

1 **Supplement 1**

2 **Trial protocol**

version 4.2.2018 (original 19.2.2008)

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5 A prospective randomized multicenter study: laparoscopic gastric bypass versus laparoscopic sleeve
6 gastrectomy in the treatment of morbid obesity

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9 Purpose of the study

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11 In recent years morbid obesity has been recognized a serious worldwide health crisis. In the US
12 obesity is considered the second most common cause of premature death after smoking. It has been
13 estimated that 400 000 deaths per year are related to obesity and its complications ⁽¹³⁾. Body mass
14 index (BMI) of Finnish people has been increasing and obesity has become more common during the
15 last two decades. In 2002 the mean BMI was 27,0 kg/m² among working age males and 25,9 kg/m²
16 among females in Finland. 66 % of the males and 49 % of the females had BMI ≥ 25 kg/m² and every
17 fifth had BMI ≥ 30 kg/m² ⁽¹⁰⁾.

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19 Obesity is related to increased morbidity and mortality. The increased mortality is mainly caused by
20 obesity related comorbidities such as insulin resistance, type 2 diabetes, hypertension and
21 dyslipidemia. ⁽¹³⁾ In addition to this, obesity is related to many other diseases such as metabolic
22 syndrome, coronary artery disease, stroke, obstructive sleep apnea, gout, gall stones, fatty liver
23 disease, arthritis, asthma and certain cancers (postmenopausal breast, uterus, colon and kidney
24 cancer ⁽²⁾.

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26 Bariatric surgery is considered superior to conservative treatment regarding weight loss and resolution
27 of comorbidities in patients with BMI ≥ 40 kg/m² ⁽¹²⁾. In two recent studies bariatric surgery decreased
28 common morbidity compared to conservative treatment ^(3, 17). Death by heart disease, diabetes and
29 cancer was less common after gastric bypass operation compared to control group ⁽³⁾.

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31 The most common operative technique worldwide is gastric bypass (65 % of all procedures) and over
32 half of these are performed by laparoscopy ⁽⁶⁾. In this operation a small 30 ml gastric pouch is created,
33 the biliopancreatic limb is measured (approximately 50 cm) by graspers and an antecolic end-to-side
34 gastrojejunostomy is created (circular or linear staplers). The alimentary limb is measured by graspers
35 at 150 cm and a side-to-side jejunostomy is created.

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37 The weight loss is based on limited food intake by the small gastric pouch, partial malnutrition by the
38 ileal bypass and possible hormonal changes. ⁽¹²⁾ Mean excessive weight loss (%) after gastric bypass
39 is 25 % at ten-year follow-up. In the same SOS study at ten-year follow-up regarding conservative

40 treatment equaled 1,6 % excessive weight gain. Surgery was also superior to conservative treatment
41 considering diabetes, hypertriglyceremia, low high density lipoprotein, hypertension and
42 hyperuricaemia. ⁽¹⁷⁾ Mortality after gastric bypass is 0,5 – 2,5 % and morbidity is 10 – 20 % ^(4, 12).

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44 Laparoscopic sleeve gastrectomy is a relatively new operative technique. It was originally intended as
45 a bridge procedure for high-risk super obese patients (BMI > 60) preceding the definitive bariatric
46 procedure ⁽¹⁵⁾. Sleeve gastrectomy is created narrow along a 33-35 Fr calibration bougie using linear
47 staplers preserving the majority of the antrum. The weight loss is based on limited food intake by the
48 narrow gastric tube created in the procedure and decrease of ghrelin hormone secreted from the
49 resected fundus of the stomach. In the last few years sleeve gastrectomy has been used as a single
50 procedure for patients with BMI 35 – 60. The initial promising results in terms of weight loss and the
51 resolution of comorbidities have been comparable to gastric bypass at short-term follow-up. However,
52 long-term results of sleeve gastrectomy are very scarce ^(9, 14).

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54 Morbid obesity by itself increases risk for venous thrombosis and pulmonary embolism. After bariatric
55 surgery, possible serious complications are hemorrhage, anastomotic or staple line leakage and
56 related infection and stricture of the anastomosis. Some of these complications must be treated by
57 reoperation. After laparoscopic gastric bypass the risk for serious complication is 0.9–5.1 % ^(7, 8, 16)
58 and mortality is 0,16 % ⁽⁶⁾. The risk for serious complication after laparoscopic sleeve gastrectomy is
59 2,9 % ⁽¹¹⁾, but studies regarding mortality and long-term results are lacking.

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61 Aim of the study

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63 The aim of the study is to compare two different operative techniques regarding weight loss,
64 resolution of comorbidities and complications. The primary endpoint is weight loss evaluated by
65 %EWL (excessive weight loss, %). The secondary endpoints include resolution of associated
66 comorbidities, improvement of QOL, mortality and morbidity of the procedures.

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68 Design of the study

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70 The study is carried out at three centers, Turku University Hospital, Vaasa Central Hospital and
71 Helsinki University Hospital (Peijas). The patients evaluated for enrollment are assigned to undergo
72 surgical treatment for morbid obesity and their treatment follows established treatment protocols.

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74 Inclusion criteria:

- 75 ▪ BMI ≥ 40 or BMI ≥ 35 with a significant obesity related comorbidity
- 76 ▪ Age 18 – 60 years
- 77 ▪ Previous successfully instituted and supervised but failed adequate diet and exercise program

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79 Exclusion criteria:

- 80 ▪ BMI > 60
- 81 ▪ Significant psychiatric disorder
- 82 ▪ Severe eating disorder, active alcohol or substance abuse
- 83 ▪ Active gastric ulcer disease
- 84 ▪ Difficult GERD with a large hiatal hernia
- 85 ▪ Previous bariatric surgery

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87 Preoperative evaluation

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89 All the patients undergo a thorough multidisciplinary evaluation (an endocrinologist, a dietician, and a
90 bariatric surgeon), and a psychiatric evaluation is obtained, if considered necessary. All patients
91 undergo upper gastrointestinal endoscopy and abdominal ultrasound examination. Possible

92 Helicobacter pylori infection and associated gastric ulcer disease are treated before surgery. Only
93 symptomatic gallstones are considered an indication for laparoscopic cholecystectomy at the time of
94 the bariatric procedure. After the clinical decision of proceeding to bariatric surgery for treating morbid
95 obesity is reached, patient eligibility for this RCT is evaluated according to the inclusion and exclusion
96 criteria. A written informed consent is received and the patients are randomized by a closed envelope
97 method either to undergo laparoscopic sleeve gastrectomy or laparoscopic gastric bypass.
98 Preoperative quality of life is measured by the Moorhead-Ardelt questionnaire at the same visit.

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100 Postoperative treatment

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102 Postoperative treatment is carried out according to established treatment protocols. Oral fluids are
103 initiated on the first postoperative day and patients are discharged from the hospital from the second
104 postoperative day onward depending on recovery. All patients are placed on multivitamins
105 postoperatively and proton pump inhibitors are routinely used for the first three months. The
106 postoperative control visits at surgical outpatient clinic are planned at 3, 6, 12, 18 months, 2, 3, 4, 5,
107 7, 10 and 15 years. At these visits the patients are measured for weight, checked for blood samples
108 according to normal treatment protocols and asked to fill the Moorehead-Ardelt quality of life
109 questionnaire. Plastic surgery consultation is obtained, if needed.

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111 Addition to 10-year follow-up, ethical amendment 4.2.2018:

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113 The incidence of gastroesophageal reflux disease (GERD) after bariatric surgery has been under vast
114 research in recent years during the SLEEVEPASS trial follow-up time, especially after sleeve
115 gastrectomy as there have been reports of increased cumulative incidence of Barrett's esophagus for
116 up to 17% at 10 years after sleeve¹⁸. The majority of these studies do not have preoperative

117 gastrointestinal endoscopy making the evaluation of de novo findings impossible. Obesity itself is also
118 a refluxogenic condition and potential GERD and endoscopic findings need to be assessed after both
119 LSG and LRYGB. In this SLEEVEPASS study, all patients underwent preoperative gastroesophageal
120 endoscopy, and thus the evaluation of de novo findings is possible. With the long-term follow-up
121 endoscopy, we will acquire important information in the actual cumulative incidence or prevalence of
122 Barrett's esophagus after bariatric surgery. This 10-year follow-up is important not only for individuals
123 (medically essential in light of recent studies), but also globally considering the major increase in the
124 number of bariatric surgery procedures in the last two decades and this is especially true for LSG, if
125 the Barrett's incidence results are validated. All available SLEEVEPASS trial patients will undergo
126 upper gastrointestinal endoscopy at 10 years, and these findings will increase the understanding of
127 the potentially required future postoperative assessments after bariatric surgery even globally. In
128 addition, the patients will fill out the GERD-HRQOL questionnaire to assess subjective GERD
129 symptoms and PPI medication use.

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131 Current state of the study

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133 The statement for approval by the ethics committee of Turku University Hospital will be submitted and
134 the approvals by the ethics committees of Vaasa Central Hospital and Helsinki University Hospital will
135 also be applied. The randomization for the study will be started during spring 2008 after the approvals
136 by the ethics committees. The researchers (Paulina Salminen, Jari Ovaska, Mika Helmiö, Mikael
137 Victorzon, Pekka Tolonen, Pipsa Peromaa, Anne Juuti and Marja Leivonen) will be personally
138 responsible for the preoperative visits, operations and postoperative visits.

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140 A summary of the addition to the ethical amendment 4.2.2018:

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142 The 5-year outcomes of the SLEEVEPASS study were published in JAMA in January 2018¹⁹. The 5-
143 year individual patient data of the SLEEVEPASS trial and a similar Swiss RCT (SM-BOSS study)
144 have been merged aiming to add to the study power of assessing outcomes by doubling the number
145 of randomized patients also adding to the generalizability of the results. Additional information on
146 T2DM was collected. The 7-year outcomes of the SLEEVEPASS trial have been collected and the
147 data is currently being analyzed. The 10-year follow-up including the additional upper gi-endoscopy
148 and a vast clinical evaluation of GERD will be conducted during 2019-2020.

149 Changes in study group: MD Risto Juusela has replaced the late MD PhD M. Victorzon at Vaasa
150 Central Hospital. In Turku, PhD student Sofia Grönroos, MD, has joined the study group for the long-
151 term outcome assessment of the study.

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154 Hypothesis and meaning of the study

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156 The results of this current RCT study enable comparison on the long-term data between the current
157 golden standard of laparoscopic gastric bypass and laparoscopic sleeve gastrectomy. The hypothesis
158 of the study is that sleeve can be considered less traumatic and easier and faster to perform

159 compared to RYGB, it could become the procedure of choice in treating morbid obesity provided that
160 long-term results of SG were comparable with those of RYGB. The results can directly be applied to
161 patient care.

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164 References

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166 1. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World
167 Health Organ Tech Rep Ser 2000; 894:i-xii, 1-253.

168 2. [Adult obesity]. *Duodecim* 2002; 118(10):1075-88.

169 3. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ,
170 Stroup AM, Hunt SC. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007;
171 357(8):753-61.

172 4. Balsiger BM, Kennedy FP, Abu-Lebdeh HS, Collazo-Clavell M, Jensen MD, O'Brien T,
173 Hensrud DD, Dinneen SF, Thompson GB, Que FG, Williams DE, Clark MM, Grant JE, Frick MS,
174 Mueller RA, Mai JL, Sarr MG. Prospective evaluation of Roux-en-Y gastric bypass as primary
175 operation for medically complicated obesity. *Mayo Clin Proc* 2000; 75(7):673-80.

176 5. Buchwald H, Estok R, Fahrback K, Banel D, Sledge I. Trends in mortality in bariatric surgery:
177 a systematic review and meta-analysis. *Surgery* 2007; 142(4):621-32; discussion 632-5.

178 6. Buchwald H, Williams SE. Bariatric surgery worldwide 2003. *Obes Surg* 2004; 14(9):1157-64.

179 7. DeMaria EJ, Sugerman HJ, Kellum JM, Meador JG, Wolfe LG. Results of 281 consecutive
180 total laparoscopic Roux-en-Y gastric bypasses to treat morbid obesity. *Ann Surg* 2002; 235(5):640-5;
181 discussion 645-7.

182 8. Higa KD, Ho T, Boone KB. Laparoscopic Roux-en-Y gastric bypass: technique and 3-year
183 follow-up. *J Laparoendosc Adv Surg Tech A* 2001; 11(6):377-82.

184 9. Himpens J, Dapri G, Cadiere GB. A prospective randomized study between laparoscopic
185 gastric banding and laparoscopic isolated sleeve gastrectomy: results after 1 and 3 years. *Obes Surg*
186 2006; 16(11):1450-6.

187 10. Lahti-Koski M, Vartiainen E, Mannisto S, Pietinen P. Age, education and occupation as
188 determinants of trends in body mass index in Finland from 1982 to 1997. *Int J Obes Relat Metab*
189 *Disord* 2000; 24(12):1669-76.

190 11. Lalor PF, Tucker ON, Szomstein S, Rosenthal RJ. Complications after laparoscopic sleeve
191 gastrectomy. *Surg Obes Relat Dis* 2008; 4(1):33-8.

192 12. Maggard MA, Shugarman LR, Suttorp M, Maglione M, Sugerman HJ, Livingston EH, Nguyen
193 NT, Li Z, Mojica WA, Hilton L, Rhodes S, Morton SC, Shekelle PG. Meta-analysis: surgical treatment
194 of obesity. *Ann Intern Med* 2005; 142(7):547-59.

195 13. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United
196 States, 2000. *Jama* 2004; 291(10):1238-45.

197 14. Moon Han S, Kim WW, Oh JH. Results of laparoscopic sleeve gastrectomy (LSG) at 1 year in
198 morbidly obese Korean patients. *Obes Surg* 2005; 15(10):1469-75.

199 15. Regan JP, Inabnet WB, Gagner M, Pomp A. Early experience with two-stage laparoscopic
200 Roux-en-Y gastric bypass as an alternative in the super-super obese patient. *Obes Surg* 2003;
201 13(6):861-4.

202 16. Schauer PR, Ikramuddin S, Gourash W, Ramanathan R, Luketich J. Outcomes after
203 laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Ann Surg* 2000; 232(4):515-29.

204 17. Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M,
205 Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos
206 AK, Lonroth H, Naslund I, Olbers T, Stenlof K, Torgerson J, Agren G, Carlsson LM. Effects of bariatric
207 surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007; 357(8):741-52.

208 18. Felsenreich DM, Kefurt R, Schermann Met al. Reflux, Sleeve Dilation, and Barrett's
209 Esophagus after Laparoscopic Sleeve Gastrectomy: Long-Term Follow-Up. *Obes Surg*.
210 2017;10.1007/s11695-017-2748-9

211 19. Salminen P, Helmio M, Ovaska Jet al. Effect of Laparoscopic Sleeve Gastrectomy vs
212 Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss at 5 Years Among Patients With Morbid
213 Obesity: The SLEEVEPASS Randomized Clinical Trial. *JAMA*. 2018;319(3):241-254.

214 New references: #18 and #19

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