 (316–627) | 21 (-214 to 256) | 0·86 |
| ·· | ·· | ·· | ·· | ·· |
| ***Glucose homeostasis*** | ·· | ·· | ·· | ·· |
| **Glycated haemoglobin (%)** | ·· | ·· | ·· | ·· |
| Baseline | 8·4 (8·1–8·7) | 7·9 (7·6–8·2) | ·· | ·· |
| One year | 6·2 (5·9–6·5) | 5·9 (5·6–6·2) | -0·30 (-0·74 to 0·14) | 0·18 |
| Change from baseline | -2·2 (-2·5 to -1·9) | -2·0 (-2·3 to -1·7) | 0·19 (-0·20 to 0·59) | 0·34 |
| **Use of diabetes medications** | ·· | ·· | ·· | ·· |
| Baseline | 50 (91%) | 46 (85%) | ·· | ·· |
| One year | 20 (37%) | 8 (15%) | 0·41 (0·19–0·84) | < 0·0001 |
| **Acute insulin response to glucose (mu·l$^{-1}$* min)†** | ·· | ·· | ·· | ·· |
| Baseline | 94 (40–148) | 86 (32–140) | ·· | ·· |
| One year | 226 (171–281) | 222 (166–277) | -4·7 (-83 to 73) | 0·91 |
| Change from baseline | 132 (81–183) | 135 ( 84–186) | 2·9 (-69 to 75) | 0·94 |
| **Insulin sensitivity (mu/l $^{-1}$ * min$^{-1}$)†** | ·· | ·· | ·· | ·· |
| Baseline | 0·8 (0·5–1·1) | 0·9 (0·6–1·2) | ·· | ·· |
| One year | 2·6 (2·3–3·0) | 2·3 (2·0–2·7) | -0·27 (-0·73 to 0·19) | 0·26 |
| Change from baseline | 1·8 (1·4–2·2) | 1·4 (1·0–1·8) | -0·39 (-0·95 to 0·22) | 0·22 |
| **HOMA2S%*** | ·· | ·· | ·· | ·· |
| Baseline | 24 (17–32) | 21 (14–29) | ·· | ·· |
| One year | 79 (72–87) | 102 (95–110) | 23 (13–34) | < 0·0001 |
| Change from baseline | 55 (46–64) | 81 (73–90) | 27 (14–39) | < 0·0001 |
| **HOMA2B%*** | ·· | ·· | ·· | ·· |
| Baseline | 82 (69–95) | 80 (67–94) | ·· | ·· |
| One year | 88 (75–102) | 85 (72–99) | -2·8 (-22 to 16) | 0·78 |
| Change from baseline | 6·3 (-5·2 to 18) | 5·0 (-6·8 to17) | -1·4 (-18 to 15) | 0·87 |
| **Fasting glucose (mmol/L)** | ·· | ·· | ·· | ·· |
| Baseline | 12·1 (11·2–13·0) | 11·7 (10·7–12·6) | ·· | ·· |
| One year | 6·5 (5·4–7·6) | 5·7 (4·6–6·9) | -0·80 (-2·4 to 0·75) | 0·31 |
| Change from baseline | -5·6 (-6·6 to -4·6) | -6·0 (-7·0 to -5·0) | -0·35 (-1·8 to 1·1) | 0·62 |
| ·· | ·· | ·· | ·· | ·· |

| | | | | |
|---|---|---|---|---|
| **Fasting insulin (pmol/L )** | ·· | ·· | ·· | ·· |
| Baseline | 208 (184–233) | 193 (168–218) | ·· | ·· |
| One year | 81 (51–111) | 48 (16–79) | -33 (-77 to 11) | 0·14 |
| Change from baseline | -127 (-159 to -95) | -145 (-178 to -112) | -17 (-63 to 28) | 0·45 |
| **Fasting C- peptide (pmol/L )** | ·· | ·· | ·· | ·· |
| Baseline | 1607 (1491–1722) | 1654 (1539–1770) | ·· | ·· |
| One year | 1007 (891–1123) | 850 (732–969) | -157 (-322 to 8·9) | 0·064 |
| Change from baseline | -600 (-712 to -489) | -804 (-917 to -691) | -204 (-363 to -45) | 0·012 |
| ·· | ·· | ·· | ·· | ·· |
| ***Body weight and composition*** | ·· | ·· | ·· | ·· |
| **Body mass index (kg/m2)** | ·· | ·· | ·· | ·· |
| Baseline | 42·1 (40·7–43·4) | 42·4 (41·1–43·7) | ·· | ·· |
| One year | 32·4 (31·0–33·7) | 30·3 (28·9–31·6) | -2·1 (-4·0 to -0·21) | 0·029 |
| Change from baseline | -9·7 (-10·3 to -9·1) | -12·1 (-12·8 to -11·5) | -2·5 (-3·3 to-1·6) | <0·0001 |
| **Body weight (kg)** | ·· | ·· | ·· | ·· |
| Baseline | 127 (121–132) | 124 (119–130) | ·· | ·· |
| One year | 97 (91–102) | 89 (84–94) | -7·8 (-15 to -0·32) | 0·041 |
| Change from baseline | -30 (-32 to -28) | -36 (-37 to -34) | -5·7 (-8·3 to -3·0) | <0·0001 |
| % Weight loss | 23 (21–24) | 29 (27–30) | 5·9 (3·9–7·8) | <0·0001 |
| **Fat mass (kg)** | ·· | ·· | ·· | ·· |
| Baseline | 58 (55–62) | 60 (57–63) | ·· | ·· |
| One year | 35 (30–36) | 29 (25–32) | -5·9 (-10 to-1·4) | 0·011 |
| Change from baseline | -24 (-25 to -22) | -31 (-33 to -29) | -7·4 (-9·9 to -5·0) | <0·0001 |
| % Fat mass loss | 40 (38–43) | 52 (50–55) | 12 (8·1–16) | <0·0001 |
| **Fat free mass (kg)** | ·· | ·· | ·· | ·· |
| Baseline | 68 (65–72) | 64 (61–68) | ·· | ·· |
| One year | 63 (59–66) | 60 (56–63) | -2·9 (-7·9 to 2·2) | 0·27 |
| Change from baseline | -5·6 (-6·4 to -4·7) | -4·6 (-5·5 to -3·7) | 0·94 (-0·30 to 2·2) | 0·14 |
| % Fat free mass loss | 8·2 (6·9–9·5) | 7·2 (5·9–8·5) | -0·97 (-2·8 to 0·86) | 0·32 |
| ·· | ·· | ·· | ·· | ·· |
| ***Energy balance*** | ·· | ·· | ·· | ·· |
| **Total energy intake (kcal)** | ·· | ·· | ·· | ·· |
| Baseline | 2800 (2552–3048) | 2601(2354–2850) | ·· | ·· |
| One year | 1462 (1207–1716) | 1609 (1354–1863) | 147 (-213 to 507) | 0·42 |
| Change from baseline | -1339 ( -1617 to -1061) | -993 (-1272 to -714) | 346 (-48 to 740) | 0·085 |
| **Daily total energy expenditure (kcal)** | ·· | ·· | ·· | ·· |
| Baseline | 3274 (3093–3454) | 3265 (3083–3447) | ·· | ·· |
| One year | 2917 (2734–3100) | 2580 (2396–2764) | -337 (-597 to -77) | 0·013 |
| Change from baseline | -357 ( -491 to -357) | -686 (-820 to -551) | -328 (-519 to -139) | 0·0007 |
| **Daily energy expenditure per kg weight (kcal/kg)** | ·· | ·· | ·· | ·· |
| Baseline | 25·9 (24·7–27·2) | 26·3 (25·1–27·6) | ·· | ·· |
| One year | 30·1 (28·8–31·4) | 29·5 (28·2–30·8) | -0·55 (-2·36 to 1·26) | 0·55 |
| Change from baseline | 4·15 (2·82–5·47) | 3·22 (1·90– 4·55) | -0·92 (-2·80 to 0·95) | 0·33 |
| **Daily Steps** | ·· | ·· | ·· | ·· |
| Baseline | 4770 (4048–5491) | 5195 (4467–5924) | ·· | ·· |
| One year | 6474 (5734–7215) | 5909 (5164–6655) | -565 (-1616 to 486) | 0·29 |
| Change from baseline | 1705 (1004–2409) | 714 (8–1420) | -991 (-1986 to 4·1) | 0·051 |
| ·· | ·· | ·· | ·· | ·· |

| | | | | |
|---|---|---|---|---|
| ***Cardiovascular risk factors*** | ·· | ·· | ·· | ·· |
| **Total cholesterol (mmol/L)** | ·· | ·· | ·· | ·· |
| Baseline | 4·6 (4·3–4·8) | 4·4 (4·2–4·7) | ·· | ·· |
| One year | 4·6 (4·3–4·8) | 3·8 (3·5–4·0) | -0·80 (-1·1 to -0·46) | <0·0001 |
| Change from baseline | -0·0023 (-0·23 to 0·22) | -0·67 (-0·89 to -0·45) | -0·67 (-0·98 to -0·35) | <0·0001 |
| **LDL cholesterol (mmol/L)** | ·· | ·· | ·· | ·· |
| Baseline | 2·56 (2·35–2·76) | 2·51 (2·31–2·72) | ·· | ·· |
| One year | 2·80 (2·60–3·01) | 2·12 (1·92–2·33) | -0·68 (-0·97 to -0·39) | <0·0001 |
| Change from baseline | 0·24 (0·04–0·45) | -0·38 (-0·59 to -0·18) | -0·63 (-0·92 to -0·35) | <0·0001 |
| **HDL cholesterol (mmol/L)** | ·· | ·· | ·· | ·· |
| Baseline | 1·04 (0·98–1·10) | 1·02 (0·98–1·08) | ·· | ·· |
| One year | 1·26 (1·20–1·32) | 1·20 (1·14–1·26) | -0·06 (-0·15 to 0·02) | 0·15 |
| Change from baseline | 0·23 (0·18–0·27) | 0·18 (0·13–0·23) | -0·04 (-0·11 to 0·02) | 0·20 |
| **Triglycerides (mmol/L)** | ·· | ·· | ·· | ·· |
| Baseline | 2·20 (1·95–2·44) | 2·23 (1·98–2·48) | ·· | ·· |
| One year | 1·33 (1·08–1·58) | 1·14 (0·88–1·39) | -0·19 (-0·55 to 0·16) | 0·29 |
| Change from baseline | -0·86 (-1·12 to -0·60) | -1·09 (-1·35 to -0·83) | -0·23 (-0·59 to -0·14) | 0·22 |
| **Systolic blood pressure (mmHg)** | ·· | ·· | ·· | ·· |
| Baseline | 132 (128–136) | 131 (127–135) | ·· | ·· |
| One year | 124 (120–128) | 123 (115–131) | -0·74 (-6·5 to 5·0) | 0·80 |
| Change from baseline | -7·5 (-12·0 to -3·1) | -8·0 (-12·5 to -3·6) | -0·5 (-6·8 to 5·8) | 0·88 |
| **Diastolic blood pressure (mmHg)** | ·· | ·· | ·· | ·· |
| Baseline | 84 (82–86) | 84 (82–86) | ·· | ·· |
| One year | 80 (78–82) | 77 (75–79) | -2·5 (-5·4 to 0·5) | 0·10 |
| Change from baseline | -4·5 (-6·9 to -2·1) | -7·1 (-9·5 to -4·7) | -2·6 (-6·0 to -0·8) | 0·14 |
| **C-Reactive Protein (hs-CRP) (mg/L)** | ·· | ·· | ·· | ·· |
| Baseline | 10 (8·2–12) | 9·6 (7·8–11) | ·· | ·· |
| One year | 2·6 (0·86–4·4) | 2·1 (0·30–4·0) | -0·54 (-3·0 to 2·0) | 0·68 |
| Change from baseline | -7·3 (-9·1 to -5·5) | -7·5 (-9·3 to -5·7) | -0·20 (-2·7 to 2·4) | 0·88 |

HbA1c = Glycated haemoglobin

Intervention effects reported as observed numbers (percentages) and crude risk ratios (95% C) for categorical variables· Mean (95% CI) and between group differences (95% CI) for continuous variables (linear mixed models).

†Intravenous glucose tolerance test (IVGTT) data for disposition index, acute insulin response to glucose and insulin sensitivity is missing in 20 (18%) & 25 (22 %) of the patients at baseline and one year respectively.

§Number of patients for disposition index per-protocol analysis at baseline are 43 and 41, at one year 44 and 45 and for change from baseline 37 and 38 in sleeve gastrectomy group and gastric bypass group respectively.

Outcome variables are reported as mean (95% CI) for continuous variables (linear mixed models) and observed numbers (percentages) and crude risk ratios (95% CI) for categorical variables.

*The Homeostasis Model Assessment (HOMA) estimates steady state beta cell function (%B) and insulin sensitivity (%S), as percentages of a normal reference population.

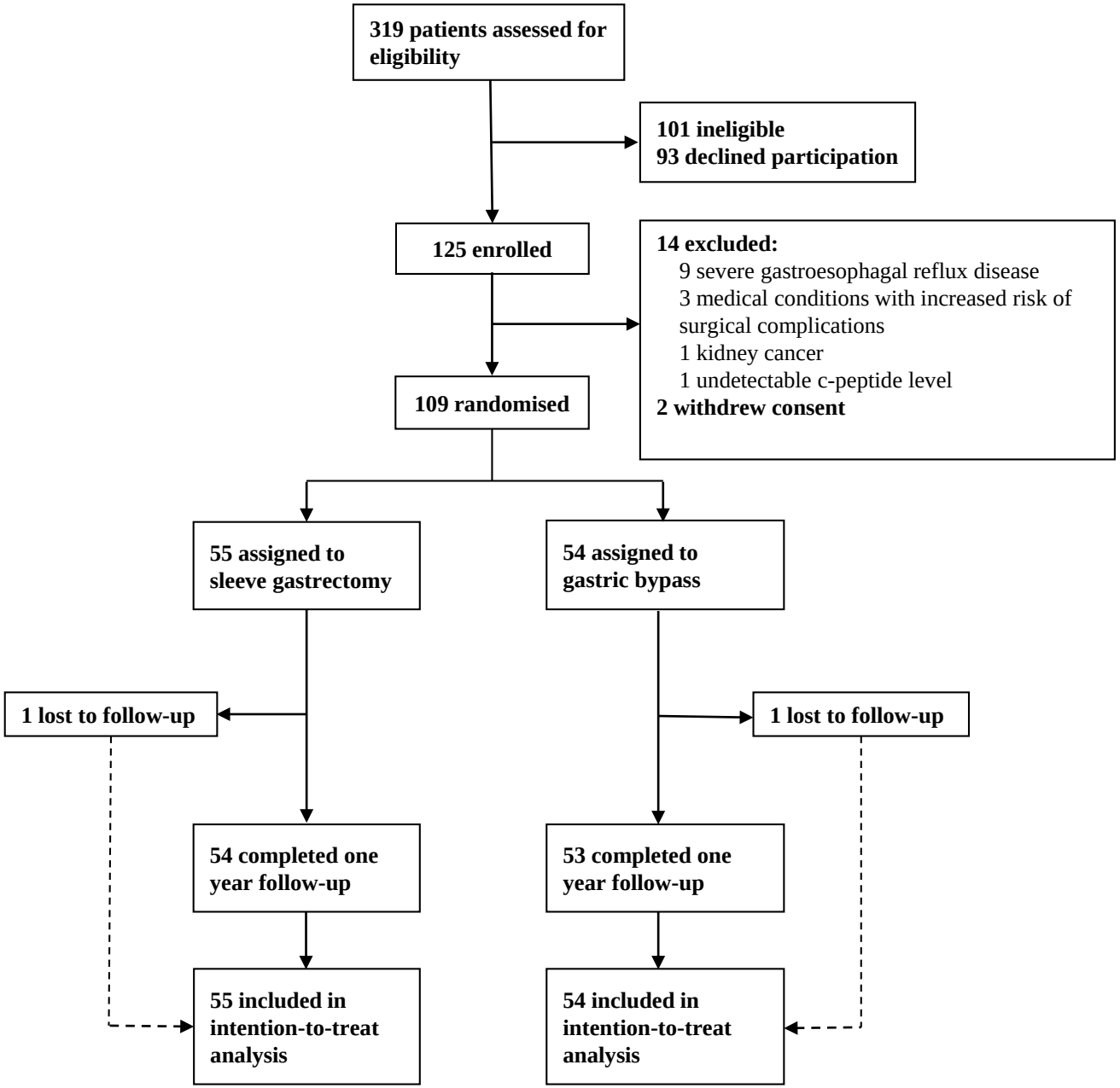
**Table 3. Adverse events***

| | | | Sleeve Gastrectomy | Gastric Bypass |
|---|---|---|---|---|
| **Early complications†** | | | **8** | **10** |
| | **Mild complications (Grade I)** | | **6** | **8** |
| | | Pulmonary infiltration | 0 | 1 |
| | | Urolithiasis | 0 | 1 |
| | | Campylobacter jejuni enteritis | 1 | 0 |
| | | Abdominal pain | 3 | 2 |
| | | Transient renal insufficiency | 0 | 1 |
| | | Fever | 0 | 1 |
| | | Hypotension | 1 | 1 |
| | | Diarrhea | 0 | 1 |
| | | Umbilical hernia | 1 | 0 |
| | **Moderate complications (Grade II)** | | **1** | **1** |
| | | Dysphagia | 1 | 0 |
| | | Clostridium difficile colitis | 0 | 1 |
| | **Severe complications (Grade III)** | | **1** | **1** |
| | | Post-operative bleeding | 1 | 0 |
| | | Anas –motic ulcer | 0 | 1 |
| | **Deaths (Grade IV)** | | **0** | **0** |
| | | | | |
| **Late side effects** | | | **22** | **17** |
| | **Medical conditions** | | | |
| | | Acute myocardial infarction | 1 | 0 |
| | | Palpitations | 0 | 1 |
| | | Chest pain | 2 | 0 |
| | | Peripheral neuropathy in lower extremities | 0 | 1 |
| | | Neuropathic pain in lower extremities | 1 | 0 |
| | | Diarrhea | 0 | 1 |
| | | Hematochezia | 1 | 0 |
| | | Transient thyroiditis | 0 | 1 |
| | | Skin infection | 0 | 1 |
| | | Tonsillitis | 0 | 1 |
| | | Urinary tract infection | 1 | 3 |
| | | Infected benign ovarian tumor | 0 | 1 |
| | | Respiratory tract infection | 0 | 2 |
| | | Otitis externa | 0 | 1 |
| | | Depression | 1 | 0 |
| | **Surgical conditions** | | | |
| | | Cholelithiasis | 1 | 1 |
| | | Appendicitis | 1 | 1 |
| | | Fecalom | 1 | 0 |
| | | Metrorrhagia | 0 | 1 |
| | | Urolithiasis | 1 | 0 |
| | | Cervical intraepithelial neoplasia | 1 | 0 |
| | | Abdominal pain | 4 | 0 |
| | | Minor traumatic musculoskeletal injuries | 3 | 1 |
| | | Minor non-traumatic musculoskeletal injuries | 3 | 0 |

Total number of events are shown. Six patients (three in each group) had two complications and two patients (both after sleeve gastrectomy) had three complications.

* Gastroesophagal reflux disease is not referred in the table because it is a key secondary endpoint in the Oseberg study which will be fully addressed in a separate scientific paper

†Early complications graded according – the Contracted Accordion Classification system (Grade I-IV) occurring within six weeks after the surgical procedure.


319 patients assessed for eligibility
101 ineligible
93 declined participation
125 enrolled
14 excluded:
9 severe gastroesophagal reflux disease
3 medical conditions with increased risk of surgical complications
1 kidney cancer
1 undetectable c-peptide level
2 withdrew consent
109 randomised
55 assigned to sleeve gastrectomy
54 assigned to gastric bypass
1 lost to follow-up
1 lost to follow-up
54 completed one year follow-up
53 completed one year follow-up
55 included in intention-to-treat analysis
54 included in intention-to-treat analysis

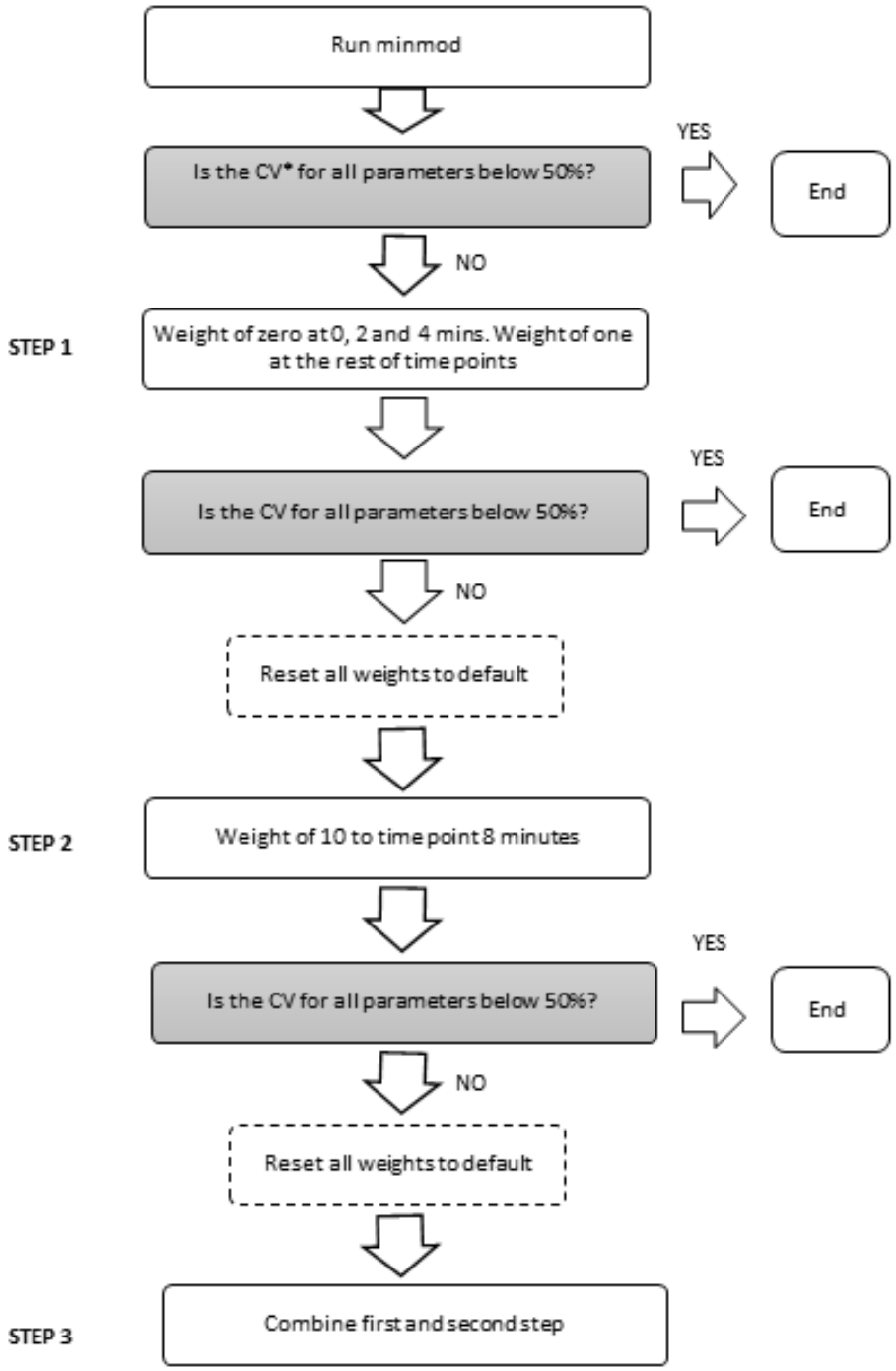
**Supplementary Appendix**

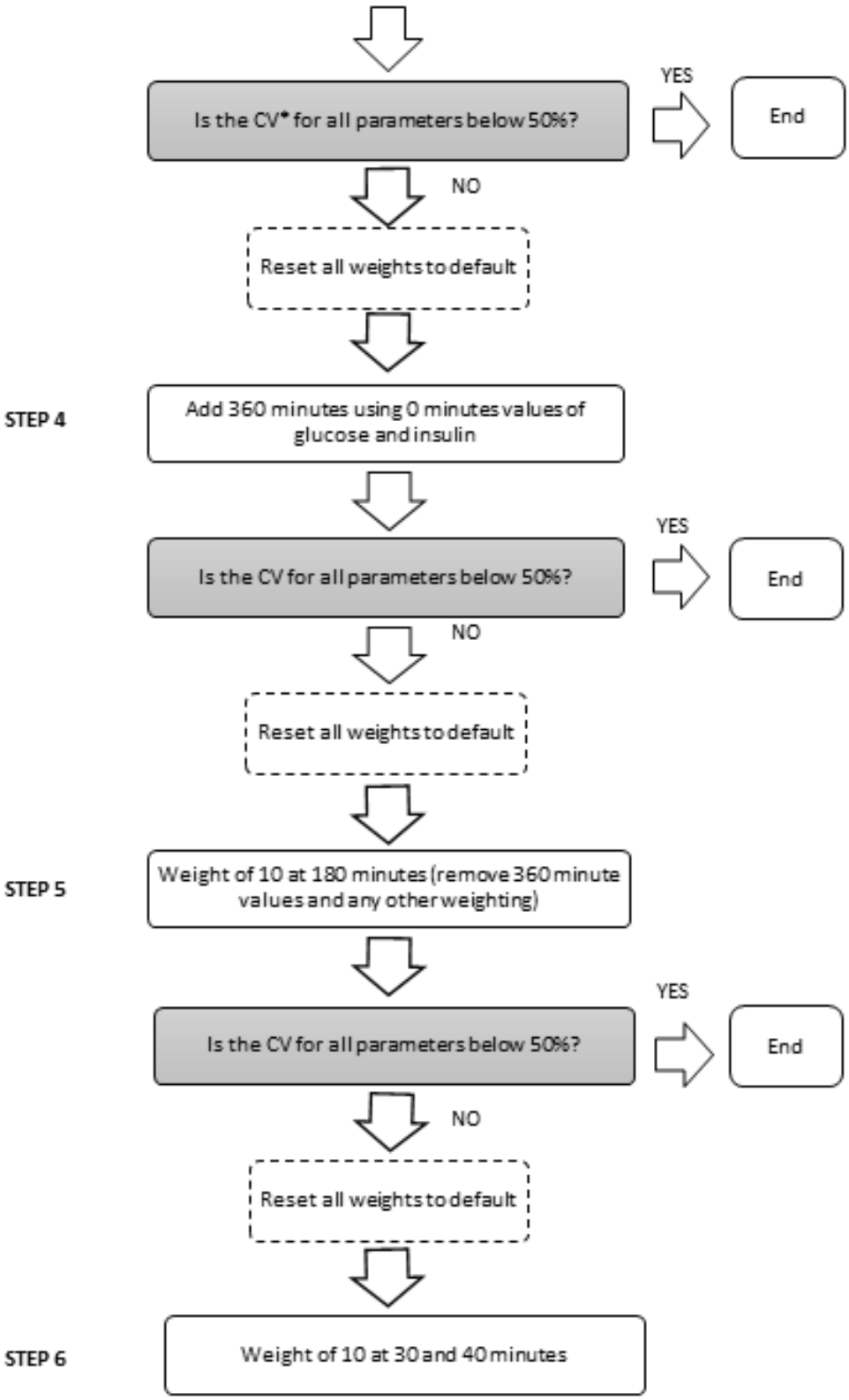
This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Gastric bypass versus sleeve gastrectomy for type 2 diabetes

The Obesity surgery in Tønsberg (Oseberg) study

## Contents


Run minmod
Is the CV* for all parameters below 50%?
YES
End
NO
STEP 1
Weight of zero at 0, 2 and 4 mins. Weight of one at the rest of time points
Is the CV for all parameters below 50%?
YES
End
NO
Reset all weights to default
STEP 2
Weight of 10 to time point 8 minutes
Is the CV for all parameters below 50%?
YES
End
NO
Reset all weights to default
STEP 3
Combine first and second step


Is the CV* for all parameters below 50%?
YES
End
NO
Reset all weights to default
STEP 4
Add 360 minutes using 0 minutes values of glucose and insulin
Is the CV for all parameters below 50%?
YES
End
NO
Reset all weights to default
STEP 5
Weight of 10 at 180 minutes (remove 360 minute values and any other weighting)
Is the CV for all parameters below 50%?
YES
End
NO
Reset all weights to default
STEP 6
Weight of 10 at 30 and 40 minutes

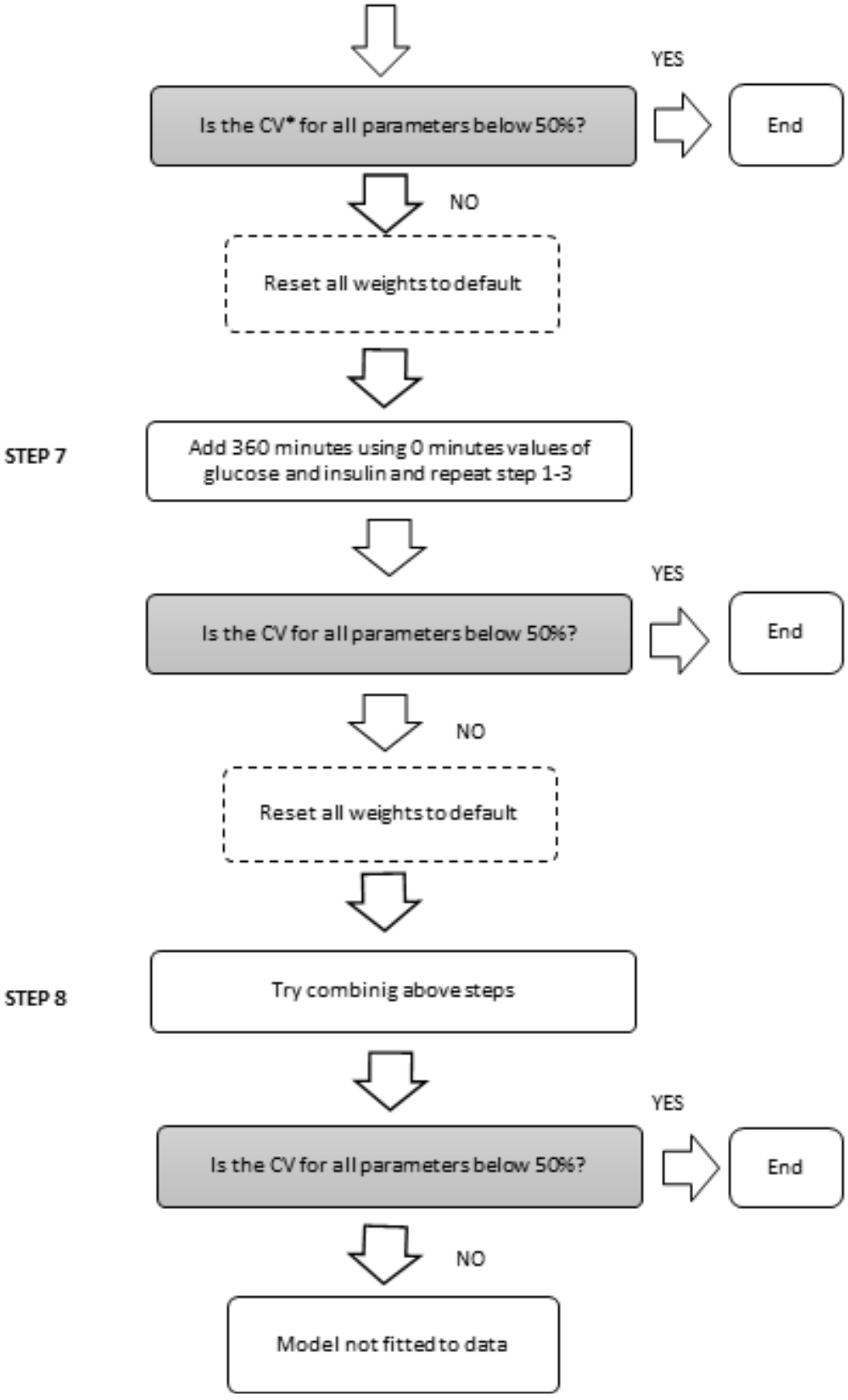



**Figure. 1. Weighting algorithm for fitting of MINMOD model to intravenous glucose tolerance test (IVGTT) data**

*CV:coefficient of variance

**Table 1. Exclusion criteria**

| |
|---|
| Not able to give informed consent |
| Previously major abdominal surgery including bariatric surgery (appendectomy, laparoscopic cholecystectomy or gynaecological procedures not included) |
| Severe endocrine-, heart-, lung-, liver- and kidney disease, cancer and other medical conditions associated with significantly increased risk of peri- and postoperative complications |
| Drug or alcohol addiction |
| Reduced compliance due to severe mental and psychiatric conditions |
| Pregnancy |
| Serum autoantibodies against glutamic acid decarboxylase (GAD) or tyrosine phosphatase (IA2) |
| Regular use (a total of 3 months cumulative use in the last 12 months) or treatment the past two months with systemic corticosteroids |
| Severe gastroesophageal reflux disease defined as Los Angeles classification grade > B, Barrett's oesophagus and/or hiatus hernia >5 cm |
| Elevated esophageal pressure (DCI >5000 mmHg*sec*cm) and symptoms of dysphagia and/or painful swallowing |

**Table 2. Glycaemic therapy – treatment algorithm**

| **Time after surgery:** | | | | |
|---|---|---|---|---|
| **< 6 weeks** | | **≥6 weeks** | | **Action:** |
| Fasting glucose (mmol/l) | <5·6 | HbA1c (%) | ≤6·0 | Reduce treatment - Stop one medication[1] |
| | 5·6 – 11·0 | | 6·1 – 6·9 | No change |
| | ≥11·1 | | ≥7·0 | Intensify treatment - Titrate to max tolerable dose of existing medication or add one new medication*. |

*Preferred anti-diabetic medication in the absence of contraindications or side effects, listed in prioritised order:

Metformin

Dipeptidyl peptidase-IV inhibitors, SGLT2-inhibitors

Pioglitazone, Sulfonylureas, Insulin analogues, GLP-1 agonists

**Table 3. Treatment algorithm for lipid-lowering therapy**

| **Low-density lipoprotein cholesterol** | **Action*** |
|---|---|
| < 2·0 mmol/l | Consider halting medical treatment |
| ≥ 2·6 mmol/l | Consider intensifying medical treatment |

*Statins should be used in patients with established cardiovascular disease or in those aged ≥ 40 years with type 2 diabetes postoperatively (not in remission) and one or more other cardiovascular risk factors.

**Table 4. Treatment algorithm for anti-hypertensive therapy**

| **Systolic blood pressure** | **Action** |
|---|---|
| < 130 mmHg or < 135 mmHg on two consecutive visits | Reduce treatment |
| ≥ 160 mmHg or ≥ 140 mmHg on two consecutive visits | Intensify treatment |

**Table 5. Treatment algorithm for reflux symptoms**

| | **GerdQ score*** | **PPIǂ treatment** | **Action** |
|---|---|---|---|
| No symptoms | 0-2 | No | No treatment |
| | | Yes | Stop PPI |
| Mild symptoms | 3-7 | No | Consider on demand treatment with H2 inhibitors‡ |
| | | Yes | Consider replacing PPI with on demand treatment with H2 inhibitors |
| Severe symptoms | 8-18 | No | PPI for eight weeks |
| | | Yes | Increase PPI dose and consider referral to gastroenterologist |

*Gastroesophageal Reflux Disease Questionnaire.

ǂProton pump inhibitors.

‡Histamine H2-receptor antagonists.

**Table 6. Treatment algorithm for vitamin and mineral supplementation**

| Vitamin/ mineral | Low levels | Intervention | High levels | Intervention |
|---|---|---|---|---|
| B1 (pmol/l) | <ref | In case of acute thiamine deficiency: Admit to hospital for parenteral thiamine treatment<br>Without symptoms:<br>Give oral thiamine 3 mg x 1 | >ref | No intervention |
| Folic acid | <ref | Give folic acid supplement: ”Nycoplus Folsyre” 400 µg x 1 | >ref | Consider discontinuation of supplement |
| B12 (pmol/l) | <ref | Initiate or give B12 injections more frequently | >ref | No intervention or consider a temporary delay in the next B12 injection |
| 25-OH-D (nmol/l) | <ref* | Add vitamin D supplement ”Nycoplus D-vitamin” 10 µg x 2<br><br>*25-OH-D < 50 nmol/l: Give general advise on diet and sun exposure | >ref | Consider discontinuation of all the vitamin D supplements |
| Ferritin | <ref | 1. Increase the dose of iron supplement<br>2. In case of anaemia (Hb <ref) and iron-deficiency, consider parenteral iron | >ref | If elevated ferritin and normal CRP: discontinue iron supplement |
| Calcium | <ref | Initiate or consider increasing vitamin D or calcium supplements | >ref | Discontinue or consider reduction of vitamin D and calcium supplements |

**Table 7. Patient visit schedule**

| | Screening | Baseline | Operation | Follow-up period | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Time (accepted variation)** | | **-3 weeks (-52 to -2)** | **0** | **5 weeks (4 to 8)** | **16 weeks (12 to 24)** | **34 weeks (28 to 40)** | **52 weeks (46 to 60)** | **2,3,4 years ±2 months** | **5 years ±4 months** |
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8-10** | **11** |
| Demographic data | | x | | | | | | | |
| Co-morbidities | | x | | | | | | | |
| Regular medication | | x | | x | x | x | x | x | x |
| Clinical examination | | x | x | x | x | x | x | x | x |
| Physician consultation | x | x | | x | x | x | x | x | x |
| Inclusion and exclusion criteria | x | | | | | | | | |
| Signed informed consent | x | | | | | | | | |
| Blood samples* | x | x | x | x | x | x | x | x | x |
| Urine samples* | | x | | x | | | x | | x |
| Bioelectrical impedance analysis | | x | | x | x | x | x | x | x |
| IVGTT | | x | | x | | | x | | x |
| Food frequency questionnaire | | x | | | | | x | | x |
| SenseWear | | x | | x | | | x | | x |
| Hypoglycaemia/dumping | | x | | x | x | x | x | x | x |
| Adverse events | | | x | x | x | x | x | x | x |

Abbreviations: IVGTT; intravenous glucose tolerance test,.

*See Table S6

**Table 8. Laboratory method principles, sample matrix, units and analytical precision of measurements**

| **Analyte** | **Method principle** | **Sample matrix** | **Unit** | **Precision** (CV, analytical) | **Time point for collection** (visit number)* |
|---|---|---|---|---|---|
| Ferritin | ECLIA | Serum | µg/l | 7 % | 1-11 |
| Iron | Photometry | Serum | µmol/l | 4 % | 1-11 |
| Transferrin | Photometry | Serum | µmol/l | 2·5 % | 1-11 |
| Vitamin B12 | ECLIA | Serum | pmol/l | 12 % | 1-11 |
| Folic acid | ECLIA | Serum | nmol/l | 12 % | 1-11 |
| C-reactive protein | Photometry | Serum | mg/l | 5 % | 1-11 |
| Creatinine | Photometry | Serum | µmol/l | 2·5 % | 1-11 |
| Sodium | ISE | Serum | mmol/l | 1·0 % | 1-11 |
| Potassium | ISE | Serum | mmol/l | 1·2 % | 1-11 |
| Calcium | Photometry | Serum | mmol/l | 1·5 % | 1-11 |
| Magnesium | Photometry | Serum | mmol/l | 3·0 % | 1-11 |
| Phosphate | Photometry | Serum | mmol/l | 2·0 % | 1-11 |
| Albumin | Photometry | Serum<br>Urine | g/l | 3·0 % | 1-11<br>2, 4, 7, 11 |
| Total protein | Photometry | Serum | g/l | 2·5 % | 1-11 |
| Uric acid | Photometry | Serum | µmol/l | 4·0 % | 1-11 |
| Glucose | Photometry | Serum/Plasma | mmol/l | 2·0 % | 1-4, 7, 11 |
| Alanine aminotransferase | Photometry | Serum | U/l | 5 % | 1-11 |
| Aspartate transaminase | Photometry | Serum | U/l | 9·0 % | 1-11 |
| Alkaline phosphatase | Photometry | Serum | U/l | 3·0 % | 1-11 |
| Gamma-glutamyl transpeptidase | Photometry | Serum | U/l | 3·0 % | 1-11 |
| Lactate dehydrogenase | Photometry | Serum | U/l | 5·5 % | 1-11 |
| Creatine kinase | Photometry | Serum<br>Urine | U/l | 5·0 % | 1-11<br>2, 4, 7, 11 |
| Bilirubin | Photometry | Serum | µmol/l | 5·0 % | 1-11 |
| Amylase | Photometry | Serum | U/l | 3·0 % | 1-11 |
| Total cholesterol | Photometry | Serum | mmol/l | 2·5 % | 1-11 |
| HDL-cholesterol | Photometry | Serum | mmol/l | 3·0 % | 1-11 |
| LDL-cholesterol | Photometry | Serum | mmol/l | 3·0 % | 1-11 |
| Triglycerides | Photometry | Serum | mmol/l | 3·0 % | 1-4, 7, 11 |

| | | | | | |
|---|---|---|---|---|---|
| Thyroid stimulating hormone | ECLIA | Serum | mIE/l | 5·0 % | 1-11 |
| Unbound triiodothyronine | ECLIA | Serum | pmol/l | 5·0 % | 1-11 |
| Unbound thyroxine | ECLIA | Serum | pmol/l | 5 % | 1-11 |
| Parathyroid hormone | ECLIA | Plasma | pmol/l | 6·0 % | 1-11 |
| 25-OH-vitamine D | ECLIA | Serum | nmol/l | 6·5 % | 1-11 |
| B-human chorionic gonadotropin[ǂ] | ECLIA | Serum | IE/l | 5·0 % | 1 |
| Paracetamol | Photometry | Serum | µmol/l | 3·0 % | 2, 4, 7, 11 |
| HbA1c | HPLC | Blood | % | 1·4 % | 1-11 |
| Complete blood count | Photometry<br>Impedance<br>Flow cytometry | Blood | g/dl<br>%<br>Cells/l | 1·0-10·0 % | 1-11 |
| Thiamin | HPLC | Serum | nmol/l | 4·5 % | 2, 4-11 |
| Bone alkaline phosphatase | CLIA | Serum | U/l | 9·5 U/L 10 %<br>45 U/L 13 % | 2, 4-11 |
| C-telopeptide of type I collagen | ECLIA | Serum | µg/l | 0·12 µg/L 13 %<br>0·32 µg/L 8 % | 2, 4-11 |
| Procollagen type I N-terminal propeptide | ECLIA | Serum | µg/l | 5 % | 2, 4-11 |
| Insulin | ECLIA | Serum | pmol/l | 4 % | 2, 4, 7, 11 |
| C-peptide | ECLIA | Serum | pmol/l | 4 % | 2, 4, 7, 11 |
| Anti-GAD | IP | Serum | ai | 0·25 ai 25 %<br>1·45 ai 8 % | 1 |
| Anti-IA2 | IP | Serum | Ai | 0·32 ai 18 %<br>1·66 ai 12 % | 1 |
| Samples for storage | | Serum, plasma, blood, urine, faeces | | | 1-4, 7, 11 |

Abbreviations: ai; antibody index, CLIA; chemiluminiscent immunoassay, CV; coefficient of variation, ECLIA; electro-chemiluminescence immunoassay, HPLC; High-performance liquid chromatography, IP; immunoprecipitation, ISE; ion selective electrode

[*]Fasting blood samples visit 2,4,7,11

[ǂ]Women only

**Table 9. Key secondary outcomes**

| |
|---|
| **Glucose homeostasis** |
| Glycated haemoglobin |
| Fasting and stimulated levels of glucose and insulin |
| Insulin sensitivity |
| Insulin secretion |
| Use of anti-diabetic medication |
| .. |
| **Body weight and composition** |
| Body mass index |
| Body weight |
| Fat mass |
| Fat free mass |
| .. |
| **Obesity-related cardiovascular risk factors** |
| Blood pressure |
| Blood lipids |
| Use of lipid lowering drugs |
| C-Reactive protein |
| .. |
| **Physical activity** |
| Daily number of steps (Sensewear) |
| .. |
| **Energy balance** |
| Daily total energy expenditure (Sensewear) |
| Daily total energy intake (Food frequency questionnaire) |
| .. |
| **Harms** |
| Surgical and medical complications |
| Hypoglycaemic episodes and early dumping |
| Vitamin and mineral deficiencies |
| Length of hospital stay |
| Number of readmissions |

**Table 10. Baseline characteristics – randomised patients versus patients excluded before randomisation**

| | Randomised patients (n=109) | Excluded before randomisation (n=16) | P value |
|---|---|---|---|
| **Sex** | .. | .. | .. |
| **Male** | 37 (34%) | 8 (50%) | 0·21 |
| **Female** | 72 (66%) | 8 (50%) | 0·21 |
| **Age (years)** | 47·7 (9·6) | 51.0 (7·6) | 0·19 |
| **White ethnicity*** | 104 (95%) | 16 (100%) | 0·38 |
| **Employed** | 56 (51%) | 7 (44%) | 0·57 |
| **High school education** | 59 (55%) | 7 (44%) | 0·26 |
| **Current smoker** | 11 (10%) | 4 (23%) | 0·36 |
| **Body mass index (kg/m²)** | 42·2 (5·3) | 42·0 (5·6) | 0·87 |
| **Body weight (kg)** | 125·5 (22·3) | 126·3 (18·2) | 0·90 |
| **Waist circumference (cm)** | 127·7 (12·1) | 126·6 (22·7) | 0·76 |
| **Duration of diabetes (years)** | .. | .. | .. |
| **Median (IQR)** | 5 (2-10 ) | 3 (1-10) | 0·61 |
| **Glycated haemoglobin (%)** | .. | .. | .. |
| **Median (IQR)** | 7·9 (6·8-9·0) | 8·2 (7·1- 9·8) | 0·39 |
| **Glycated hemoglobin (mmol/mol)** | .. | .. | .. |
| **Median (IQR)** | 63 (51-75) | 67 (53-86) | 0·39 |
| **Diabetes medication** | 96 (88%) | 15 (94%) | 0·50 |
| **Insulin** | 22 (20%) | 6 (38%) | 0·12 |
| **Diabetes complications*** | 13 (12%) | 2 (13%) | 0·95 |
| **History ischaemic heart disease*** | 8 (7%) | 0 (0%) | 0·23 |
| **Antihypertensive medication** | 73 (67%) | 10 (63%) | 0·72 |
| **Lipid lowering medication** | 49 (45%) | 8 (53%) | 0·54 |

*Race, diabetes complications (retinopathy, neuropathy and nephropathy /albuminuria) and ischemic heart disease are self-reported

**Table 11. Overview of IVGTT data modeling at baseline, 5 weeks and one year**

| | **Sleeve gastrectomy** (n=55) | **Gastric bypass** (n=54) |
|---|---|---|
| **Baseline -** n (%) | | |
| Test not performed * | 8 (15) | 8 (15) |
| Model not accepted | 3 (6) | 1 (2) |
| Model accepted without modifications | 15 (27) | 22 (41) |
| Model accepted with modifications | 29 (53) | 23 (43) |
| | | |
| **Five weeks -** n (%) | | |
| Test not performed* | 13 (24) | 10 (19) |
| Model not accepted | 0 (0) | 0 (0) |
| Model accepted without modifications | 33 (60) | 33 (61) |
| Model accepted with modifications | 9 (16) | 11 (20) |
| | | |
| **One year -** n (%) | | |
| Test not performed* | 13 (24) | 14 (26) |
| Model not accepted | 2 (4) | 0 (0) |
| Model accepted without modifications | 33 (60) | 38 (70) |
| Model accepted with modifications | 7 (13) | 2 (4) |

* Inadequate intravenous access was the most common cause for not performing the test

**Table 12. Medication use at baseline, 5 weeks, 16 weeks, 34 weeks and one year**

| Medications | Baseline | | 5 weeks | | 16 weeks | | 34 weeks | | One year | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sleeve Gastrectomy (n=55) | Gastric Bypass (n=54) | Sleeve Gastrectomy (n=54) | Gastric Bypass (n=54) | Sleeve Gastrectomy (n=54) | Gastric Bypass n=54 | Sleeve Gastrectomy n=54 | Gastric Bypass n=54 | Sleeve Gastrectomy n=54 | Gastric Bypass n=53 |
| **Diabetes medication -** n (%) | | | | | | | | | | |
| Metformin | 43 (78) | 42 (78) | 28 (52) | 25 (46) | 20 (37) | 17 (32) | 18 (33) | 9 (17) | 16 (30) | 7 (13)* |
| Sulfonylurea | 11 (20) | 4 (7·4) | 1 (1·9) | 0 (0) | 1 (1·9) | 0 (0) | 1 (1·9) | 1 (1·9) | 1 (1·9) | 1 (1·9) |
| DPP IV Inhibitors | 15 (27) | 14 (26) | 8 (15) | 5 (9·3) | 6 (11) | 4 (7·4) | 1 (1·9) | 1 (1·9) | 3 (5·6) | 1 (1·9) |
| Glitazones | 1 (1·8) | 1 (1·9) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| GLP 1 Inhibitors | 7 (13) | 15 (28) | 0 (0) | 3 (5·6) | 0 (0) | 2 (3·7) | 0 (0) | 2 (3·7) | 0 (0) | 2 (3·8) |
| SGLT2 Inhibitors | 1 (1·8) | 1 (1·9) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Insulin | 11 (20) | 11 (20) | 9 (17) | 6 (11) | 8 (15) | 5 (9·3) | 8 (15) | 4 (7·4) | 7 (13) | 3 (5·7) |
| No medications | 5 (9·1) | 8 (15) | 21 (39) | 27 (50) | 30 (56) | 35 (65) | 33 (61) | 44 (82)* | 34 (63) | 45 (85)* |
| | | | | | | | | | | |
| **Cardiovascular medication -** n (%) | | | | | | | | | | |
| Antihypertensive agents | 36 (66) | 37 (69) | 31 (57) | 29 (54) | 25 (46) | 21 (39) | 23 (43) | 18 (33) | 23 (43) | 19 (36) |
| Anticoagulants | 10 (18) | 14 (26) | 11 (20) | 13 (24) | 10 (19) | 12 (22) | 10 (19) | 12 (22) | 10 (19) | 11 (21) |
| Lipid lowering agents | 28 (51) | 21 (39) | 23 (43) | 20 (37) | 18 (33) | 13 (24) | 16 (30) | 13 (24) | 18 (33) | 9 (17)* |

*** P value between groups <0.05.**

**Table 13. Vitamin and mineral supplementation use at baseline, 5 weeks, 16 weeks, 34 weeks and one year**

| Vitamin and mineral supplementations - n (%) | Baseline | | 5 weeks | | 16 weeks | | 34 weeks | | one year | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sleeve Gastrectomy (n=55) | Gastric Bypass (n=54) | Sleeve Gastrectomy (n=54) | Gastric Bypass (n=53) | Sleeve Gastrectomy (n=53) | Gastric Bypass (n=54) | Sleeve Gastrectomy (n=54) | Gastric Bypass (n=54) | Sleeve Gastrectomy (n=54) | Gastric Bypass (n=53) |
| Iron | 1 (1.8) | 2 (3.7) | 23 (43) | 19 (36) | 18 (34) | 27 (50) | 17 (32) | 26 (48) | 15 (28) | 24 (45) |
| Calcium | 2 (3.6) | 2 (3.7) | 53 (98) | 51 (96) | 49 (93) | 48 (89) | 50 (93) | 52 (96) | 47 (87) | 49 (93) |
| Vitamin D | 18 (33) | 22 (41) | 50 (93) | 52 (98) | 50 (94) | 52 (96) | 49 (91) | 52 (96) | 49 (91) | 50 (94) |
| Vitamin B 12 | 0 (0) | 8 (15)* | 46 (85) | 39 (74) | 50 (94) | 53 (98) | 50 (93) | 51 (94) | 53 (98) | 53 (100) |
| Multivitamin | 8 (15) | 4 (7.4) | 52 (96) | 52 (98) | 49 (93) | 51 (94) | 49 (91) | 51 (94) | 54 (100) | 53 (100) |

**Table 14. Hemoglobin, mineral and vitamin levels**

| Outcome variable* | Sleeve Gastrectomy (n=55) | Gastric Bypass n=54 | Between group differenceɪ (95 % CI) |
|---|---|---|---|
| Hemoglobin - g/dl | | | |
| Baseline | 13·8 (13·5–14·1) | 13·7 (13·4–14·0) | |
| One year | 13·6 (13·3–13·9) | 13·3 (13·0–13·6) | -0·26 (-0·63–0·12) |
| Change from baseline | -0·2 (-0·45–-0·02) | -0·4 (-0·59–-0·16 ) | -0·14 (-0·44–0·17) |
| | | | |
| Iron - µmol/L | | | |
| Baseline | 15·1 (13·8–16·4) | 13·9 (12·6–15·2) | |
| One year | 17·8 (16·5– 19·1) | 16·2 (14·9–17·6) | -1·5 (-3·4–0·34 ) |
| Change from baseline | 2·7 (1·3–4·0) | 2·3 (0·96–3·7) | -0·33 (-2·3–1·6) |
| | | | |
| Total iron binding capacity - µmol/L | | | |
| Baseline | 65·6 (63·1–68·0) | 64·9 (62·4–67·4) | |
| One year | 63·0 (60·5–65·6) | 61·1 (58·6–63·6) | -2·0 (-5·5–1·6) |
| Change from baseline | -2·5 (-0·62–-4·4) | -3·8 (-1·9–-5·7) | -1·3 (-3·9–1·4 ) |
| | | | |
| Transferrin saturation - % | | | |
| Baseline | 23·2 (21·0– 25·4) | 22·1 (19·8– 24·3) | |
| One year | 28·9 (26·6– 31·2) | 27·5 (25·2– 29·8) | -1·4 (-4·6–1·8) |
| Change from baseline | 5·7 (3·5– 7·9) | 5·4 ( 3·1– 7·6) | -0·30 (-3·5–2·8) |
| | | | |
| Ferritin - µg/L | | | |
| Baseline | 160 (137–183) | 145 (121–168) | |
| One year | 99 (75–122) | 92 (68–115) | -7·1 (-40–26) |
| Change from baseline | -61 (-46–-77) | -53 (-38–-69) | 8·3 (-13–30) |
| | | | |
| Vitamin B12 - pmol/L | | | |
| Baseline | 302 (236–269) | 333 (265–401) | |
| One year | 529 (461–596) | 455 (386–523) | -74 (-170–22) |
| Change from baseline | 226 (140–313) | 122 (34–209) | -104 (-228–18) |
| | | | |
| Folate - nmol/l | | | |
| Baseline | 17 (14–20) | 15 (12–18) | |
| One year | 19 (16–22) | 21 (18–24) | 1·7 (-2·7–6·1) |
| Change from baseline | 2·5 (-1·3–6·3) | 6·3 (2·5–10) | 3·8 (-1·6–9·1) |
| | | | |
| Thiamin B1 - nmol/L | | | |
| Baseline | 154 (146–161) | 153 (145–160) | |
| One year | 161 (153–169) | 160 (153–168) | -0·56 (-12–10) |
| Change from baseline | 7·1 (-0·50–14·7 ) | 7·6 (-0·09–15·4 ) | 0·54 (-10–11) |
| | | | |
| Calcium (Albumin corrected) - mmol/L | | | |
| Baseline | 2·32 (2·30–2·34) | 2·33 (2·31–2·35) | |
| One year | 2·37 (2·35–2·39) | 2·36 (2·34–2·38) | -0·02 (-0·04–0·01) |
| Change from baseline | 0·05 (0·03–0·07) | 0·03 (0·006–0·05) | -0·02 (-0·05–0·004) |
| | | | |
| Vitamin D - nmol/L | | | |
| Baseline | 59 (53–65) | 60 (54–66) | |
| One year | 73 (67–79) | 70 (64–76) | -2·6 (-11–5·9) |
| Change from baseline | 14 (9·0–18) | 10 (5·8–15) | -3·2 (-9·6–3·3) |
| | | | |
| Parathyroid hormone - pmol/L | | | |
| Baseline | 9·6 (8·8–10·4) | 8·3 (7·5–9·1) | |

| | | | |
|---|---|---|---|
| One year | 6·8 (6·0–7·6) | 7·5 (6·7–8·4) | 0·75 (-0·41–1·9) |
| Change from baseline | -2·8 (-3·7–2·0) | -0·78 (-1·7–0·1 ) | 2·1– (0·81–3·2) |

*Outcome variables are reported as estimated mean (95% CI) from linear mixed models.
ŧBetween group difference, sleeve gastrectomy is the reference group.

**Table 15. Number of patients having at least one verified symptomatic hypoglycaemia at baseline and one-year follow-up after sleeve gastrectomy and gastric bypass.**

| | Sleeve Gastrectomy | Gastric Bypass | P-value[1] |
|---|---|---|---|
| **Baseline[2]** | n=55 | n=54 | |
| **All** | 5 (9%) | 5 (9%) | 1·00 |
| **Insulin and/or sulfonylurea users** | 3 (6%) | 4 (7%) | 0·716 |
| **Not using insulin or sulfonylurea** | 2 (4%) | 1 (2%) | 1·00 |
| **Postprandial** | 1 (2%) | 1 (2%) | 1·00 |
| | | | |
| **5 weeks[3]** | n=54 | n=54 | |
| **All** | 3 (6%) | 3 (6%) | 1·00 |
| **Insulin and/or sulfonylurea users** | 1 (2%) | 1 (2%) | 1·00 |
| **Not using insulin or sulfonylurea** | 2 (4%) | 2 (4%) | 1·00 |
| **Postprandial** | 2 (4%) | 1 (4%) | 1·00 |
| | | | |
| **16 weeks[3]** | n=55 | n=54 | |
| **All** | 1 (2%) | 4 (7%) | 0·206 |
| **Insulin and/or sulfonylurea users** | 1 (2%) | 1 (2%) | 1·00 |
| **Not using insulin or sulfonylurea** | 0 (0%) | 3 (6%) | 0·118 |
| **Postprandial** | 0 (0%) | 1 (2 %) | 0·495 |
| | | | |
| **34 weeks[3]** | n=54 | n=54 | |
| **All** | 4 (7%) | 6 (11%) | 0·742 |
| **Insulin and/or sulfonylurea users** | 3 (6%) | 1 (2%) | 0·618 |
| **Not using insulin or sulfonylurea** | 1 (2%) | 5 (9%) | 0·205 |
| **Postprandial** | 1 (2%) | 1 (2%) | 1·00 |
| | | | |
| **1 year[3]** | n=54 | n=53 | |
| **All** | 3 (6%) | 8 (15%) | 0·123 |
| **Insulin and/or sulfonylurea users** | 2 (4%) | 0 (0%) | 0·495 |
| **Not using insulin or sulfonylurea** | 1 (2%) | 8 (15%) | 0·016 |
| **Postprandial** | 0 (0%) | 5 (9%) | 0·027 |

[1]Fisher's exact test
[2]The year preceding enrolment.
[3]Since last visit

**Table 16. Symptoms of early and late dumping in everyday living quantified using the Arts' questionnaire at baseline and one-year follow-up after sleeve gastrectomy and gastric bypass.**

| | Sleeve Gastrectomy | Gastric Bypass | P-value[1] |
|---|---|---|---|
| **Baseline[2]** | n=55 | n=54 | |
| **Arts' early dumping score** | 0 (0-6) | 0 (0-6) | 0·477 |
| **Arts' late dumping score** | 0 (0-3) | 0 (0-6) | 0·975 |
| | | | |
| **5 weeks[3]** | n=54 | n=54 | |
| **Arts' early dumping score** | 1·5 (0-9) | 2 (0-11) | 0·650 |
| **Arts' late dumping score** | 0 (0-3) | 0 (0-3) | 0·754 |
| | | | |
| **16 weeks[3]** | n=55 | n=54 | |
| **Arts' early dumping score** | 1 (0-8) | 1 (0-9 | 0·344 |
| **Arts' late dumping score** | 0 (0-3) | 0 (0-10) | 0·154 |
| | | | |
| **34 weeks[3]** | n=54 | n=54 | |
| **Arts' early dumping score** | 1 (0-10) | 1 (0-8) | 0·590 |
| **Arts' late dumping score** | 0 (0-7) | 0 (0-5) | 0·639 |
| | | | |
| **1 year[3]** | n=54 | n=53 | |
| **Arts' early dumping score** | 0 (0-8) | 2 (0-7) | 0·025 |
| **Arts' late dumping score** | 0 (0-4) | 0 (0-4) | 0·119 |

Data presented as median (range).

[1]Mann–Whitney U test

[2]The year preceding enrolment.

[3]Since last visit

# Statistical analysis plan

**A single-centre, triple blinded, randomised, one year, parallel-group, superiority study to compare the effects of Roux-en-Y gastric bypass and sleeve gastrectomy on remission of type 2 diabetes and β-cell function in subjects with morbid obesity**
**The *O*besity surg*e*ry in Tøns*berg* (*Oseberg*) study**

**Trial registration number:** ClinicalTrials.gov Identifier: NCT01778738

**SAP version:** 1.0
**Date:** 04.04.2019
**Protocol version:** 7.0
**SAP revisions:**
**Roles and responsibilities:** Småstuen MC (PhD), Borgeraas H, Hofsø D (PhD), Fatima F (MD) and Hjelmesæth J (Professor) contributed to the development of the SAP.

# Introduction

Bariatric surgery is associated with long-term weight reduction and improvement of comorbidities, but also with adverse events and side effects[1,2]. Roux-en-Y gastric bypass was for many years considered the 'gold standard' of bariatric surgery, but recently sleeve gastrectomy, a technically easier and faster to perform procedure, has gained popularity and is now the most common bariatric procedure in the US[3].

For subjects with type 2 diabetes and obesity, bariatric surgery is a particularly effective treatment option, and a number of randomised trials have demonstrated the superiority of surgery over medical care for glycaemic control and remission of diabetes[2,4-8]. The improved glycaemic homeostasis following bariatric surgery is to a large extent explained by the hypo-caloric state and weight reduction. However, as improvements often is observed even before changes in body weight occur, some of the effect appears to be independent of weight loss and possibly related to the specific surgical procedure. Both gastric bypass and sleeve gastrectomy reduce the size of the stomach, but only gastric bypass includes a bypass of the duodenum and proximal small intestine. Thus particularly after gastric bypass there is a rapid delivery of undigested food to the small intestine that enhances the release of gut-derived incretin hormones, such as glucagon like peptide-1 (GLP-1) which further stimulate insulin secretion from pancreatic β-cells. Indeed, greater enhancement in postprandial GLP-1 levels have been observed after gastric bypass compared with sleeve gastrectomy[9], while others have reported no significant differences[10-12]. The higher postprandial incretin hormone levels may be causally linked with the improved β-cell function observed after gastric bypass[13-15] and sleeve gastrectomy[16]. However, bariatric surgery is also accompanied with changes in other gut- and pancreatic derived hormones, which directly or indirectly influence glycaemic control[17].

A limited number of high quality studies have compared the effect of gastric bypass and sleeve gastrectomy on remission of type 2 diabetes. Prior to the initiation of the present study, only one randomised controlled study had addressed glycaemic control in subjects with type 2 diabetes and obesity after gastric bypass and sleeve gastrectomy[18]. The STAMPEDE trial showed similar reduction in HbA1c one year after the two surgical procedures. In the following years, results from comparable randomised controlled trails have been published[19-22] including three and five years follow-up data from the STAMPEDE trial[4,23]. The remission rates of type 2 diabetes between the two procedures have not been statistically different in these trials. Thus, there is currently no conclusive evidence showing superiority of gastric bypass or sleeve gastrectomy for patients with type 2-diabetes and obesity. Also, the impact of altered insulin secretion and action, gut microbiota, hepatic steatosis and gastric emptying on glycaemia after gastric bypass compared with sleeve gastrectomy is not clear. Additional relevant outcomes, including changes in body weight, obesity-related cardiovascular risk factors, symptoms and findings of gastroesophageal reflux disease, health-related quality of life, psychosocial status, eating behaviour, bone health, vitamin and mineral deficiencies, surgical complications and side effects, need further examination.

# Objectives

## Primary objectives

The primary objectives of this study are to assess the effects of gastric bypass and sleeve gastrectomy on glycaemic control and β-cell function.

## Secondary objectives

Secondary objectives are to explore changes in variables that are related to the primary endpoint of the study (i.e. body weight and composition, insulin sensitivity, liver fat content, energy intake, stomach emptying rate and intestinal microbiota). Moreover, we will explore cardiovascular risk factors influenced by weight reduction and possibly by changes in gut hormones (i.e. blood pressure, arterial stiffness, albuminuria and lipids). Finally, we will examine possible differences in vitamin and mineral deficiencies, bone density, gastroesophageal reflux disease, hypoglycaemia, dumping syndrome, health related quality of life, psychological distress, obesity-related symptoms, eating behaviour, nutrient intake, gastrointestinal symptoms and surgical and medical complications related to the two operations.

# Study methods

## Trial design

This study is a single centre, triple-blinded, two-armed trial randomising patients with type 2 diabetes and obesity in a 1:1 allocation ratio to either gastric bypass or sleeve gastrectomy.

## Randomisation

The allocation sequence was created using a computerized random number generator (randomization.com) using block sizes of 10.

## Sample size

This study has two primary endpoints and was powered thereafter. Based on previous research addressing glycaemic response of gastric bypass and sleeve gastrectomy in type 2 diabetic subjects[8,18,24,25] remission rates of 75 % and 50 % were assumed, in the first and second group, respectively.

Data on disposition index after sleeve gastrectomy derived from a frequent sample intravenous glucose tolerance test was not available before study start, and data from a study addressing beta-cell function after gastric bypass and a low calorie diet was therefore used for sample size determination[26]. Mean standard deviation (SD) disposition index was 268 (232) after gastric bypass and 94 (92) after a low calorie diet. Based on these figures mean (SD) disposition index after gastric bypass and sleeve gastrectomy was estimated to be 270 (160) and 180 (160) one year after surgery, respectively.

Given a five percent significance level and 80 % power and an equal distribution to the two groups, a total study sample of 110 (remission) or 100 (disposition index) subjects was required to reveal a difference between groups. In order to accommodate possible dropouts (5% in previous study at our centre)[8] we planned to include 120 subjects in the study. Due to a higher than expected number of excluded patients after baseline examinations, the baseline study population was increased to 125.

### Framework

A superiority study comparing the effect of gastric bypass and sleeve gastrectomy on remission of type 2 diabetes.

### Statistical interim analyses and stopping guidance

Interim analyses have not been performed. Members of the steering committee met every sixth months to safeguard the interests of trial participants and monitor the overall conduct of the clinical trial. Adverse events are consecutively reported.

### Timing of final analysis

The final analysis will be performed after all patients have completed one year follow-up.

### Timing of outcome assessments

The Oseberg study includes test and examinations at 5 weeks, 16 weeks, 34 weeks, one year (primary outcome) and two to five years. This comprehensive follow-up enables us to evaluate very early, medium and long-term effects of gastric bypass and sleeve gastrectomy with varying degrees of weight-loss. Clinical examinations and tests with scheduled time points for assessment are listed in Table 2, and a list of the blood, urine and faeces samples that have been and will be collected, including time points for collection, is shown in Table 3. One-year follow-up will be completed in March 2019 and the end of the study period is in December 2023.

## Statistical principles

### Confidence intervals and P values

All applicable statistical tests will be 2-sided, and p-values<0.05 will be considered significant. All confidence intervals will be 95 % and two-sided.

As there are two primary endpoints in this study, we will pay special attention to p-values <0.025 to prevent type 1 errors.

### Protocol deviations

Protocol violations will be registered at every study visit.

### Analysis populations

Data will be analysed according to both the intervention into which patients were randomized (intention-to-treat analysis) and per-protocol (completers).

## Trial population

### Screening data

An overview of examinations, test and data collected at baseline is shown in Table 1 in the attachment section of the protocol.

### Eligibility

The trial inclusion and exclusion criteria, and also details of the number of patients screened and how many were excluded, are specified in the protocol.

### Recruitment

A CONSORT flow diagram will be used to summarize the people screened, eligible, consented, randomized, receiving their allocated treatment and withdrawing/lost to follow-up.

### Withdrawal/follow-up

Withdrawals will be registered consecutively.

### Baseline patient characteristics

Baseline characteristics to be summarized include age, gender, ethnicity employment/education, smoking status, weight, BMI, waist circumference, hip circumference, fat mass, fat free mass, HbA1c, duration of diabetes, blood pressure, lipid levels, activity calorie intake, both overall and separately for the two randomized groups.

Categorical data will be summarized by counts and percentages, and continuous data will be summarized by mean and SD if data are normal and median, interquartile range and range if data are skewed. Clinical importance of any imbalance at baseline will be noted, but test of significance will not be performed.

# Analysis

## Outcome definitions

This study has two primary endpoints, 1) Proportion of participants with complete remission of type 2 diabetes (HbA1c ≤6.0 % in the absence of glucose lowering drug therapy)[27], one year after surgery and 2) The disposition index, obtained from a frequently sampled intravenous glucose tolerance test (FSIGT)[28-30] and measured as a continuous variable, one year after surgery.

Key secondary outcomes include body weight, blood pressure, cholesterol and triglyceride levels, gastroesophageal reflux disease, fatty liver disease, gut microbiota and health related quality of life. The summary measures for the two surgical groups include mean/median with range or standard deviation and counts with proportions, as appropriate. Outcome variables include changes from baseline, final values and time to events and will be measured at baseline, 5 weeks, 16 weeks, 34 weeks, 1 year, and annually for 4 more years.

## Analysis methods

Remission of diabetes at one year will be presented as counts and percentages of patients with remission in each group. In the complete cases analysis (patients who have undergone randomization and have measured the outcome variables at the 1 year visit), Pearson's chi square test will be used to calculate the difference in remission rates between the two groups. Association between remission and group variables will also be analyzed according to intention-to-treat (including all patients who underwent randomization) using mixed effects

logistic regressions for repeated measures. The relative risk (RR) with 95% confidence interval (CI) and risk difference (95 % CI) will also be presented.

Disposition index at one year will be presented as the mean value with standard deviation, or median (interquartile range if the data are skewed) in each of the surgical groups. Data will be analyzed according to intention to treat principle using linear mixed effects models for repeated measures. The results will be presented as the estimated means at selected time points and change from baseline to one year both for between and within groups. In addition, complete cases analyses will be performed using independent samples t-test (for disposition index) or, if the variables are not normally distributed, the variables will be log transformed or a non-parametric test (Mann-Whitney U test) will be used.

Secondary outcomes will be analyzed using the same methods as the primary outcomes.

## Sensitivity analyses

To examine the robustness of the results, different HbA1c cut offs will be used when calculating the difference in proportions of patients with type 2 diabetes remission in the surgery groups.

1. <6.5 % without use of anti-diabetic medications (partial remission)
2. ≤5.6 % without use of anti-diabetic medications ("normal" HbA1c) [31].

## Missing data

Imputation of missing data will not be performed as mixed models analyses do not require complete data.

## Additional analyses

Multiple regression models will be fitted to explore the independent effects of weight change and other variables on primary and secondary outcomes.

To assess a possible mediating effect of weight change on remission and to estimate the total, direct, and indirect effects of group on remission, we used the 2-stage regression method proposed by Baron and Kenny, also known as the product method for mediation. The outcome (remission) will be modelled using Poisson regression and the results expressed as RR and percentages mediated.

## Harms

Surgical complications will be graded according to the Accordion severity grading system[32]. The contracted classification alternative which have four levels (mild complications, moderate complications, severe complications and death) will be used and divided into early and late complications.

Hypoglycaemia is defined as a blood glucose level of less than 2.8 mmol/l or the presence of typical symptoms and signs of hypoglycaemia without other apparent cause[33]. Hypoglycaemic episodes will be categorised according to severity [Severe (requiring medical assistance), moderate (requiring help from another person) and minor (able to treat themselves)], frequency and its relation to food and/or liquid intake (Postprandial: 60 to 180 minutes after a meal). Relief of symptoms when the glucose level is raised to normal will be recorded. During the glucose tolerance test the Arts' questionnaire[34] will be used for differentiating between early and late (caused by hypoglycaemia) dumping. The questionnaire will also be completed at every post-operative visit to identify symptoms of early and late dumping occurring in daily living. Vitamin and mineral deficiencies and bone mineral turn over will be monitored using biochemical analyses depicted in the protocol. Bone mineral density will be estimated by DEXA scanning.

Adverse events are included as secondary endpoints.

## Statistical software

Statistical analyses were performed with STATA 15.0 (STATA Data Analysis and Statistical Software; StataCorp LP, College Station, TX, USA) and IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

# References


1. Puzziferri N, Roshek ITB, Mayo HG, Gallagher R, Belle SH, Livingston EH. Long-term follow-up after bariatric surgery: A systematic review. JAMA - Journal of the American Medical Association 2014;312:934-42.
2. Jakobsen G, Småstuen M, Sandbu R, et al. Association of bariatric surgery vs medical obesity treatment with long-term medical complications and obesity-related comorbidities. JAMA 2018;319:291-301.
3. Estimate of Bariatric Surgery Numbers, 2011-2016. 2016. (Accessed 10.04.18, 2018, at https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers.)
4. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. N Engl J Med 2017;376:641-51.
5. Courcoulas AP, Belle SH, Neiberg RH, et al. Three-year outcomes of bariatric surgery vs lifestyle intervention for type 2 diabetes mellitus treatment a randomized clinical trial. JAMA Surgery 2015;150:931-40.
6. Halperin F, Ding SA, Simonson DC, et al. Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: Feasibility and 1-year results of a randomized clinical trial. JAMA Surgery 2014;149:716-26.
7. Ikramuddin S, Korner J, Lee WJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: The diabetes surgery study randomized clinical trial. JAMA - Journal of the American Medical Association 2013;309:2240-9.
8. Hofso D, Nordstrand N, Johnson LK, et al. Obesity-related cardiovascular risk factors after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. Eur 2010;163:735-45.
9. Ramon JM, Salvans S, Crous X, et al. Effect of Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy on Glucose and Gut Hormones: A Prospective Randomised Trial. Journal of Gastrointestinal Surgery 2012;16:1116-22.
10. Peterli R, Woelnerhanssen B, Kern B, et al. Improvement in glucose metabolism after bariatric surgery: Comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: A prospective randomized trial. Obesity Surgery 2009;19 (8):1006.
11. Peterli R, Steinert RE, Woelnerhanssen B, et al. Metabolic and hormonal changes after laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy: A randomized, prospective trial. Obesity Surgery 2012;22:740-8.
12. Romero F, Nicolau J, Flores L, et al. Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-En-Y gastric bypass surgery for morbidly obese type 2 diabetic subjects. Surg Endosc 2012;26:2231-9.
13. Morinigo R, Lacy AM, Casamitjana R, Delgado S, Gomis R, Vidal J. GLP-1 and changes in glucose tolerance following gastric bypass surgery in morbidly obese subjects. Obes Surg 2006;16:1594-601.
14. Hofso D, Jenssen T, Bollerslev J, et al. Beta cell function after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. Eur2011:231-8.
15. Lin E, Liang Z, Frediani J, et al. Improvement in β-cell function in patients with normal and hyperglycemia following Roux-en-Y gastric bypass surgery. American Journal of Physiology - Endocrinology and Metabolism 2010;299:E706-E12.
16. Basso N, Capoccia D, Rizzello M, et al. First-phase insulin secretion, insulin sensitivity, ghrelin, GLP-1, and PYY changes 72 h after sleeve gastrectomy in obese diabetic patients: the gastric hypothesis. Surg Endosc 2011;25:3540-50.
17. Meek CL, Lewis HB, Reimann F, Gribble FM, Park AJ. The effect of bariatric surgery on gastrointestinal and pancreatic peptide hormones. Peptides 2016;77:28-37.

18. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. New England Journal of Medicine 2012;366:1567-76.
19. Peterli R, Wölnerhanssen B, Peters T, et al. Effect of laparoscopic sleeve gastrectomy vs laparoscopic roux-en-y gastric bypass on weight loss in patients with morbid obesity: The sm-boss randomized clinical trial. JAMA 2018;319:255-65.
20. Salminen P, Helmio M, Ovaska J, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss at 5 Years Among Patients With Morbid Obesity: The SLEEVEPASS Randomized Clinical Trial. JAMA 2018;319:241-54.
21. Keidar A, Hershkop KJ, Marko L, et al. Roux-en-Y gastric bypass vs sleeve gastrectomy for obese patients with type 2 diabetes: a randomised trial. Diabetologia 2013;56:1914-8.
22. Yang J, Wang C, Cao G, et al. Long-term effects of laparoscopic sleeve gastrectomy versus roux-en-Y gastric bypass for the treatment of Chinese type 2 diabetes mellitus patients with body mass index 28-35 kg/m(2). BMC surgery 2015;15:88.
23. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes - 3-Year outcomes. N Engl J Med 2014;370:2002-13.
24. Lee WJ, Chong K, Ser KH, et al. Gastric bypass vs sleeve gastrectomy for type 2 diabetes mellitus: A randomized controlled trial. Archives of Surgery 2011;146:143-8.
25. Pournaras DJ, Aasheim ET, Sovik TT, et al. Effect of the definition of type II diabetes remission in the evaluation of bariatric surgery for metabolic disorders. Br J Surg 2012;99:100-3.
26. Plum L, Ahmed L, Febres G, et al. Comparison of glucostatic parameters after hypocaloric diet or bariatric surgery and equivalent weight loss. Obesity (Silver Spring) 2011;19:2149-57.
27. Buse JB, Caprio S, Cefalu WT, et al. How do we define cure of diabetes? Diabetes Care 2009;32:2133-5.
28. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest 1981;68:1456-67.
29. Steil GM, Volund A, Kahn SE, Bergman RN. Reduced sample number for calculation of insulin sensitivity and glucose effectiveness from the minimal model. Suitability for use in population studies. Diabetes 1993;42:250-6.
30. Mari A. Assessment of insulin sensitivity and secretion with the labelled intravenous glucose tolerance test: improved modelling analysis. Diabetologia 1998;41:1029-39.
31. 16. Diabetes Advocacy: Standards of Medical Care in Diabetes-2019. Diabetes Care 2019;42:S182-s3.
32. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. Ann Surg 2009;250:177-86.
33. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410-8.
34. Arts J, Caenepeel P, Bisschops R, et al. Efficacy of the long-acting repeatable formulation of the somatostatin analogue octreotide in postoperative dumping. Clin Gastroenterol Hepatol 2009;7:432-7.

# Research protocol:
# Glycaemia, insulin secretion and action in morbidly obese subjects with type 2 diabetes after sleeve gastrectomy and Roux-en-Y gastric bypass:

## A randomised single centre study

## *O*besity *s*urg*e*ry in T*ø*ns*berg* (*Oseberg*) study

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**Organisational responsibilities:**

***Executive committee***

Design and conduct of the Oseberg study
Recruitment of patients
Preparation of protocol, CRFs [Case Report Forms] and revisions
Organising steering committee meetings
Maintenance of trial IT system and data entry
Data verification

***Steering committee***

Agreement of final protocol
Reviewing progress of study and if necessary agreeing changes to the protocol to facilitate the smooth running of the study
Meetings twice a year
Safety monitoring

# Introduction

## Obesity and bariatric surgery

Estimates indicate that more than 500 million people are obese [body mass index (BMI) ≥ 30 kg/m$^2$] worldwide (1). In Norway more than one out of five people is obese (2). Subjects with BMI ≥ 40 or ≥ 35 kg/m$^2$ with at least one obesity related co-morbidity are referred to as morbidly obese and may, according to national and international guidelines, qualify for bariatric surgery (3,4). About 2 % of the Norwegian adult population is morbidly obese. Obesity and two of its most common metabolic consequences, hyperglycemia and high blood pressure, alongside tobacco usage and physical inactivity, represent the five leading global risks to mortality (5). Due to the limited long-term success of medical management of obesity, various surgical techniques (bariatric surgery) have been developed during the last few decades (6-8). In 2008 around 340 000 bariatric procedures were performed worldwide (9). To date, the annual number of operations in Norway is around 2500 (D. Hofsø, personal communication). Bariatric surgery results in substantial long-term weight reduction and improvements in several metabolic conditions such as type 2 diabetes and hypertension, psychosocial functioning and health related quality of life (HRQoL), and is associated with reduced mortality (10-28). Severe surgical short-term complications occur in approximately 5% of patients, and many patients experience gastrointestinal side- effects and vitamin deficiencies (29).

## Sleeve gastrectomy and Roux-en-Y gastric bypass

The Roux-en-Y gastric bypass operation combines restrictive and malabsorptive principles (Figure 1). It is the most commonly performed bariatric procedure both in Norway (~ 90 %) (30,31) and worldwide (~ 50 %). Vertical (sleeve) gastrectomy, on the other hand, is a purely restrictive procedure (Figure 1). The operation, which originally was a part of the duodenal switch operation, has gained popularity and is now accepted as a valid stand-alone procedure (32) accounting for approximately five percent of the bariatric procedures performed worldwide

(31). Similar trends are observable in Norway, with some hospitals in western Norway offering sleeve gastrectomy as their sole surgical procedure.

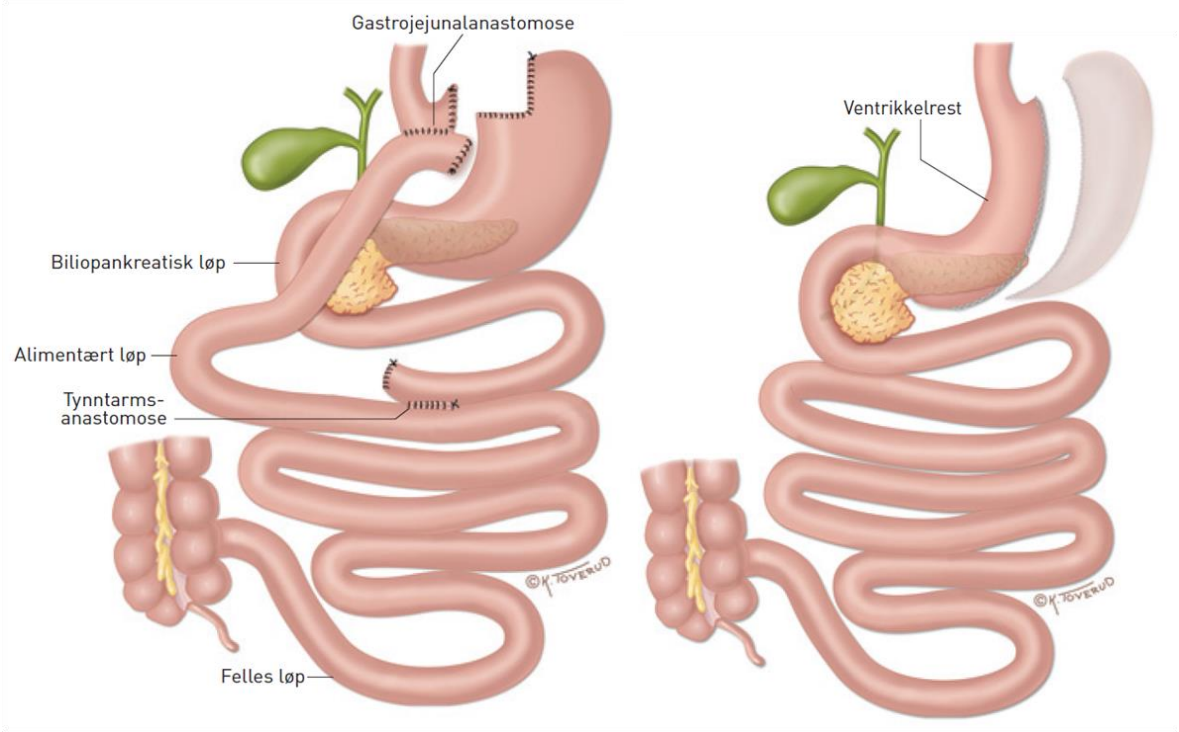


Figure 1. Gastric bypass (left) and sleeve gastrectomy (right). Figure by Kari C. Tover (29).

Despite its growing popularity, the possible beneficial and adverse effects of sleeve gastrectomy have not yet been fully elucidated. The results from a few small randomised controlled studies (33-42), a large US prospective observational study (43) and three reviews including numerous case series (44-46) indicate that the effect of sleeve gastrectomy on weight and metabolic conditions such as type 2 diabetes and hypertension and the procedure`s complication rate is positioned somewhere between gastric banding and gastric bypass. Possible differences between gastric bypass and sleeve gastrectomy, as discussed in the literature, are listed and graded in Table 1.

Table 1. Possible differences between gastric bypass and sleeve gastrectomy.

| | Gastric bypass | Sleeve gastrectomy | References |
|---|---|---|---|
| Weight | ↓↓↓ | ↓↓(↓) | (33-46) |
| HbA1c | ↓↓↓ | ↓↓(↓) | (33,34,47) |
| Vitamin and mineral deficiencies | ↑↑↑ | ↑ | (48,49) |
| Surgical complications (overall) | ↑↑ | ↑ | (43) |
| Intestinal obstruction | ↑ | - | (50) |
| Side effects | | | |
| Dumping | ↑↑ | - | (51) |
| Reflux disease | ↓ | ↑ | (50,52) |
| Health related quality of life | ↑↑↑ | ↑↑(↑) | (53) |

**Type 2 diabetes**

Hand in hand with the rising obesity rate is the substantial increase in diabetes worldwide (54-56). Insulin secretion from pancreatic beta-cells is tightly regulated by blood glucose levels. When beta-cell function is impaired i.e. insulin secretion is insufficient for the prevailing insulin sensitivity, hyperglycaemia occurs. Diabetes is diagnosed in subjects with either fasting blood glucose ≥ 7.0 mmol/l, blood glucose ≥ 11.1 mmol/l two hours after ingestion of 75 g glucose, or HbA1c ≥ 6.5% on two occasions (57). The scientific evidence for the current thresholds is mainly based upon an increased risk of retinopathy above these cut-off levels (58,59).

Blood glucose stimulates insulin secretion and production. However, orally ingested glucose leads to a greater insulin response compared to intravenously administered glucose.

This might be explained by gut-derived factors which in a glucose dependent manner stimulate insulin secretion from pancreatic β-cells. This phenomenon is called the incretin effect and was first described in 1964 (60). In humans two incretin hormones have been identified; namely glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1). Of these, GLP-1, which is probably mainly secreted from ileal L-cells in response to intraluminal nutrients, has the greatest insulinotropic effect.

The remission rate of type 2 diabetes one to two years after bariatric surgery is approximately 70% (15,17,20,21). In a randomised controlled study by Lee et al. (34) the remission rate of type 2 diabetes was significantly higher one year after gastric bypass than after sleeve gastrectomy (93 % versus 47 %). In another study by Schauer et al., obese subjects with type 2 diabetes were given intensive medical treatment and randomised to no surgical treatment, gastric bypass or sleeve gastrectomy (33). After one year the reduction in HbA1c was similar in the surgically treated groups, with a greater number of patients using anti-diabetic drugs in the sleeve gastrectomy group. In both studies weight reduction was significantly greater in those treated with gastric bypass surgery. Larger weight loss can clearly contribute to somewhat greater improvement in glucose homeostasis after gastric bypass than after sleeve gastrectomy. Still, Lee et al. and others (40,61-63) speculate that changes in gut hormones may contribute to higher remission rates of type 2 diabetes after gastric bypass than after sleeve gastrectomy. This notion is supported by one study which reported greater enhancement in postprandial GLP-1 after gastric bypass than after sleeve gastrectomy (64). By contrast, no significant differences in postprandial GLP-1 have been reported by others (36,42,65). Improved β-cell function observed after gastric bypass surgery (66-68) may indeed be linked to higher postprandial levels of GLP-1 as seen after gastric bypass surgery (36,42,64,65). Beta cell function has, to our knowledge, only been addressed in one previous study of sleeve gastrectomy, with the authors reporting an increased first-phase insulin secretion three days after the procedure (69).

We are aware of four ongoing randomised controlled trials comparing the effect of gastric bypass and sleeve gastrectomy on several endpoints including weight and comorbidities (ClinicalTrial.gov identifiers: NCT00722995, NCT00356213, NCT00793143, and NCT00667706). However, these studies include both subjects with and without type 2 diabetes and are therefore not powered to detect between-group differences in HbA1c and beta-cell function in the diabetic patients.

In conclusion, the effect of gastric bypass and sleeve gastrectomy on glycaemia has not yet been fully explored. Moreover, the impact of altered beta-cell function on glycaemia post surgery requires additional research. We hypothesise that greater improvement in beta-cell function after gastric bypass than after sleeve gastrectomy translates into better glycaemic control in subjects with type 2 diabetes one year after surgery.

**Hypertension and the vasculature**

Arterial stiffness is an independent predictor of cardiovascular morbidity and mortality (70,71) and is increasingly recognized as a valid surrogate endpoint of cardiovascular disease (72,73). GLP-1 receptors are expressed in many organs and probably expedite biologic actions in the arterial system and blood pressure regulation (74). Several lines of evidence suggest that GLP-1 analogues have both a blood pressure lowering and arterial softening effect that is independent of weight loss (74-76). Consequently, the effect of gastric bypass and sleeve gastrectomy on blood pressure and arterial stiffness may differ according to different levels of incretin hormones after surgical procedures .

**Gastrointestinal factors**

Gastroesophageal reflux disease (GERD) has been found in 25 to 70 % of obese patients and there is positively correlated to BMI (77,78). It has been suggested that the patophysiology of GERD in morbidly obese patients might differ from that of non-obese patient (78). Analyses of motility and reflux disorders of the esophagus before and after bariatric surgery will add to our

knowledge of the patophysiology of GERD in morbidly obese subjects and also maybe, how this may be treated.

### Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease is common in morbidly obese subjects and has been shown to improve after gastric bypass surgery (79). The effect of sleeve gastrectomy on non-alcoholic fatty liver disease is less well known, indeed, the effect of gastric bypass and sleeve gastrectomy has, to our knowledge, not been explored in a randomised setting.

## Gastrointestinal microbiota

Analyses of gut microbiota have shown that obese subjects have a lower proportion of Bacteroidetes and a higher proportion of Firmicutes compared to lean subjects, moreover, this proportion increases with weight loss. (80). In addition, transplantation of gut flora from obese mice into germ-free recipients resulted in a significantly greater increase in total body fat than colonization with gut flora from lean mice (81). These findings indicate a possible causal association between intestinal microbiota and obesity. Interestingly, in post-bypass individuals Firmicutes were reduced and Proteobacteria increased (82). Similarly, a significant increase in Proteobacteria has been demonstrated in rats after gastric bypass (83). Finally, in one study gut microbiota was analysed in 30 patients before and after gastric bypass surgery, with the authors finding higher concentrations of Escherichia coli species post- surgery (84). These findings show that the intestinal microbiota may be altered by surgical procedures and that these changes may impact upon both body weight and glucose metabolism.

### Behavioural and psychosocial factors

Evidence explaining the effect of gastric bypass versus sleeve gastrectomy on behavioural and psychosocial outcomes is sparse. A large number of studies have concluded that weight loss following bariatric surgery is associated with improvements in general and obesity specific health related quality of life (HRQoL) and psychosocial status (symptoms of depression and

anxiety, self-esteem, and body image) (25,28,85). However, in some patients caloric intake increases during the postoperative period and a significant weight regain may occur. Poor adherence to a postoperative diet and overeating may also result in gastrointestinal discomfort, including nausea, “plugging”, vomiting, and gastric dumping (85). The degree of decreased gastro-intestinal HRQoL varies between surgical procedures, where the most restrictive procedures are associated with the largest degree of discomfort.

## Objectives

### Primary objective

The primary objective of this study is to assess the effects of gastric bypass and sleeve gastrectomy on glycaemic control and beta-cell function.

### Secondary objectives

Secondary objectives are to explore changes in variables that either are or could be related to the primary endpoint of the study (body weight and composition, insulin sensitivity, fat liver content, energy intake, stomach emptying rate and intestinal microbiota). Moreover, other cardiovascular risk factors influenced by weight reduction and possibly by changes in gut hormones (blood pressure, arterial stiffness, albuminuria and lipids) will be explored. Finally, possible differences in vitamin and mineral deficiencies, bone density, surgical and medical complications including hypoglycaemia, quality of life, psychological distress, obesity-related symptoms, and gastrointestinal symptoms will be explored.

# Methods

## Participants

Patients on the waiting list for bariatric surgery at the Morbid Obesity Centre at Vestfold Hospital Trust who according to their case record file fulfil the inclusions criteria and do not have any exclusion criteria will be contacted by phone. Potential candidates for study participation will be invited to an information meeting which includes a screening examination a few moths prior to the randomisation.

The centre is a tertiary health care resource centre with a catchment area of about 900 000 inhabitants. Approximately 5000 consultations are performed annually, as are 200 to 250 bariatric operations. The operations, tests and follow-up visits will be performed at the resource centre. The flow of study participants from screening examination to the end of the study is shown in Figure 2.

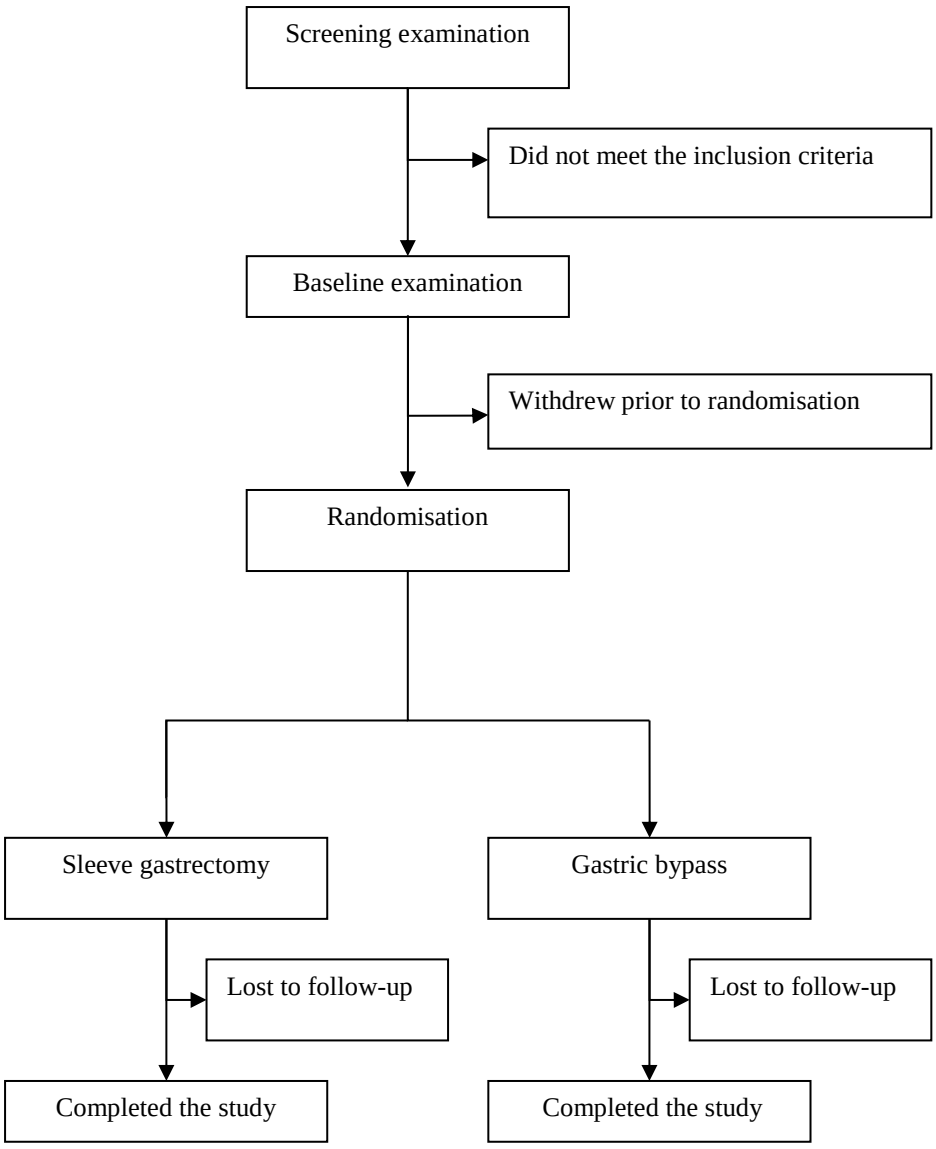


Figure 2. Flow of study participants.

Inclusion and exclusion criteria

**Inclusion criteria:**

- Previously verified BMI ≥ 35.0 kg/m$^2$ and current BMI ≥ 33.0 kg/m$^2$
- HbA1c ≥ 6.5 % or use of anti-diabetic medications with HbA1c ≥ 6.1 %
- Age ≥ 18 years

**Exclusion criteria:**

- Not able to give informed consent
- Previously major abdominal surgery (appendectomy, laparoscopic cholecystectomy or gynaecological procedures not included)
- Severe endocrine-, heart-, lung-, liver- and kidney disease, cancer and other medical conditions associated with significantly increased risk of peri- and postoperative complications
- Drug or alcohol addiction
- Reduced compliance due to severe mental and psychiatric conditions
- Pregnancy
- Serum autoantibodies against glutamic acid decarboxylase (GAD) or tyrosine phosphatase (IA2)
- Regular use (a total of 3 months cumulative use in the last 12 months) or treatment the past two months with systemic corticosteroids
- Reflux disease Los Angeles classification grade > B, Barrett's oesophagus and/or hiatus hernia > 5cm
- Elevated esophageal pressure (DCI >5000 mmHg*sec*cm) and symptoms of dysphagia and/or painfull swallowing

## Intervention

### General

All patients will complete a low calorie diet (3.3-3.8 MJ/day equal to 800-900 kcal/day) in the two weeks preceding surgery. To optimise the results of the procedures all patients will be encouraged to normalise their eating behaviour and to increase their physical activity level. Surgical procedures are performed under general anaesthesia by skilled anaesthetists familiar with obesity surgery. Induction and maintenance of anaesthesia is achieved by combining desfluran (gas) and remifentanil infusion. Pre-operative antibiotic prophylaxis with oral trimetoprim-sulpha before surgery will be used.

All operations will be performed laparoscopicly by skilled surgeons. Gastric bypass has been performed at our hospital since 2004 and sleeve gastrectomy since 2007. During the past

two years approximately 400 gastric bypass procedures and 40 sleeve gastrectomies have been performed at the centre. Sleeve gastrectomy is performed with increasing frequency and accounts for approximately 20% of operations.

For both procedures we shall use a Natansons retractor on a Martins arm to lift the liver. Insufflation of CO2 gas into the abdominal cavity will be administrated in order to maintain an intraabdominal pressure of 15mmHg. Ultrasound energy (Harmonic Ace, Ethicon EndoSurgery) will be used for dissection and hemostasis and occasionally monopolar diathermy. Echelon Flex (Ethicon EndoSurgery) or EndoGIA Ultra Universal Stapler (Covidian) will be used for stampling. The troacars will then be removed under visual guidance in order to inspect for bleeding after the intraabdominal pressure is reduced to 10 mmHg. No drains will be used.

**Sleeve gastrectomy**

The vertical sleeve gastrectomy is performed with 4 troacars in addition to the Nathanson's retractor. The greater curvature will be dissected free from the omentum with ultrasonic energy, Harmonic Ace, from the middle of the ventricle to the angle of Hiss. The left crus will be visualised and inspected for hiatal hernia. Small sliding hernias and wide hiatus will be left in situ. The rest of the greater curvature will then be dissected down to 4-5 cm from the pylorus. The ventricle will then be lifted and any adhesions in the lesser sac divided. A 34 Fr bougie will be placed down to the pylorus before division begins. A tubular ventricle along the bougie using linear staplers will then be created. The first two loads are always green (Ethicon) or purple (Covidien), blue (Ethicon) or tan (Covidien) loads are then used for the rest of the ventricle. The last stapler will be placed 2-5 mm laterally to the angle of Hiss. The staple line will then be inspected and secured with clips for additional hemostasis. The use of buttressing

material and running oversewing of the staple line is not a matter of routine. A leak test will then be performed with 100ml methylene blue.

**Roux-en-Y gastric bypass**

A Roux-en-Y gastric bypass is performed with 4 troacars in addition to Nathansons retractor. The left crus will be dissected free and any hiatal hernia left in place. The minor curvature will be opened at the second vessel and the lesser sac entered. A 25ml gastric pouch will be created by firing one horizontal and 1-2 vertical 45 mm blue (Ethicon) or tan (Covidien) staple loads. The ligament of Treitz will then be identified and a proximal loop of small intestine lifted above the omentum and transverse colon towards the gastric pouch. The small intestine will be anastomosed to the pouch 60 cm from the ligament of Treitz with one firing of a 45 mm linear stapler (white or tan load) using the full length of the stapler. The opening created by the stapler will be closed by a single row, running absorbable suture which will create an antecolic, antegastric alimantary limb. An entero-enteroanastomosis will then be made 120 cm distal of the gastro-enteroanastomosis by firing one 45 mm white load (Ethicon) or tan (Covidien). The introductory opening will be closed with a single row, running absorbable suture. Finally, the small intestine will be divided with one 45 mm white load (Ethicon) or tan (Covidien) between the gastro-entero- and the entero-enteroanastomosis in order to complete the bypass. No dividing of the mesentery will be performed. The omentum will only be divided if needed. A leak-test with metylene-blue will be performed and the pouch inspected on both sides. The mesenteric opening under the entero-enteroanastomosis and at Peterson’s space will be closed with a running, non-absorbable suture.

**Post-operative treatment**

All patients will follow standard post-operative care with observation in a post-operative ward the first few hours after surgery with early mobilisation before transfer to the gastrointestinal surgery ward. Patients will be observed in a gastrointestinal surgery ward and visited daily by a bariatric surgeon.

On the day of the operation patients will not be allowed to drink. The first week after surgery clear liquids followed by full liquid intake are allowed. Patients will be allowed mashed food during week 2 and 3 post-surgery and be encouraged to gradually eat normal food thereafter. During surgery and hospitalisation compression stockings grade II will be used. Low molecular heparin will be given 6 hours after surgery and daily for 14 days, unless there is an indication that longer treatment is required. Patients will be submitted from hospital 1-3 days after surgery depending on the distance to their home. All patients will receive a prescription for a proton pump inhibitor to be used post-operatively for 4 weeks.

## Primary endpoint

The primary objective of this study is to compare the effect of gastric bypass and sleeve gastrectomy on glycaemic control and beta-cell function one year after surgery. Insulin secretion is related to insulin sensitivity and a disposition index (which adjusts insulin secretion for the prevailing insulin sensitivity) will therefore be calculated. The primary endpoints of this study are:

- Complete remission of type 2 diabetes (HbA1c $\leq$ 6.0 % without glucose lowering drugs) (86)
- Disposition index (based on intravenous glucose tolerance test (IVGTT) (87-89))

## Secondary endpoints

### Glucose homeostasis

Since insulin secretion is related to the route in which glucose is administrated (oral versus intravenous), insulin secretion will also be assed using an oral glucose tolerance test (OGTT).

Secondary endpoints related to changes in glucose homeostasis include:

- HbA1c
- Fasting and stimulated glucose, insulin, pro-insulin and c-peptide
- Use of anti-diabetic medication
- Matsuda insulin sensitivity index (OGTT) (90)
- Oral glucose insulin sensitivity model (OGTT) (91)
- Stumvoll's insulin sensitivity and secretion indices (OGTT) (92,93)
- Insulinogenic index (OGTT) (94)
- Incretin hormones (OGTT)
- Intestinal absorption rate of paracetamol (OGTT)

### Body weight and composition

Changes in body weight, anthropometric measures and body composition are secondary endpoints:

- Body weight
- Waist and hip circumference
- Body composition (bioelectrical impedance analysis and DEXA)

### Obesity related comorbidities

Changes in outcomes related to blood pressure, obstructive sleep apnea, lipid profile, fatty liver disease and end organ damage will be explored and the following outcome variables are therefore included as secondary endpoints:

- Blood pressure at rest
- 24-h ambulatory blood pressure
- Obstructive sleep apnea
- Use of blood pressure lowering drugs
- Cholesterol and triglyceride levels
- Fatty liver disease (MRI)
- Pulse wave velocity (The Sphygmocor system)
- Microalbuminuria

**Physical activity**

Self reported and measured physical activity will be recorded.

**Quality of life, dietary intake and symptom scores**

Questionnaires will be used for the assessment of changes in quality of life, psychological distress, obesity-related symptoms, eating behaviour, dietary intake and gastrointestinal symptoms.

## Trial design

This study is a single centre triple-blinded two armed randomised controlled superiority trial. Participants will be consecutively randomised in a one-to-one ratio to either sleeve gastrectomy or Roux-en-Y gastric bypass. Sealed and sequentially numbered envelopes containing the treatment assignment will be stored at the study coordinating office. Randomisation will be performed in the operating room on the day of the operation. Neither the patient nor the personnel who will conduct the post surgical patient follow-ups nor the team who will analyse the data will be aware of which treatment the patients have been randomised to. Post surgical follow-up and treatment will be identical. The surgical description will include information about the Oseberg-study, the study participant including study identification number, standardised descriptions of both procedures, and a description of any peroperative incidents. A list linking name and study identification number with study procedure will at all time be available at the study office and in the emergency department. All patients will be made aware of this. The randomisation code will be broken if there is a need for reoperation or if unexpected complications occur. The code will be broken after one year. The surgeon will then be

responsible for including the actual type of surgery in the patient record file and for informing the patient.

## Safety endpoints

Surgical complications will be graded according to the Accordion severity grading system (95). The contracted classification alternative which have four levels (mild complications, moderate complications, severe complications and death) will be used. Other safety endpoints include:

- Symptoms of hypoglycaemia and its intensity, fervency and relation to food intake
- Symptoms and objective signs of reflux disease and marginal ulcerations
- Vitamin and mineral deficiencies
- Bone density and metabolism
- Length of hospital stay
- Readmissions

## Study Procedures

The Oseberg study includes several tests and examinations shortly after surgery when weight loss is expected to be low (five weeks), after expected maximal weigh loss (one year) and during possible weight regain (one to five years). This comprehensive follow up makes it possible to evaluate very early, medium and long term effects of gastric bypass and sleeve gastrectomy with varying degree of weight loss. The examinations and tests planned for the Oseberg study are listed in Table 2 of the "Attachment" section. Participants will be examined approximately 3 weeks prior to (baseline) and 5, 16, 34 and 52 weeks after randomisation and thereafter annually for four more years. If scheduled surgery needs to be postponed upon completion of the baseline examination, relative weight stability (< 5% weight change) is mandatory. At baseline demographic data and medical history will be assessed. All visits will include a clinical examination (body weight, anthropometric measures and blood pressure), laboratory analyses and a registration of supplementation and medication used. Post operative visits will in addition include registration of complications and side effects. Additionally, four times during the study

period (three weeks prior to and five weeks and one and five years after randomisation) the following examinations will be performed on two consecutive days at the Morbid obesity centre and at home.

- Oral glucose tolerance test
- Intravenous glucose tolerance test
- Measuring of pulse wave velocity
- Questionnaires
- Bio-impedance
- Magnetic resonance imaging (MRI)
- 24-h ambulatory blood pressure
- SenseWear
- Apnelink
- Urine samples
- Faecal samples

The questionnaires will be completed annually up to the end of the study. In addition, upper endoscopy, dual-energy X-ray absoptiometry (DEXA) scanning, electro cardiogram (ECG) and structured interview recording dietary intake will also be performed three weeks prior to and one and five years after randomisation.

## Type 2 diabetes

Anti-diabetic treatment will be in accordance with the guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (96). The treatment goal is HbA1c < 7.0% and the anti-diabetic treatment will be started or intensified according to a predefined algorithm (Table 3 in the "Attachment" section). Metformin will, in the absence of prevalent contraindications, be the first-line drug and will also be the last to be discontinued after surgical treatment. Anti-diabetic medications which may cause hypoglycaemia or weight gain, and/or which need to be injected (insulin, sulfonylureas, glitazones, and GLP-1 agonist) will be avoided if possible. Reductions in glucose lowering agents immediately after surgery will be based on glucose measurements. After six weeks,

HbA1c will be used for the evaluation of glycaemic control. Glucose lowering agents will be reduced or discontinued in subjects with HbA1c ≤ 6.0%.

Partial remission is defined as HbA1c < 6.5% and complete remission as ≤ 6.0 % in the absence of active pharmacologic therapy (86).

**Glucose tolerance tests**

Two glucose tolerance tests will be performed in order to calculate insulin secretion and action: 1) The insulin-modified frequent sample intravenous glucose tolerance tests (FSIGT) (87-89) and 2) The OGTT (90-94). Patients will be asked to avoid vigorous physical activity one week prior to the glucose tolerance. Moreover, the patients will be told to terminate treatment with long acting GLP-1 analogues and other anti-diabetic medications 6 weeks and 48 hours prior to the tests, respectively. The participants will not be allowed to drink (up to 2 dl of water is allowed), eat, or smoke 8 hours prior to the tests. Other morning medications will be delayed until after the tests. A cannula will be inserted into a cubital vein and the cannulated arm wrapped in a heat pad throughout the experiment for the collection of arterialised blood samples. For the intravenous tests a cannula will be inserted in the contralateral cubital vein for glucose and insulin infusion. Due to patient safety the upper limit of fasting blood glucose prior to FSIGT and OGTT was set to < 20 mmol/l and < 25 mmol/l, respectively. During the insulin-modified FSIGT blood samples will be drawn two time before (-5 and 0 minutes) and after 2, 4, 8, 19, 22, 30, 40, 50, 70, 90 and 180 minutes after the intravenous glucose load (300 mg/kg body weight). After 20 minutes a bolus of insulin will be administrated (0.03 U/kg body weight). The Bergman minimal model (MINIMOD Millennium software) will be used for the calculation of SI and AIRg. During the OGTT the respective measuring points will be -5, 0, 15, 30, 60, 90, 120 and 180 minutes after the 25 oral glucose load. The glucose will be dissolved in water and ingested over 5 min.

Circulating proinsulin-to-insulin (PI/I) ratio, especially stimulated PI/I ratio (97), has previously been used as an estimate of the beta cell`s ability to transform proinsulin to insulin. Indeed, an elevated PI/I ratio has been associated with IGT (97) and reduced insulin secretion (98). PI/I ratios in a fasting and stimulated state will therefore be calculated.

In addition to insulin sensitivity and secretion indices derived from the glucose tolerance tests, homeostasis model assessment (HOMA) insulin sensitivity and secretion indices based on fasting insulin and glucose will be calculated using the computer based HOMA Calculator (99).

Both gastric bypass and sleeve gastrectomy may alter the intestinal absorption rate (100). An oral paracetamol test will therefore be used to calculate intestinal absorption as a measure of gastric emptying rate (101). Paracetamol (1.0 g) will be dissolved in the glucose solution used for the OGTT and serum paracetamol concentrations will be measured at the same time points as the measurements of insulin and glucose.

During both glucose tolerance test blood will at all time points be collected in 1) one tube which will be centrifuged after 30 minutes, serum will then be put on ice and stored at -80 °C until the analysis of insulin, c-peptide and pro-insulin, and 2) one tube containing lithium heparin which will be centrifuged immediately before the analysis of plasma glucose and paracetamol (only OGTT) the same day. During the OGTT, blood will also be collected in two chilled tubes containing EDTA and EDTA plus aprotinin for the analysis of gut hormones and glucagon, respectively. Both tubes will be centrifuged immediately at 4 °C before plasma is separated from cells and put on ice and stored at -80 C.

## Laboratory analysis

Table 4 of the "Attachment" section lists the blood, urine and faeces samples that will be collected at the different visits. Samples will either be stored or analysed on the day of collection.

## Body weight and composition

Body weight and composition will be measured with patients wearing light clothing and no shoes using bioelectrical impedance analysis (InBody) and DEXA. Anthropometric measures will be recorded with patients in an upright position. Height will be measured using wall mounted stadiometers; waist circumference (WC) will be measured at the point midway between the lowest rib margin and the iliac crest; hip circumference (HC) will be measured at the widest point over the greater trochanters. Height and circumferences will be measured to nearest 0.5 cm and weight to the nearest 0.1 kg.

## Obesity related comorbidities

### Blood pressure

Resting blood pressure will be measured to the nearest 1 mmHg three times in a sitting position after at least five minutes of rest. The average of the second and third measurements will be registered.

Ambulatory 24-h blood pressure monitoring (ABPM) will be performed using a portable automated computer-programmed oscillometric device from Custo screen 100, Custom made, Germany. The first day of the physical activity assessment will be performed simultaneously. Blood pressure will be measured every 20 minutes during daytime (between 06:00 and 23:00) and every hour during night time. Arm circumference will be measured on the non-dominant arm in order to ensure the use of a correct cuff size. The recording will be performed by a trained nurse/research assistant at the Morbid Obesity Centre. Blood pressure recordings will

be considered invalid if the data lacks an interval of two hours or if the study participants have an irregular rest-activity schedule during the monitoring or if the night time sleep period is of less than six hours (102).

Subjects with blood pressure ≥ 140/90 are classified as having hypertension (103). Anti-hypertensive drugs will be prescribed according to international guidelines (103,104). The treatment algorithm for blood pressure used in a recent publication addressing glycaemic control in diabetic subjects after bariatric surgery and intensive medical treatment will be used (Table 5 of the "Attachment" section (33)). This implies that anti-hypertensive medication will be reduced in subjects with systolic blood pressure below 130 – 135 mmHg and intensified in subjects with systolic blood pressure equal to or above 140 – 160 mmHg. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists are preferred drugs.

**Lipids**

Postoperatively statin therapy will be prescribed according to international guidelines and will be considered in subjects with low-density lipoprotein (LDL) cholesterol ≥ 2.6 mmol/l (104,105). In case of an "optimal" LDL cholesterol level < 2.0 mmol/l (106), no cardiovascular disease and age < 40 years without other cardiovascular risk factors, statin therapy will be considered discontinued (Table 6 of the "Attachment" section).

**Arterial stiffness**

The Sphygmocor system (Artcor, Sidney, Australia) and a single high-fidelity applanation tonometer (Millar®) will be used to measure pulse wave velocity (PWV). Pulse waves will be obtained sequentially from the carotid and femoral artery. The PWV will be calculated from the transit time and the distance between these two arterial sites, determined in relation to the R-wave of the ECG, with patients lying in a horizontal position. Three complete sets of data will be sampled and the average value used as a result.

**Obstructive sleep apnoea**

Obstructive sleep apnoea will be assessed using the ApneaLink™, a portable screening device for obstructive sleep apnea, which recently has been validated in morbidly obese patients by our group (107). Our results suggest that the ApneaLink™ is a useful and reliable instrument in the screening of OSA in morbidly obese patients. Compared with Embletta™ as reference, the ApneaLink™ was also highly sensitive in identifying patients with various severities of OSA. The patients will be instructed in how to use the device and the registration will be done at home.

**Fatty liver disease**

MRI (Siemens Aera 1.5 T) and Chemical Shift Imaging (108) will be used to quantify the fat-fraction content of the liver. Fat- and water-protons have different precession frequencies in the magnetic field which enables use of chemical shift imaging to accurately detect and quantify fatty infiltration. This frequency difference causes tissues containing fat and water to lose signal intensity when the proton magnetizations are opposed in out-of phase imaging. The signal-loss can be observed when out-of phase images are compared with in-phase images, which are acquired with the fat and water proton magnetizations in phase with each other to provide an additive signal. While normal liver parenchyma exhibits similar signal intensity on in-phase and out-of-phase images, liver parenchyma with fatty infiltration shows diminished signal intensity in out-of-phase images, with the reduction being more evident in the presence of severe fatty infiltration.

To quantify the fat content we will use the modified Dixon method (109). The percentage of liver-fat (FSP) is estimated by the formula: FSP = [(SI RIP-SI ROP/2 x (SIRIP)] x 100. SI RIP is defined as the ratio of hepatic signal intensity to splenic signal intensity in in-phase T1-weighted images, while SI ROP is the ratio of hepatic signal intensity to splenic signal intensity in out-of phase T1-weighted images. The signal intensity in liver is normalized to

spleen. Quantification with the Dixon method allows detection of a fat percentage of 15% or more. Normal liver usually has a fat content of less than 5%.

**Physical activity**

The SenseWear Armband (BodyMedia, Pittsburgh, PA) placed on the dominant upper arm will be used to monitor physical activity. The armband, which simultaneously integrates motion data from a biaxial accelerometer and physiological metrics from multiple sensors to provide minute-by-minute estimates of energy expenditure at different intensity levels, has been shown to produce valid energy expenditure estimates when evaluated against indirect calorimetry and doubly labeled water (110,111). The armband will be used for a total of four days of which the first also includes the 24-hour blood pressure monitoring.

**Questionnaires**

The following questionnaires will be used for the assessment of quality of life, obesity related symptoms, gastrointestinal symptoms, affective symptoms, and eating behaviour:

1. *Short Form Quality of Life questionnaire (SF-36)*
   The SF-36 (112) is a 36-item measure of general HRQOL consisting of eight subscales (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health) and two summary scores [Physical Component Summary (PCS) and Mental Component Summary (MCS)]. Summary scores represent independent (orthogonal) indices based on factor analysis of subscale scores using the Medical Outcomes Study data (113). Scores on all subscales range from 0 to 100, where the score 100 represents the best HRQOL. Scores for PCS and MCS are norm-based, with a mean of 50 and a standard deviation of 10, with higher scores representing better HRQOL. Estimates of internal consistency for the SF-36 typically have exceeded 0.80 for all subscales across diverse patient groups (114,115).

2. *Impact on Weight Questionnaire IWQOL-Lite*
   The IWQOL-Lite (116) is a 31-item measure of weight-related quality of life. There are five domain scores (Physical Function, Self-Esteem, Sexual Life, Public Distress and Work) and a total score. Scores for all domains and total score range from 0-100, with lower scores indicating greater impairment. The IWQOL-Lite has demonstrated excellent reliability and validity (116-118).

3. *Weight-Related Symptom Measure (WRSM)*
   The WRSM (119) is a 20-item, self-report measure for the presence and bothersomeness of weight-related symptoms (Shortness of breath, tiredness, sleep problems, sensitivity to cold, increased thirst, increased irritability, back pain, frequent urination, pain in the joints, water retention, foot problems, sensitivity to heat, snoring, increased appetite, leakage of urine, lightheadedness, increased sweating, loss of sexual desire, decreased physical stamina, and skin irritation). The bothersomeness scores of the symptoms are reported on a six-point likert scale. Two sum scores are calculated; an additive sum score of presence of symptoms ranging from 1 to 20 and bothersomeness sum score for all symptoms. Scores on the bothersomeness of symptoms range from 0 to 120, with higher scores indicating a higher or worse total symptom burden.

4. *Beck Depression Inventory*
   This is a 21-item scale that assesses depressive symptoms and mood dysphoria and has well established psychometric properties (120). It has been widely used with diverse populations, including bariatric surgery patients (121), and is an accepted assessment of depression. Total scores on the 21-item scale range from 0 to 63, with higher scores indicating greater depressive symptomatology. Scores of 0-13 suggest minimal symptoms of depression, while values of 14-19, 20-28, and 29-63 reflect mild, moderate, and severe symptomatology, respectively.

5. *Power of Food Scale*

This scale was developed to assess both the psychological impact and respondent's responsiveness to a food-abundant environment (such as that found in developed countries) (122). This is a 15-item scale whose items pertain to three situations: food being readily available in the environment but not physically present, food is physically present, but not tasted, and food is first tasted but not already consumed. This scale has previously been used in studies of gastric bypass patients (123).

6. *Binge Eating Scale (BES)*
   This 16-item scale assesses the extent to which obese individuals experience binge eating problems, including eating in secret, loss of control and guilt following binge eating (124). Scores range between 0-46, with higher scores indicating greater binge eating problems. Cut-off scores have been established to determine binge severity, with "severe" represented by scores $\geq$ 27, "moderate" by scores 18-26, and "mild-none" by scores $\leq$ 17 (125). The BES has shown responsiveness to change following gastric bypass (126).

7. *Gastrointestinal Symptom Rating Scale (GSRS)*
   This 15-item scale assesses common symptoms of gastrointestinal disorders (127,128). The GSRS contains five scales: abdominal pain (abdominal pain, hunger pains and nausea); reflux syndrome (heartburn and acid regurgitation), diarrhoea syndrome (diarrhoea, loose stools and urgent need for defecation), indigestion syndrome (borborygmus, abdominal distension, eructation and increased flatus) and constipation syndrome (constipation, hard stools, and feeling of incomplete evacuation). Higher scores indicate greater severity of symptoms. The GSRS in European patient populations has a good internal consistency reliability and acceptable construct validity and responsiveness (128,129).

8. *Food Tolerance Questionnaire*
   This is an 11-item questionnaire that assesses overall quality of alimentation, timing of food intake, tolerance of different types of food, and frequency of vomiting (130).

Scores range from 1-27, with higher scores representing greater food tolerance. In one study, patients undergoing diverse bariatric surgery procedures (gastric bypass, gastric banding, sleeve gastrectomy, and biliopancreatic diversion with duodenal switch) differed in food tolerance scores at different points in time (131), suggesting that this questionnaire may be useful in the current protocol.

9. *Gastroesophageal Reflux Disease Questionnaire (GerdQ)*
   GerdQ is a 6-tem questionnaire validated patient reported outcome questionnaires for reflux disease (132). It includes 4 items related to positive predictors for GERD; heartburn, regurgitation, sleep disturbances due to heartburn or reflux, and the use of over the counter medication. The four items are scored from 0-3, where 0 is little complaints and 3 is severe complaints. The last two items are negative predictors for GERD; epigastric pain and nausea. These 2 items score from 3-0, ie in reverse order to the positive predictors, where 0=4-7 days, 1=2-3 days, 2=1 day and 3=no day of the individual item during the previous week. The sum score of these 6 items therefore range between 0-18. A validate Norwegian version of the questionnaire (133) is used in the present study.

10. *International Physical Activity Questionnaires (IPAQ)*
    The short version of IPAQ will be used and comprises a set of four questionnaires related to time spend in vigorous and moderate physical activity, walking and sitting, respectively. The instrument has been examined for validity and reliability in an international study and deemed acceptable for use in physical activity research (134).

11. *Food frequency questionnaire (FFQ)*
    Dietary intake during the preceding year will be assessed through structured interviews performed by registered dieticians. Data will be recorded on an optically readable FFQ (Department of Nutrition, University of Oslo, Norway). The present version of the FFQ which has been developed to assess the habitual dietary intake of Norwegian adults has

been validated according to similar questionnaires using weighted records and provides a good estimate of a person's average energy intake (135-137). Patients will be asked to describe their dietary habits during the previous year, and report how often and in what quantity the different food items and courses will be used (per day, week and month). Units and household measures will be used to help patients estimate portion sizes. Dietary assessment methods based on FFQs are susceptible to reporting bias due to both inaccurate recall and social desirability. However, the FFQ method has been shown to capture more realistic energy intake and distribution in obese individuals than other similar methods such as 24-hour dietary recalls (138). Questionnaire data will be scanned using Teleform 10.0 (Cambridge, UK). Dietary intake will be calculated using a database assembled from official food composition tables (Norwegian Nutrition Council, 1995).

The Power of Food Scale and the Food Tolerance Questionnaire will be translated to Norwegian through a standard forward-backward procedure. With the exception of FFQ, all questionnaires will utilise SurveyXact (www.surveyxact.no), an internet based survey system. Patients will be guided into an office and asked to complete the questionnaires and they may, if necessary, ask a study nurse for help. The completion time is estimated to 40 minutes. The completed web-based questionnaires will only contain the respondents project number as identification. After completion, the online data will be downloaded to a local computer at the University of Agder and stored password protected behind the University's firewalls as a part of the University's ordinary information safety protocols (139).

**Complications and side- effects**

All complications and side-effects will be registered at the follow-up visits. At every visit patients will be examined for possible complications and new ones registered. All complications must be verified by objective measures.

*Surgical complications* will be graded according to the contracted Accordion classification (95) and divided into early and late complications.

*Hypoglycaemia* has increasingly arisen as a problem after gastric bypass (20,140) and is a well known side-effect of glucose lowering agents (141). Patients will therefore be examined for symptoms of hypoglycaemia and encouraged to measure blood glucose during possible hypoglycaemic episodes. Hypoglycaemia is defined as a blood glucose level of less than 2.8 mmol/L or the presence of typical symptoms and signs of hypoglycaemia without other apparent cause (141). Hypoglycaemic episodes will be categorised according to severity [Severe (requiring medical assistance), moderate (requiring help from another person) and minor (able to treat themselves)], frequency and its relation to food and/or liquid intake (Postprandial: 60 to 180 minutes after a meal). Relief of symptoms when the glucose level is raised to normal will be recorded. During the glucose tolerance test the Arts' questionnaire (142) will be used for differentiating between early and late (caused by hypoglycaemia) dumping. The questionnaire will also be completed at every post operative visit to identify symptoms of early and late dumping occurring in daily living.

*Reflux disease* may occur after sleeve gastrectomy (32). Upper endoscopy, 24 hour ph-impedance and ph-metry will therefore be performed both before and after surgical treatment. Endoscopic images will be taken and evaluated by two gastroenterologists blinded for the type of procedure (ventricle mucosa will be covered by a black circle on the image). The severity of the disease will be graded according to the Los Angeles classification (143) and treated adequately. Postoperatively reflux disease will be treated according to international guideline (144). At each postoperative visit symptoms of reflux disease will be graded according to the

GerdQ questionnaire (132) and treated according to a predefined algorithm (Table 6 of the "Attachment" section). In short, proton pump inhibitors will be stopped or considered stopped in patients with no (GerdQ score ≤ 2) or mild (GerdQ score 3-7) symptoms. On demand treatment with histamine H2-receptor antagonists may be prescribed to subjects with mild symptoms. In patients with severe symptoms (GerdQ ≥ 8) treatment with proton pump inhibitors will be started or intensified and referral to gastroenterologist considered.

*Vitamin and mineral deficiencies and reduced bone mineral density* have been observed after gastric bypass surgery (145,146). Sleeve gastrectomy probably has a more modest effect on micronutrient status within the first year after intervention (48,49) and no accepted supplementation regime exists. Vitamin D may play a role in type 2 diabetes (147) and supplementation of only one of the groups could potentially influence the primary outcome. In the same manner, other between-group differences in the supplementation regimes could introduce confounding factors. All patients will therefore be prescribed a standardised supplementation regime post-surgery containing: two multivitamin/mineral tablets (Nycoplus multi), vitamin D/calcium tablets (Calcigran Forte, 20 µg vitamin $D_3$/1000 mg calcium carbonate), iron tablets (Duroferon, 100 mg ferrous sulphate to premenopausal women), and vitamin B-12 intramuscular injections every 3 months (Betolvex, 1 mg cyanocobalamine). In the case of low levels after surgery the first step is to ensure that the patient is actually taking the supplements. Thereafter supplementation of vitamin and mineral deficiencies will follow predefined regimes listed in Table 8 of the "Attachment" section. Four to six weeks after adjustment of supplements, new blood samples will be taken at the obesity centre (alternatively at the general practitioner). If side effects occur (e.g. gastrointestinal side effects of iron supplements) changes or discontinuations of the supplementation regime will be considered. Vitamin and mineral status and bone metabolism will be monitored using biochemical analysis (Table 4). Bone mineral density will be estimated by DEXA scanning.

## Sample size

This study has two primary endpoints and is powered thereafter:

1. *Complete remission of type 2 diabetes*
   Based on previous reports addressing glycaemic response of gastric bypass and sleeve gastrectomy in type 2 diabetic subjects (20,33,34,47) remission rates of 75% and 50% after one year are assumed.

2. *Beta cell-function*
   Disposition index after sleeve gastrectomy has, to the best of our knowledge, not been published previously. Data from a recent study addressing beta-cell function after gastric bypass and a low calorie diet has therefore been used for sample size determination (148). Mean (SD) disposition index was 268 (232) after gastric bypass and 94 (92) after a low calorie diet. Based on these figures mean (SD) disposition index after gastric bypass and sleeve gastrectomy is estimated to be 270 (160) and 180 (160) one year after surgery, respectively.

A five percent significance level and 80% power was chosen. Given these figures and an equal distribution to the two groups a total study sample of 110 (remission) or 100 (disposition index) subjects is required. In order to accommodate possible dropouts (5% in previous study at our centre (20)) 120 subjects will be included in the study.

## Statistical methods

Data will be analysed according to both the programme into which patients were randomised (intention-to-treat analysis) and per-protocol. Descriptive data will be presented as mean (SD), median (range) or number (%). Between-group comparisons will be analysed using independent samples t-test, repeated measures analysis of variance, mixed model analysis and

Mann-Whitney U test for continuous variables and $\chi 2$ or Fisher`s exact test for categorical variables as appropriate. Regression analysis will be used for the exploration of the independent effects of weight reduction and other variables on primary and secondary outcomes.Ethical considerations

Both the short and long- term benefits and side- effects of gastric bypass surgery are well known. By contrast, the effect of sleeve gastrectomy on weight and obesity related comorbidities, as well as its surgical complications and side-effects, have not been fully explored. Despite a lack of data, sleeve gastrectomy is gaining popularity both at a national and global level. Current data indicate that sleeve gastrectomy may have an effect on weight and glucose metabolism that is either comparable or somewhat lower to that of gastric bypass. However, the existing data are conflicting and more research is needed to verify or reject previous findings. In addition, the present study aims to explore possible differences between the two procedures in glucoregulatory mechanisms (e.g. insulin secretion and action), markers of micro- and macrovascular complications, and the frequency and seriousness of hypoglycaemic episodes. Finally, we aim to examine possible differences between the procedures with respect to several important health measures and side-effects. The results will hopefully add knowledge which may help doctors and patients with type 2-diabetes to choose an appropriate procedure.

After a thorough evaluation of the existing literature, and after balancing clinical effects and side-effects, we believe that there is no conclusive evidence showing gastric bypass or gastric sleeve to be a better choice for patients with type 2-diabetes. Our research assistants and patients will be fully informed about this before the start of the study. We therefore find it ethically appropriate to randomise patients to either treatment.

## Publications

The protocol and the results of the study will be published in international peer review journals and we will adhere to the ICMJE-criteria for authorship (http://www.icmje.org/ethical_1author.html). The executive and steering committees will actively contribute to the involvement and inclusion of authors and the order of authorships in the planning of publications. Moreover, primary and secondary endpoints will be published after one and five years.

## Financing

The study is organised and financed by Vestfold Hospital Trust and the Morbid Obesity Centre. All employees receive a salary from their respective departments. In addition, applications for external funding will be submitted for future postdoctoral- and PhD-fellows and specific laboratory analyses.

## Insurance

Regular patient insurance applies (Patients' Rights Act (149)).

## Approvals

The study protocol was approved by the regional ethics committee the 12th of September 2012 and registered in an international trial register (www.clinicaltrials.gov.) the 3rd of December 2012. Moreover, the study will be conducted according to the declaration of Helsinki and the steering committee will monitor metabolic effects and adverse events during the study period.

# References


1. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN, Farzadfar F, Riley LM, Ezzati M: National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9-À1 million participants. *The Lancet* 377:557-567, 2011
2. Midthjell K, Lee C, Krokstad S, Langhammer A, Holmen T, Hveem K, Colagiuri S, Holmen J: Obesity and type 2 diabetes still increase while other cardiovascular disease risk factors decline. The HUNT Study, Norway. (Abstract). *Obesity Reviews* 11 Supplement 1:58, 2010
3. Fried M, Hainer V, Basdevant A, Buchwald H, Deitel M, Finer N, Greve JW, Horber F, Mathus-Vliegen E, Scopinaro N, Steffen R, Tsigos C, Weiner R, Widhalm K, Bariatric Scientific Collaborative Group: Interdisciplinary European guidelines for surgery for severe (morbid) obesity. *Obes Surg* 17:260-270, 2007
4. Helse- og omsorgsdepartementet: Utredning og behandling av sykelig overvekt i spesialisthelsetjenesten, Voksne. [article online], 2007.
5. World Health Organization. GLOBAL HEALTH RISKS Mortality and burden of disease attributable to selected major risks. http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf. 2009.
6. Jenkins NL, Johnson JO, Mageau RP, Bowen JB, Pofahl WE: Who's who in bariatric surgery: the pioneers in the development of surgery for weight control. *Curr Surg* 62:38-44, 2005
7. Buchwald H, Buchwald JN: Evolution of operative procedures for the management of morbid obesity 1950-2000. *Obes Surg* 12:705-717, 2002
8. Scopinaro N: The IFSO and obesity surgery throughout the world. International Federation for the Surgery of Obesity. *Obes Surg* 8:3-8, 1998
9. Buchwald H, Oien DM: Metabolic/Bariatric Surgery Worldwide 2008. *Obes Surg* 2009
10. Sugerman HJ, Wolfe LG, Sica DA, Clore JN: Diabetes and hypertension in severe obesity and effects of gastric bypass-induced weight loss. *Ann Surg* 237:751-756, 2003
11. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, Barakat HA, deRamon RA, Israel G, Dolezal JM: Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg* 222:339-350, 1995
12. Schauer PR, Burguera B, Ikramuddin S, Cottam D, Gourash W, Hamad G, Eid GM, Mattar S, Ramanathan R, Barinas-Mitchel E, Rao RH, Kuller L, Kelley D: Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. *Ann Surg* 238:467-484, 2003
13. Lee WJ, Huang MT, Wang W, Lin CM, Chen TC, Lai IR: Effects of obesity surgery on the metabolic syndrome. *Arch Surg* 139:1088-1092, 2004
14. Makary MA, Clarke JM, Shore AD, Magnuson TH, Richards T, Bass EB, Dominici F, Weiner JP, Wu AW, Segal JB: Medication Utilization and Annual Health Care Costs in Patients With Type 2 Diabetes Mellitus Before and After Bariatric Surgery. *Arch Surg* 145:726-731, 2010
15. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjostrom CD, Sullivan M, Wedel H, Swedish Obese Subjects

Study Scientific Group: Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 351:2683-2693, 2004

16. O'Brien PE, Dixon JB, Laurie C, Skinner S, Proietto J, McNeil J, Strauss B, Marks S, Schachter L, Chapman L, Anderson M: Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: a randomized trial. *Ann Intern Med* 144:625-633, 2006
17. Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, Proietto J, Bailey M, Anderson M: Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA* 299:316-323, 2008
18. Mingrone G, Greco AV, Giancaterini A, Scarfone A, Castagneto M, Pugeat M: Sex hormone-binding globulin levels and cardiovascular risk factors in morbidly obese subjects before and after weight reduction induced by diet or malabsorptive surgery. *Atherosclerosis* 161:455-462, 2002
19. O'Brien PE, Sawyer SM, Laurie C, Brown WA, Skinner S, Veit F, Paul E, Burton PR, McGrice M, Anderson M, Dixon JB: Laparoscopic adjustable gastric banding in severely obese adolescents: a randomized trial. *JAMA* 303:519-526, 2010
20. Hofso D, Nordstrand N, Johnson LK, Karlsen TI, Hager H, Jenssen T, Bollerslev J, Godang K, Sandbu R, Roislien J, Hjelmesaeth J: Obesity-related cardiovascular risk factors after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. *Eur J Endocrinol* 163:735-745, 2010
21. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K: Bariatric surgery: a systematic review and meta-analysis. *JAMA* 292:1724-1737, 2004
22. Maggard MA, Shugarman LR, Suttorp M, Maglione M, Sugerman HJ, Livingston EH, Nguyen NT, Li Z, Mojica WA, Hilton L, Rhodes S, Morton SC, Shekelle PG: Meta-analysis: surgical treatment of obesity. *Ann Intern Med* 142:547-559, 2005
23. Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lonroth H, Naslund I, Olbers T, Stenlof K, Torgerson J, Agren G, Carlsson LM, Swedish Obese SS: Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 357:741-752, 2007
24. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC: Long-term mortality after gastric bypass surgery. *N Engl J Med* 357:753-761, 2007
25. Herpertz S, Kielmann R, Wolf AM, Langkafel M, Senf W, Hebebrand J: Does obesity surgery improve psychosocial functioning? A systematic review. *Int J Obes Relat Metab Disord* 27:1300-1314, 2003
26. Karlsson J, Taft C, Ryden A, Sjostrom L, Sullivan M: Ten-year trends in health-related quality of life after surgical and conventional treatment for severe obesity: the SOS intervention study. *Int J Obes* 31:1248-1261, 2007
27. Kolotkin RL, Crosby RD, Gress RE, Hunt SC, Adams TD: Two-year changes in health-related quality of life in gastric bypass patients compared with severely obese controls. *Surgery for Obesity & Related Diseases* 5:250-256, 2009
28. Colquitt JL, Picot J, Loveman E, Clegg AJ: Surgery for obesity. [Review] [157 refs][Update of Cochrane Database Syst Rev. 2005;(4):CD003641; PMID: 16235331]. *Cochrane Database of Systematic Reviews (2):CD003641, 2009*CD003641, 2009
29. Hofso D, Aasheim ET, Sovik TT, Jakobsen GS, Johnson LK, Sandbu R, Aas AT, Kristinsson J, Hjelmesaeth J: [Follow-up after bariatric surgery]. [Review] [Norwegian]. *Tidsskr Nor Laegeforen* 131:1887-1892, 2011
30. Aasheim ET, Mala T, Sovik TT, Kristinsson J, Bohmer T: Surgical treatment of morbid obesity. *Tidsskr Nor Laegeforen* 127:38-42, 2007

31. Buchwald H, Oien DM: Metabolic/bariatric surgery Worldwide 2008. *Obes Surg* 19:1605-1611, 2009
32. Rosenthal RJ: International Sleeve Gastrectomy Expert Panel Consensus Statement: best practice guidelines based on experience of >12,000 cases. *Surgery for Obesity and Related Diseases* 8:8-19, 2012
33. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, Thomas S, Abood B, Nissen SE, Bhatt DL: Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes. *N Engl J Med* 366:1567-1576, 2012
34. Lee WJ, Chong K, Ser KH, Lee YC, Chen SC, Chen JC, Tsai MH, Chuang LM: Gastric bypass vs sleeve gastrectomy for type 2 diabetes mellitus: a randomized controlled trial. *Arch Surg* 146:143-148, 2011
35. Himpens J, Dapri G, Cadi+¿re G: A Prospective Randomized Study Between Laparoscopic Gastric Banding and Laparoscopic Isolated Sleeve Gastrectomy: Results after 1 and 3 Years. *Obes Surg* 16:1450-1456, 2006
36. Peterli RM, Wolnerhanssen BM, Peters TM, Devaux NM, Kern BM, Christoffel-Court, Drewe JM, von Flue MM, Beglinger CM: Improvement in Glucose Metabolism After Bariatric Surgery: Comparison of Laparoscopic Roux-en-Y Gastric Bypass and Laparoscopic Sleeve Gastrectomy: A Prospective Randomized Trial. *Ann Surg* 250:234-241, 2009
37. Karamanakos SNM, Vagenas KM, Kalfarentzos FM, Alexandrides TKM: Weight Loss, Appetite Suppression, and Changes in Fasting and Postprandial Ghrelin and Peptide-YY Levels After Roux-en-Y Gastric Bypass and Sleeve Gastrectomy: A Prospective, Double Blind Study. *Ann Surg* 247:401-407, 2008
38. Woelnerhanssen B, Peterli R, Steinert RE, Peters T, Borbely Y, Beglinger C: Effects of postbariatric surgery weight loss on adipokines and metabolic parameters: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy--a prospective randomized trial. *Surgery for Obesity & Related Diseases* 7:561-568, 2011
39. Kehagias I, Karamanakos SN, Argentou M, Kalfarentzos F: Randomized clinical trial of laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy for the management of patients with BMI[THIN SPACE]<[THIN SPACE]50 kg/m2. *Obes Surg* 21:1650-1656, 2011
40. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, Nanni G, Pomp A, Castagneto M, Ghirlanda G, Rubino F: Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes. *N Engl J Med* 366:1577-1585, 2012
41. Helmio M, Victorzon M, Ovaska J, Leivonen M, Juuti A, Jaser N, Peromaa P, Tolonen P, Hurme S, Salminen P: SLEEVEPASS: A randomized prospective multicenter study comparing laparoscopic sleeve gastrectomy and gastric bypass in the treatment of morbid obesity: preliminary results. *Surg Endosc* 2012
42. Peterli R, Steinert R, Woelnerhanssen B, Peters T, Christoffel-Court, Gass M, Kern B, von Fluee M, Beglinger C: Metabolic and Hormonal Changes After Laparoscopic Roux-en-Y Gastric Bypass and Sleeve Gastrectomy: a Randomized, Prospective Trial. *Obes Surg* 22:740-748, 2012
43. Hutter MM, Schirmer BD, Jones DB, Ko CY, Cohen ME, Merkow RP, Nguyen NT: First report from the American College of Surgeons Bariatric Surgery Center Network: laparoscopic sleeve gastrectomy has morbidity and effectiveness positioned between the band and the bypass. *Ann Surg* 254:410-420, 420
44. Brethauer SA, Hammel JP, Schauer PR: Systematic review of sleeve gastrectomy as staging and primary bariatric procedure. *Surgery for Obesity and Related Diseases* 5:469-475, 2009

45. Abu-Jaish W, Rosenthal RJ: Sleeve gastrectomy: a new surgical approach for morbid obesity. *Expert review of gastroenterology and hepatology* 4:101-119, 2010
46. Shi X, Karmali S, Sharma A, Birch D: A Review of Laparoscopic Sleeve Gastrectomy for Morbid Obesity. *Obes Surg* 20:1171-1177, 2010
47. Pournaras DJ, Aasheim ET, Sovik TT, Andrews R, Mahon D, Welbourn R, Olbers T, le Roux CW: Effect of the definition of type II diabetes remission in the evaluation of bariatric surgery for metabolic disorders. *Br J Surg* 99:100-103, 2012
48. Gehrer S, Kern B, Peters T, Christoffel-Court, Peterli R: Fewer Nutrient Deficiencies After Laparoscopic Sleeve Gastrectomy (LSG) than After Laparoscopic Roux-Y-Gastric Bypass (LRYGB)GÇöa Prospective Study. *Obes Surg* 20:447-453, 2010
49. Damms-Machado A, Friedrich A, Kramer KM, Stingel K, Meile T, Kuper MA, Konigsrainer A, Bischoff SC: Pre- and postoperative nutritional deficiencies in obese patients undergoing laparoscopic sleeve gastrectomy. *Obes Surg* 22:881-889, 2012
50. Hamdan K, Somers S, Chand M: Management of late postoperative complications of bariatric surgery. *Br J Surg* 98:1345-1355, 2011
51. Frezza EE: Laparoscopic vertical sleeve gastrectomy for morbid obesity. The future procedure of choice?. [Review] [30 refs]. *Surg Today* 37:275-281, 2007
52. Carter PR, LeBlanc KA, Hausmann MG, Kleinpeter KP, deBarros SN, Jones SM: Association between gastroesophageal reflux disease and laparoscopic sleeve gastrectomy. *Surgery for Obesity and Related Diseases* 7:569-572, 2011
53. Mohos E, Schmaldienst E, Prager M: Quality of life parameters, weight change and improvement of co-morbidities after laparoscopic Roux Y gastric bypass and laparoscopic gastric sleeve resection--comparative study. *Obes Surg* 21:288-294, 2011
54. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS: Diabetes trends in the U.S.: 1990-1998. *Diabetes Care* 23:1278-1283, 2000
55. Lipscombe LL, Hux JE: Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study. *Lancet* 369:750-756, 2007
56. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:1047-1053, 2004
57. American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care* 33:S62-S69, 2010
58. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183-1197, 1997
59. McCance DR, Hanson RL, Charles MA, Jacobsson LT, Pettitt DJ, Bennett PH, Knowler WC: Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ* 308:1323-1328, 1994
60. MCINTYRE N, HOLDSWORTH CD, TURNER DS: New interpretation of oral glucose tolerance. *Lancet* 2:20-21, 1964
61. Laferrere B, Teixeira J, McGinty J, Tran H, Egger JR, Colarusso A, Kovack B, Bawa B, Koshy N, Lee H, Yapp K, Olivan B: Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. *J Clin Endocrinol Metab* 93:2479-2485, 2008
62. le Roux CW, Welbourn R, Werling M, Osborne A, Kokkinos A, Laurenius A, nroth H, ndriks L, Ghatei MA, Bloom SR, Olbers T: Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. *Annals of Surgery*
63. Goldfine AB, Mun EC, Devine E, Bernier R, Baz-Hecht M, Jones DB, Schneider BE, Holst JJ, Patti ME: Patients with neuroglycopenia after gastric bypass surgery have exaggerated incretin and insulin secretory responses to a mixed meal. *J Clin Endocrinol Metab* 92:4678-4685, 2007

64. Ram+¦n J, Salvans S, Crous X, Puig S, Goday A, Benaiges D, Trillo L, Pera M, Grande L: Effect of Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy on Glucose and Gut Hormones: a Prospective Randomised Trial. *J Gastrointest Surg*1-7,
65. Romero F, Nicolau J, Flores L+, Casamitjana R, Ibarzabal A, Lacy A, Vidal J: Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-En-Y gastric bypass surgery for morbidly obese type 2 diabetic subjects. *Surg Endosc*1-9,
66. Morinigo R, Lacy AM, Casamitjana R, Delgado S, Gomis R, Vidal J: GLP-1 and changes in glucose tolerance following gastric bypass surgery in morbidly obese subjects. *Obes Surg* 16:1594-1601, 2006
67. Hofso D, Jenssen T, Jens B, Ueland T, Godang K, Stumvoll M, Sandbu R, Roislien J, Hjelmesaeth J: Beta cell function after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. *Eur J Endocrinol*EJE-10, 2010
68. Lin E, Liang Z, Frediani J, Davis SS, Jr., Sweeney JF, Ziegler TR, Phillips LS, Gletsu-Miller N: Improvement in s-cell function in patients with normal and hyperglycemia following Roux-en-Y gastric bypass surgery. *American Journal of Physiology - Endocrinology & Metabolism* 299:E706-E712, 2010
69. Basso N, Capoccia D, Rizzello M, Abbatini F, Mariani P, Maglio C, Coccia F, Borgonuovo G, De Luca M, Asprino R, Alessandri G, Casella G, Leonetti F: First-phase insulin secretion, insulin sensitivity, ghrelin, GLP-1, and PYY changes 72-áh after sleeve gastrectomy in obese diabetic patients: the gastric hypothesis. *Surg Endosc* 25:3540-3550, 2011
70. Laurent Sp, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A: Aortic Stiffness Is an Independent Predictor of All-Cause and Cardiovascular Mortality in Hypertensive Patients. *Hypertension* 37:1236-1241, 2001
71. Laurent Sp, Katsahian S, Fassot C+, Tropeano AI, Gautier I, Laloux B, Boutouyrie P: Aortic Stiffness Is an Independent Predictor of Fatal Stroke in Essential Hypertension. *Stroke* 34:1203-1206, 2003
72. Vlachopoulos C, Aznaouridis K, Stefanadis C: Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness: A Systematic Review and Meta-Analysis. *J Am Coll Cardiol* 55:1318-1327, 2010
73. Lim HE, Park CG, Shin SH, AHN JC, Seo HS, Oh DJ: Aortic pulse wave velocity as an independent marker of coronary artery disease. *Blood Press* 13:369-375, 2004
74. Sivertsen J, Rosenmeier J, Holst JJ, Vilsboll T: The effect of glucagon-like peptide 1 on cardiovascular risk. *Nat Rev Cardiol* 9:209-222, 2012
75. Gutzwiller JP: Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. *J Clin Endocrinol Metab* 89:3055-3061, 2004
76. Yamamoto H, Kishi T, Lee CE, Choi BJ, Fang H, Hollenberg AN, Drucker DJ, Elmquist JK: Glucagon-Like Peptide-1-Responsive Catecholamine Neurons in the Area Postrema Link Peripheral Glucagon-Like Peptide-1 with Central Autonomic Control Sites. *The Journal of Neuroscience* 23:2939-2946, 2003
77. Mejia-Rivas MA, Herrera-Lopez A, Hernandez-Calleros J, Herrera MF, Valdovinos MA: Gastroesophageal reflux disease in morbid obesity: the effect of Roux-en-Y gastric bypass. *Obes Surg* 18:1217-1224, 2008
78. Fisichella PM, Patti MG: Gastroesophageal reflux disease and morbid obesity: is there a relation?. [Review] [35 refs]. *World J Surg* 33:2034-2038, 2009
79. Weiner RA: Surgical Treatment of Non-Alcoholic Steatohepatitis and Non-Alcoholic Fatty Liver Disease. *Dig Dis* 28:274-279, 2010
80. Ley RE, Turnbaugh PJ, Klein S, Gordon JI: Microbial ecology: Human gut microbes associated with obesity. *Nature* 444:1022-1023, 2006

81. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI: An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444:1027-1131, 2006
82. Zhang H, DiBaise JK, Zuccolo A, Kudrna D, Braidotti M, Yu Y, Parameswaran P, Crowell MD, Wing R, Rittmann BE, Krajmalnik-Brown R: Human gut microbiota in obesity and after gastric bypass. *Proceedings of the National Academy of Sciences* 106:2365-2370, 2009
83. Li JV, Ashrafian H, Bueter M, Kinross J, Sands C, le Roux CW, Bloom SR, Darzi A, Athanasiou T, Marchesi JR, Nicholson JK, Holmes E: Metabolic surgery profoundly influences gut microbialGÇôhost metabolic cross-talk. *Gut* 60:1214-1223, 2011
84. Furet JP, Kong LC, Tap J, Poitou C, Basdevant A, Bouillot JL, Mariat D, Corthier G+, Dor+® Jl, Henegar C, Rizkalla S, Cl+®ment K: Differential Adaptation of Human Gut Microbiota to Bariatric SurgeryGÇôInduced Weight Loss. *Diabetes* 59:3049-3057, 2010
85. Sarwer DB, Fabricatore AN, Jones-Corneille LS, Allison KC, Faulconbridge L, Wadden TA: **Psychological Issues Following Bariatric Surgery**. *Primary Psychiatry* 15:50-55, 2008
86. Buse JB, Caprio S, Cefalu WT, Ceriello A, Del PS, Inzucchi SE, McLaughlin S, Phillips GL, Robertson RP, Rubino F, Kahn R, Kirkman MS: How do we define cure of diabetes? *Diabetes Care* 32:2133-2135, 2009
87. Bergman RN, Phillips LS, Cobelli C: Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest* 68:1456-1467, 1981
88. Steil GM, Volund A, Kahn SE, Bergman RN: Reduced sample number for calculation of insulin sensitivity and glucose effectiveness from the minimal model. Suitability for use in population studies. *Diabetes* 42:250-256, 1993
89. Mari A: Assessment of insulin sensitivity and secretion with the labelled intravenous glucose tolerance test: improved modelling analysis. *Diabetologia* 41:1029-1039, 1998
90. Matsuda M, DeFronzo RA: Insulin sensitivity indices obtained from oral glucose tolerance testing: Comparison with the euglycemic insulin clamp. *Diabetes Care 22(9)()(pp 1462-1470), 1999 Date of Publication: Sep 1999*1462-1470, 1999
91. Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ: A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. *Diabetes Care 24(3)()(pp 539-548), 2001 Date of Publication: 2001*539-548, 2001
92. Stumvoll M, Mitrakou A, Pimenta W, Jenssen T, Yki-Jarvinen H, Van HT, Renn W, Gerich J: Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. *Diabetes Care 23(3)()(pp 295-301), 2000 Date of Publication: Mar 2000*295-301, 2000
93. Stumvoll M, Van HT, Fritsche A, Gerich J: Oral glucose tolerance test indexes for insulin sensitivity and secretion based on various availabilities of sampling times. *Diabetes Care* 24:796-797, 2001
94. Pacini G, Mari A: Methods for clinical assessment of insulin sensitivity and beta-cell function. [Review] [83 refs]. *Best Practice & Research Clinical Endocrinology & Metabolism* 17:305-322, 2003
95. Strasberg SM, Linehan DC, Hawkins WG: The accordion severity grading system of surgical complications. [Review] [143 refs]. *Ann Surg* 250:177-186, 2009
96. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR: Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach. *Diabetes Care* 2012

97. Larsson H, Ahren B: Relative hyperproinsulinemia as a sign of islet dysfunction in women with impaired glucose tolerance. *J Clin Endocrinol Metab* 84:2068-2074, 1999
98. Fritsche A, Madaus A, Stefan N, Tschritter O, Maerker E, Teigeler A, Haring H, Stumvoll M: Relationships among age, proinsulin conversion, and beta-cell function in nondiabetic humans. *Diabetes* 51:S234-S239, 2002
99. Wallace TM, Levy JC, Matthews DR: Use and abuse of HOMA modeling. *Diabetes Care 27(6)()(pp 1487-1495), 2004 Date of Publication: Jun 2004*1487-1495, 2004
100. Ardila-Hani A, Soffer EE: Review article: the impact of bariatric surgery on gastrointestinal motility. *Alimentary Pharmacology & Therapeutics* 34:825-831, 2011
101. Heading RC, Nimmo J, Prescott LF, Tothill P: The dependence of paracetamol absorption on the rate of gastric emptying. *Br J Pharmacol* 47:415-421, 1973
102. Hermida RnC, Ayala DE, Moj+¦n A, Fern+índez JR: Bedtime Dosing of Antihypertensive Medications Reduces Cardiovascular Risk in CKD. *J Am Soc Nephrol* 22:2313-2321, 2011
103. Mancia G, De BG, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, ESH-ESC Task Force on the Management of Arterial Hypertension: 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension.[Erratum appears in J Hypertens. 2007 Oct;25(10):2184]. *J Hypertens* 25:1751-1762, 2007
104. Standards of Medical Care in DiabetesGÇö2012. *Diabetes Care* 35:S11-S63, 2012
105. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation* 106:3143, 2002
106. Dixon JB, Zimmet P, Alberti KG, Rubino F, International Diabetes Federation Taskforce on Epidemiology and Prevention: Bariatric surgery: an IDF statement for obese Type 2 diabetes.[Reprint in Surg Obes Relat Dis. 2011 Jul-Aug;7(4):433-47; PMID: 21782137]. *Diabet Med* 28:628-642, 2011
107. Fredheim, J. M. and Hjelmeland, H. VALIDATION OF A SLEEP APNEA SCREENING DEVICE (APNEALINK™) IN MORBIDLY OBESE SUBJECTS. 30-8-0012.
108. Cassidy FH, Yokoo T, Aganovic L, Hanna RF, Bydder M, Middleton MS, Hamilton G, Chavez AD, Schwimmer JB, Sirlin CB: Fatty liver disease: MR imaging techniques for the detection and quantification of liver steatosis. *Radiographics* 29:231-260, 2009
109. Ma X, Holalkere NS, Kambadakone RA, Mino-Kenudson M, Hahn PF, Sahani DV: Imaging-based quantification of hepatic fat: methods and clinical applications. [Review] [129 refs]. *Radiographics* 29:1253-1277, 2009
110. Jakicic JM, Marcus M, Gallagher KI, Randall C, Thomas E, Goss FL, Robertson RJ: Evaluation of the SenseWear Pro Armband to assess energy expenditure during exercise. *Medicine & Science in Sports & Exercise* 36:897-904, 2004
111. Johannsen DL, Calabro MA, Stewart J, Franke W, Rood JC, Welk GJ: Accuracy of armband monitors for measuring daily energy expenditure in healthy adults. *Medicine & Science in Sports & Exercise* 42:2134-2140, 2010
112. Ware J SKKMGB: *SF-36 Health Survey: Manual and Interpretation Guide.* Boston, The Health Institute, New England Medical Center, 1993
113. Ware JE, Jr., Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A: Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Med Care* 33:Suppl-79, 1995

114. McHorney CA, Ware JE, Jr., Raczek AE: The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 31:247-263, 1993
115. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD: The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 32:40-66, 1994
116. Kolotkin RL, Crosby RD, Kosloski KD, Williams GR: Development of a brief measure to assess quality of life in obesity. *Obes Res* 9:102-111, 2001
117. Kolotkin RL, Crosby RD: Psychometric evaluation of the impact of weight on quality of life-lite questionnaire (IWQOL-lite) in a community sample. *Qual Life Res* 11:157-171, 2002
118. Kolotkin, R. L., Davidson, L. E., Crosby, R. D., Hunt, S. C., and Adams, T. D. Six-year changes in health-related quality of life in gastric bypass patients versus obese comparison groups. Surg Obes Relat Dis . 2012.
119. Patrick DL, Bushnell DM, Rothman M: Performance of two self-report measures for evaluating obesity and weight loss. *Obes Res* 12:48-57, 2004
120. Beck A.T., Steer R.A., Brown B.K.: *Beck Depression Inventory Manual, 2nd edn* . San Antonio (TX), Psychological Corporation., 1996
121. Strain GW, Faulconbridge L, Crosby RD, Kolotkin RL, Heacock L, Gagner M, Dakin G, Pomp A: Health-related quality of life does not vary among patients seeking different surgical procedures to assist with weight loss. *Surgery for Obesity & Related Diseases* 6:521-525, 2010
122. Cappelleri JC, Bushmakin AG, Gerber RA, Leidy NK, Sexton CC, Karlsson J, Lowe MR: Evaluating the Power of Food Scale in obese subjects and a general sample of individuals: development and measurement properties. *Int J Obes* 33:913-922, 2009
123. Schultes B, Ernst B, Wilms B, Thurnheer M, Hallschmid M: Hedonic hunger is increased in severely obese patients and is reduced after gastric bypass surgery. *Am J Clin Nutr* 92:277-283, 2010
124. Gormally J, Black S, Daston S, Rardin D: The assessment of binge eating severity among obese persons. *Addict Behav* 7:47-55, 1982
125. Marcus MD, Wing RR, Lamparski DM: Binge eating and dietary restraint in obese patients. *Addict Behav* 10:163-168, 1985
126. Malone M, Alger-Mayer S: Binge status and quality of life after gastric bypass surgery: a one-year study. *Obes Res* 12:473-481, 2004
127. Svedlund J, Sjodin I, Dotevall G: GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Digestive Diseases & Sciences* 33:129-134, 1988
128. Dimenas E, Glise H, Hallerback B, Hernqvist H, Svedlund J, Wiklund I: Quality of life in patients with upper gastrointestinal symptoms. An improved evaluation of treatment regimens? *Scand J Gastroenterol* 28:681-687, 1993
129. Dimenas E, Glise H, Hallerback B, Hernqvist H, Svedlund J, Wiklund I: Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. *Scand J Gastroenterol* 30:1046-1052, 1995
130. Suter M, Calmes JM, Paroz A, Giusti V: A new questionnaire for quick assessment of food tolerance after bariatric surgery. *Obes Surg* 17:2-8, 2007
131. Schweiger C, Weiss R, Keidar A: Effect of different bariatric operations on food tolerance and quality of eating. *Obes Surg* 20:1393-1399, 2010
132. JONES R, JUNGHARD O, Dent J, VAKIL N, HALLING K, WERNERSSON B, LIND T: Development of the GerdQ, a tool for the diagnosis and management of gastro-

oesophageal reflux disease in primary care. *Alimentary Pharmacology & Therapeutics* 30:1030-1038, 2009
133. Hatlebakk JG, Emken BE, Glazkov V, Hoff DA, Hausken T: Correct use of proton pump inhibitors for gastro-oesophageal reflux disease. *Tidsskr Nor Laegeforen* 133:43-46, 2013
134. CRAIG CL, MARSHALL AL, SJ+ûSTR+ûM MICH, BAUMAN AE, BOOTH ML, AINSWORTH BE, PRATT MICH, EKELUND ULF, YNGVE AGNE, SALLIS JF, OJA PEKK: International Physical Activity Questionnaire: 12-Country Reliability and Validity. *Medicine & Science in Sports & Exercise* 35: 2003
135. Carlsen MH, Karlsen A, Lillegaard IT, Gran JM, Drevon CA, Blomhoff R, Andersen LF: Relative validity of fruit and vegetable intake estimated from an FFQ, using carotenoid and flavonoid biomarkers and the method of triads. *Br J Nutr* 105:1530-1538, 2011
136. Andersen LF, Solvoll K, Johansson LR, Salminen I, Aro A, Drevon CA: Evaluation of a food frequency questionnaire with weighed records, fatty acids, and alpha-tocopherol in adipose tissue and serum. *Am J Epidemiol* 150:75-87, 1999
137. Carlsen MH, Lillegaard IT, Karlsen A, Blomhoff R, Drevon CA, Andersen LF: Evaluation of energy and dietary intake estimates from a food frequency questionnaire using independent energy expenditure measurement and weighed food records. *Nutrition Journal* 9:37, 2010
138. Lissner L, Troiano RP, Midthune D, Heitmann BL, Kipnis V, Subar AF, Potischman N: OPEN about obesity: recovery biomarkers, dietary reporting errors and BMI. *Int J Obes* 31:956-961, 2007
139. Safety protocols, University of Agder . [article online], 2012.
140. Marsk R, Jonas E, Rasmussen F, Näslund E: Nationwide cohort study of post-gastric bypass hypoglycaemia including 5,040 patients undergoing surgery for obesity in 1986-2006 in Sweden. *Diabetologia* 53:2307-2311, 2010
141. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, Woodward M, Ninomiya T, Neal B, MacMahon S, Grobbee DE, Kengne AP, Marre M, Heller S: Severe Hypoglycemia and Risks of Vascular Events and Death. *N Engl J Med* 363:1410-1418, 2010
142. Arts J, Caenepeel P, Bisschops R, Dewulf D, Holvoet L, Piessevaux H, Bourgeois S, Sifrim D, Janssens J, Tack J: Efficacy of the long-acting repeatable formulation of the somatostatin analogue octreotide in postoperative dumping. *Clinical Gastroenterology & Hepatology* 7:432-437, 2009
143. Armstrong D, Bennett JR, Blum AL, Dent J, De Dombal FT, Galmiche JP, Lundell L, Margulies M, Richter JE, Spechler SJ, Tytgat GN, Wallin L: The endoscopic assessment of esophagitis: A progress report on observer agreement. *Gastroenterology* 111:85-92, 1996
144. Katz PO, Gerson LB, Vela MF: Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 108:308-328, 2013
145. Gasteyger C, Suter M, Gaillard RC, Giusti V: Nutritional deficiencies after Roux-en-Y gastric bypass for morbid obesity often cannot be prevented by standard multivitamin supplementation. *Am J Clin Nutr* 87:1128-1133, 2008
146. Fleischer J, Stein EM, Bessler M, Della BM, Restuccia N, Olivero-Rivera L, McMahon DJ, Silverberg SJ: The decline in hip bone density after gastric bypass surgery is associated with extent of weight loss. *J Clin Endocrinol Metab* 93:3735-3740, 2008
147. Mitri J, Muraru MD, Pittas AG: Vitamin D and type 2 diabetes: a systematic review. [Review]. *Eur J Clin Nutr* 65:1005-1015, 2011

148. Plum L, Ahmed L, Febres G, Bessler M, Inabnet W, Kunreuther E, McMahon DJ, Korner J: Comparison of glucostatic parameters after hypocaloric diet or bariatric surgery and equivalent weight loss. *Obesity* 19:2149-2157, 2011
149. Patients' Rights Act. [article online], 2012.

# Attachments

**Table 2. Patient visit schedule**

| | Screening | Baseline | Operation | Follow-up period | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Time<br>(accepted variation) | | -3 weeks<br>(-52 to -2) | 0 | 5 weeks<br>(4 to 8) | 16 weeks<br>(12 to 24) | 34 weeks<br>(28 to 40) | 52 weeks<br>(46 to 60) | 2,3,4 years<br>±2 months | 5 years<br>±4 months |
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8-10** | **11** |
| Demographic data | | x | | | | | | | |
| Co-morbidities | | x | | | | | | | |
| Regular medication | | x | | x | x | x | x | x | x |
| Clinical examination | | x | x | x | x | x | x | x | x |
| Physician consultation | x | x | | x | x | x | x | x | x |
| Inclusion and exclusion criteria | x | | | | | | | | |
| Signed informed consent | x | | | | | | | | |
| Blood samples[1] | x | x | x | x | x | x | x | x | x |
| Urine samples[1] | | x | | x | | | x | | x |
| Faecal sample[1] | | x | | x | | | x | | x |
| Pulse wave velocity | | x | | x | | | x | | x |
| Bioelectrical impedance analysis | | x | | x | x | x | x | x | x |
| ECG | | x | | | | | x | | x |
| OGTT and IVGTT | | x | | x | | | x | | x |
| PROMs questionnaires (web) | | x | | x | | | x | x | x |
| Food frequency questionnaire | | x | | | | | x | | x |
| DEXA | | x | | | | | x | | x |
| MRI | | x | | x | | | x | | x |
| Upper endoscopy | | x | | | | | x | | x |
| Manomentry | | x | | | | | x | | x |
| pH-measurement | | x | | | | | x | | x |
| 24-h ambulatory blood pressure | | x | | x | | | x | | x |
| SenseWear | | x | | x | | | x | | x |
| ApneaLink™ | | x | | x | | | x | | x |
| Hypoglycaemia/dumping | | x | | x | x | x | x | x | x |
| Adverse events | | | x | x | x | x | x | x | x |

Abbreviations: ECG; electrocardiography, IVGTT; intravenous glucose tolerance test, OGTT; oral glucose tolerance test, PROMs; patient reported outcome measures, DEXA; dual energy x-ray absorptiometry, MRI; magnetic resonance imaging.

[1]See Table 4

**Table 3. Glycaemic therapy – treatment algorithm**

| Time after surgery: | | | | |
|---|---|---|---|---|
| < 6 weeks | | ≥6 weeks | | Action: |
| Fasting glucose (mmol/l) | <5.6 | HbA1c (%) | ≤6.0 | Reduce treatment - Stop one medication[1] |
| | 5.6 – 11.0 | | 6.1 – 6.9 | No change |
| | ≥11.1 | | ≥7.0 | Intensify treatment - Titrate to max tolerable dose of existing medication or add one new medication[1]. |

[1]Preferred anti-diabetic medication in the absence of contraindications or side effects, listed in prioritised order:
Metformin
Dipeptidyl peptidase-IV inhibitors, SGLT2-inhibitors
Pioglitazone, Sulfonylureas, Insulin analogues, GLP-1 agonists

**Table 4. Laboratory method principles, sample matrix, units and analytical precision of measurements**

| Analyte | Method principle | Sample matrix | Unit | Precision (CV, analytical) | Time point for collection (visit number)[1] |
|---|---|---|---|---|---|
| Ferritin | ECLIA | Serum | µg/l | 7 % | 1-11 |
| Iron | Photometry | Serum | µmol/l | 4 % | 1-11 |
| Transferrin | Photometry | Serum | µmol/l | 2.5 % | 1-11 |
| Vitamin B12 | ECLIA | Serum | pmol/l | 12 % | 1-11 |
| Folic acid | ECLIA | Serum | nmol/l | 12 % | 1-11 |
| C-reactive protein | Photometry | Serum | mg/l | 5 % | 1-11 |
| Creatinine | Photometry | Serum | µmol/l | 2.5 % | 1-11 |
| Sodium | ISE | Serum | mmol/l | 1.0 % | 1-11 |
| Potassium | ISE | Serum | mmol/l | 1.2 % | 1-11 |
| Calcium | Photometry | Serum | mmol/l | 1.5 % | 1-11 |
| Magnesium | Photometry | Serum | mmol/l | 3.0 % | 1-11 |
| Phosphate | Photometry | Serum | mmol/l | 2.0 % | 1-11 |
| Albumin | Photometry | Serum<br>Urine | g/l | 3.0 % | 1-11<br>2, 4, 7, 11 |
| Total protein | Photometry | Serum | g/l | 2.5 % | 1-11 |
| Uric acid | Photometry | Serum | µmol/l | 4.0 % | 1-11 |
| Glucose | Photometry | Serum/Plasma | mmol/l | 2.0 % | 1-4, 7, 11 |
| Alanine aminotransferase | Photometry | Serum | U/l | 5 % | 1-11 |
| Aspartate transaminase | Photometry | Serum | U/l | 9.0 % | 1-11 |
| Alkaline phosphatase | Photometry | Serum | U/l | 3.0 % | 1-11 |
| Gamma-glutamyl transpeptidase | Photometry | Serum | U/l | 3.0 % | 1-11 |
| Lactate dehydrogenase | Photometry | Serum | U/l | 5.5 % | 1-11 |
| Creatine kinase | Photometry | Serum<br>Urine | U/l | 5.0 % | 1-11<br>2, 4, 7, 11 |
| Bilirubin | Photometry | Serum | µmol/l | 5.0 % | 1-11 |
| Amylase | Photometry | Serum | U/l | 3.0 % | 1-11 |
| Total cholesterol | Photometry | Serum | mmol/l | 2.5 % | 1-11 |
| HDL-cholesterol | Photometry | Serum | mmol/l | 3.0 % | 1-11 |
| LDL-cholesterol | Photometry | Serum | mmol/l | 3.0 % | 1-11 |
| Triglycerides | Photometry | Serum | mmol/l | 3.0 % | 1-4, 7, 11 |

| | | | | | |
|---|---|---|---|---|---|
| Thyroid stimulating hormone | ECLIA | Serum | mIE/l | 5.0 % | 1-11 |
| Unbound triiodothyronine | ECLIA | Serum | pmol/l | 5.0 % | 1-11 |
| Unbound thyroxine | ECLIA | Serum | pmol/l | 5 % | 1-11 |
| Parathyroid hormone | ECLIA | Plasma | pmol/l | 6.0 % | 1-11 |
| 25-OH-vitamine D | ECLIA | Serum | nmol/l | 6.5 % | 1-11 |
| B-human chorionic gonadotropin[2] | ECLIA | Serum | IE/l | 5.0 % | 1 |
| Paracetamol | Photometry | Serum | µmol/l | 3.0 % | 2, 4, 7, 11 |
| HbA1c | HPLC | Blood | % | 1.4 % | 1-11 |
| Complete blood count | Photometry<br>Impedance<br>Flow cytometry | Blood | g/dl<br>%<br>Cells/l | 1.0-10.0 % | 1-11 |
| Thiamin | HPLC | Serum | nmol/l | 4.5 % | 2, 4-11 |
| Bone alkaline phosphatase | CLIA | Serum | U/l | 9.5 U/L 10 %<br>45 U/L 13 % | 2, 4-11 |
| C-telopeptide of type I collagen | ECLIA | Serum | µg/l | 0.12 µg/L 13 %<br>0.32 µg/L 8 % | 2, 4-11 |
| Procollagen type I N-terminal propeptide | ECLIA | Serum | µg/l | 5 % | 2, 4-11 |
| Insulin | ECLIA | Serum | pmol/l | 4 % | 2, 4, 7, 11 |
| C-peptide | ECLIA | Serum | pmol/l | 4 % | 2, 4, 7, 11 |
| Anti-GAD | IP | Serum | ai | 0.25 ai 25 %<br>1.45 ai 8 % | 1 |
| Anti-IA2 | IP | Serum | Ai | 0.32 ai 18 %<br>1.66 ai 12 % | 1 |
| Samples for storage | | Serum, plasma, blood, urine, faeces | | | 1-4, 7, 11 |

Abbreviations: ai; antibody index, CLIA; chemiluminiscent immunoassay, CV; coefficient of variation, ECLIA; electro-chemiluminescence immunoassay, HPLC; High-performance liquid chromatography, IP; immunoprecipitation, ISE; ion selective electrode

[1]Fasting blood samples visit 2,4,7,11

[2]Women only

**Table 5. Treatment algorithm for anti-hypertensive therapy**

| Systolic blood pressure | Action |
|---|---|
| < 130 mmHg<br>or<br>< 135 mmHg on two consecutive visits | Reduce treatment |
| ≥ 160 mmHg<br>or<br>≥ 140 mmHg on two consecutive visits | Intensify treatment |

**Table 6. Treatment algorithm for lipid-lowering therapy**

| Low-density lipoprotein cholesterol | Action[1] |
|---|---|
| < 2,0 mmol/l | Consider halting medical treatment |
| ≥ 2,6 mmol/l | Consider intensifying medical treatment |

[1]Statins should be used in patients with established cardiovascular disease or in those aged ≥ 40 years with type 2 diabetes postoperatively (not in remission) and one or more other cardiovascular risk factors.

**Table 7. Treatment algorithm for reflux symptoms**

| | GerdQ score[1] | PPI[2] treatment | Action |
|---|---|---|---|
| No symptoms | 0-2 | No | No treatment |
| | | Yes | Stop PPI |
| Mild symptoms | 3-7 | No | Consider on demand treatment with H2 inhibitors[3] |
| | | Yes | Consider replacing PPI with on demand treatment with H2 inhibitors |
| Severe symptoms | 8-18 | No | PPI for eight weeks |
| | | Yes | Increase PPI dose and consider referral to gastroenterologist |

[1]Gastroesophageal Reflux Disease Questionnaire, [2]Proton pump inhibitors, [3]Histamine H2-receptor antagonists

**Table 8. Treatment algorithm for vitamin and mineral supplementation**

| Vitamin/ mineral | Low levels | Intervention | High levels | Intervention |
|---|---|---|---|---|
| B1 (pmol/l) | <ref | In case of acute thiamine deficiency: Admit to hospital for parenteral thiamine treatment<br>Without symptoms:<br>Give oral thiamine 3 mg x 1 | >ref | No intervention |
| Folic acid | <ref | Give folic acid supplement: ”Nycoplus Folsyre” 400 µg x 1 | >ref | Consider discontinuation of supplement |
| B12 (pmol/l) | <ref | Initiate or give B12 injections more frequently | >ref | No intervention or consider a temporary delay in the next B12 injection |
| 25-OH-D (nmol/l) | <ref* | Add vitamin D supplement ”Nycoplus D-vitamin” 10 µg x 2<br><br>*25-OH-D < 50 nmol/l: Give general advise on diet and sun exposure | >ref | Consider discontinuation of all the vitamin D supplements |
| Ferritin | <ref | 1. Increase the dose of iron supplement<br>2. In case of anaemia (Hb <ref) and iron-deficiency, consider parenteral iron | >ref | If elevated ferritin and normal CRP: discontinue iron supplement |
| Calcium | <ref | Initiate or consider increasing vitamin D or calcium supplements | >ref | Discontinue or consider reduction of vitamin D and calcium supplements |

# Changes to the protocol

| Changes to the protocol | |
|---|---|
| **2014-Jan** | The inclusion criteria were extended to include subjects with a current BMI between 33-34.9 kg/m$^2$ and previous morbid obesity (initially only subject with current BMI of ≥35 kg/m$^2$ were included). Also, while the inclusion criteria previously did not include a lower HbA1c-limit among subjects using anti-diabetics, a limit was set to 6.1%. Further, use of insulin, GLP-1 analogues, inhaled corticosteroids and unselective beta-blockers were removed from the list of exclusion criteria. At the same time, oesophagitis grading was specified, hiatus hernia was included and use of proton pump inhibitors removed from the exclusion list.<br>The glucose load during the oral glucose tolerance test was reduced from 75g to 25g after one patient experienced severe dumping symptoms 5 weeks after surgery. |
| **2013-Aug** | Iron supplementation changed from 65 mg for men and 130 mg for all women to 100 mg for pre-menopausal women only. |
| **2014-Jun** | Inclusion of a control group of patients with the same inclusion criteria as the other Oseberg patients, but without diabetes. These patients will function as a control group for secondary outcomes related to gastroesophageal reflux disease. |
| **2018-Jan** | The five-year visit was extended to include all examinations included at the one year visit. |
| **2018-May** | Co-workers no longer taking part in the study was removed and several new co-workers were added. |
| **2019-Feb** | SGLT2-inhibitors (anti-diabetic drug initially regarded as a third-line treatment), were now considered a second-line medication. |