



King's Research Portal

DOI:

[10.1016/j.diabet.2017.12.007](https://doi.org/10.1016/j.diabet.2017.12.007)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Capristo, E., Panunzi, S., De Gaetano, A., Raffaelli, M., Guidone, C., Iaconelli, A., ... Mingrone, G. (2017). Intensive lifestyle modifications with or without liraglutide 3mg vs sleeve gastrectomy: A three-arm non-randomized, controlled, pilot study. *DIABETES AND METABOLISM*. <https://doi.org/10.1016/j.diabet.2017.12.007>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Accepted Manuscript

Title: Intensive lifestyle modifications with or without liraglutide 3mg vs sleeve gastrectomy: A three-arm non-randomized, controlled, pilot study<!--<RunningTitle>Medical vs surgical weight-loss programme</RunningTitle-->



Author: Esmeralda Capristo Simona Panunzi Andrea De Gaetano Marco Raffaelli Caterina Guidone Amerigo Iaconelli Luca L'Abbate Andreas L. Birkenfeld Rocco Bellantone Stefan Bornstein Geltrude Mingrone

PII: S1262-3636(17)30589-X
DOI: <https://doi.org/doi:10.1016/j.diabet.2017.12.007>
Reference: DIABET 964

To appear in: *Diabetes & Metabolism*

Received date: 2-9-2017
Accepted date: 19-12-2017

Please cite this article as: Capristo E, Panunzi S, De Gaetano A, Raffaelli M, Guidone C, Iaconelli A, L'Abbate L, Birkenfeld AL, Bellantone R, Bornstein S, Mingrone G, Intensive lifestyle modifications with or without liraglutide 3mg vs sleeve gastrectomy: A three-arm non-randomized, controlled, pilot study<!--<RunningTitle>Medical vs surgical weight-loss programme</RunningTitle-->, *Diabetes and Metabolism* (2017), <https://doi.org/10.1016/j.diabet.2017.12.007>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

without liraglutide 3 mg vs sleeve gastrectomy: A three-arm non-randomized, controlled, pilot study<!--<RunningTitle>Medical vs surgical

Andrea De Gaetano^b, Marco Raffaelli^c, Caterina Guidone^a, Amerigo Iaconelli^a, Luca L'Abbate^a, Andreas L. Birkenfeld^{d,e,f}, Rocco Bellantone^g

General Surgery, Catholic University, Rome, Italy

and Computer Science (IASI), BioMatLab, Rome, Italy

University, Rome, Italy

Städtisches Klinikum Carl Gustav Carus an der Technischen Universität Dresden, Dresden, Germany

St Thomas' Hospital, Guy's Campus, King's College London, London, United Kingdom

at the Helmholtz Centre Munich at University Hospital Dresden, a member of the German Centre for Diabetes Research (DZD e.V.)

Catholic University, Largo A. Gemelli 8 – 00168 Rome, Italy</PA>

For clinically eligible subjects choose to undergo surgical treatment for obesity, other options should be investigated. This study aimed to assess the effect of liraglutide daily vs sleeve gastrectomy (SG) on BMI after 1 year.

Conducted at an Italian university hospital, non-diabetic patients eligible for bariatric surgery were recruited from a weight-loss clinic and had the allocation of 25 subjects in each arm matched by BMI and age. ILM consisted in 813 kcal of a very low-calorie diet (VLCD) for 1 month, followed by 1500 kcal plus 30 min of brisk walking daily and at least 3 h of aerobic exercise weekly. SG patients followed a VLCD for 1 month and a free diet thereafter.

Retention was 100% in the SG and 85% in the two medical arms. SG reduced BMI by 32% ($P < 0.001$ vs medical arm), while ILM + liraglutide by 26% ($P < 0.001$). More women allocated themselves to the ILM + liraglutide group. Weight loss was 43 kg with SG, 26 kg with ILM + liraglutide, 10 kg with SG, -6.3 kg with ILM and -8.3 kg with ILM + liraglutide. Prevalence of prediabetes was significantly lower with ILM + liraglutide, and 39% with SG vs 39% by ILM alone. Cardiometabolic risk factors were greatly reduced in all three groups.

liraglutide 3.0 mg once daily associated with drastic calorie-intake restriction and intensive physical activity promoted a 24% weight loss, which was maintained with SG, while preserving lean body mass. Although this study was non-randomized, it was designed to explore the efficacy of medical treatment compared to bariatric surgery.

Keywords: bariatric surgery; Lifestyle modifications; Liraglutide; Obesity; Very low-calorie diet

.gov

Obesity-related diseases such as type 2 diabetes (T2D) and cardiovascular disease (CVD) [1–3]. The number of people affected by morbid or class-III obesity in the US, contributed to 20% of the total per capita healthcare expenditures in 2000 [5].

Individuals with a BMI $> 35 \text{ kg/m}^2$ in the presence of obesity complications, are eligible for bariatric surgery [6]. In the face of low mortality rates—0.08% with bariatric surgery, including reduction of long-term mortality [8] and T2D remission [9–11]. However, due to the public's perception as well as those of the medical community, in fact, only 1% of clinically eligible subjects choose to undergo surgical treatment for obesity [12].

Individuals who are eligible for bariatric surgery yet who are neither willing nor able to undergo the operation should, however, be offered other therapeutic options. A randomized controlled trial comparing intensive lifestyle modification (ILM) intervention with or without a 3-mg daily liraglutide injection vs sleeve gastrectomy (SG) with free access to bariatric surgery, was on a voluntary basis: they were invited to choose their own allocation to one of the three arms.

Liraglutide, a GLP-1 analogue approved for the treatment of obesity at a dose of 3 mg/day and marketed under the name Saxenda, has been proven to reduce weight in patients taking a placebo [13]. More important, this weight reduction was maintained for up to 3 years, as shown by le Roux et al. [14]. Patients who wish to be considered for bariatric surgery.

A very low-calorie diet (VLCD) has been reported to allow weight loss of around 20 kg in men and nearly 16 kg in women [15]. However, the weight-reduction is often not maintained. Methods to maintain weight loss. One possible option is a low-carbohydrate, high-fat, high-protein diet, which has been associated with relevant weight loss and preservation of lean body mass [16,17]. Therefore, our present pilot study started with a VLCD for the first month to match the diet usually prescribed for VLCD, high-protein diet over the subsequent 11 months to achieve substantial weight loss.

an operation widely performed worldwide, it has earned its place as a primary bariatric operation [18]. Similarly, the regimen of a VLCD with anti-obesity drugs such as orlistat [19] and sibutramine [20]. Indeed, this dietary combination was recently proposed for the Diabetes Remission Clinical Trial programme is delivered in a routine primary-care setting to T2D patients to achieve long-lasting normoglycaemia [21].

and the medical options for treatment of morbid obesity beyond bariatric surgery.

METHODS

Patients from the Catholic University Hospital in Rome, Italy, and eligible for bariatric surgery were given the option to choose any one of three possible treatment arms and matched for BMI and age. The basic design of the study is shown in Fig. 1. Patients were also informed that, while they had to pay for the intervention, in any case, all patients in the medical arms were also offered the possibility to undergo surgery on completion of the study.

The study was approved by the ethics committee of our institution, and conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. An additional written informed consent was signed before SG surgery.

The primary endpoint was change in baseline BMI at 1 year, while secondary endpoints were changes at 1 year from baseline in weight, body composition, plasma glucose, homocysteine, lipid profile and modification of dysglycaemia. The study was conducted between 2 November 2015 and 31 January 2017. Inclusion criteria were BMI $> 40 \text{ kg/m}^2$, or $> 35 \text{ kg/m}^2$ if one or more comorbidities (hypertension, sleep apnoea, severe hip or knee arthritis) were present. Exclusion criteria were history of pancreatitis, or major depressive or other severe psychiatric disorders; and family or personal history of multiple endocrine cancers or

intervention consisted of 1 month of a VLCD with 813 kcal/day [$3 \times 200 \text{ mL}$ Fortimel (Nutricia Advanced Medical Nutrition, Schiphol, The Netherlands) = 600 kcal; 90 kcal; and All-Bran cereal (50 g; Kellogg Company, Battle Creek, MI, USA) = 123 kcal, 20 g of fibre], followed by an LCD (12 kcal/kg/day) for 11 months together with intensive physical exercise (30 min/day of brisk walking plus at least 3 h/week of aerobic exercise) with or without 3 months of liraglutide treatment starting at a dose of 0.6 mg and followed by weekly 0.6-mg increments up to 3.0 mg to reduce side-effects.

The intervention was medically prescribed and paid for by the patients. Also, patients were evaluated at baseline and at 1, 3, 6, 9 and 12 months after starting the intervention. General practitioners and physicians every week to report any weight changes, the frequency and intensity of their exercise as well as any side-effects, and received

The intervention involves longitudinal resection of the stomach along its greater curvature, with complete excision of the fundus and part of the body and antrum. It is a vertical tube-shaped gastric 'sleeve' with a capacity of approximately 100 mL.

All patients followed the same dietary regimen as those in the medical arms: 813 kcal/day of a VLCD. During the subsequent 11 months, they were followed by a dietitian at each follow-up visit. Patients were evaluated at baseline and at 1, 3, 6, 9 and 12 months after starting the intervention.

using calibrated scales, and with subjects wearing light clothing and no shoes. Body composition was measured by dual-energy X-ray absorptiometry (DXA), which provides results for both lean body mass (LBM) and fat mass (FM).

Blood pressure (SBP and DBP) were measured twice by an experienced nurse with patients sitting and rested. Hypertension was defined as SBP \geq 140 mmHg and/or DBP \geq 90 mmHg.

Physical activity was assessed at baseline and at the 6-month and 1-year follow-up visits, using the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire, which assesses physical activities over a typical week over the past 4 weeks and the corresponding time spent, quantified into broad categories (< 1 h, 1–2 h, 3–4 h, 5–6 h, 7–8 h, 9–10 h, 11–12 h, 13–14 h, 15–16 h, 17–18 h, 19–20 h, 21–22 h, 23–24 h).

Blood samples were obtained at baseline and at each visit to determine plasma glucose, insulin and serum lipoprotein concentrations.

Plasma glucose was measured using a glucose oxidase method (Analox Sensor Technology, Stokesley, North Yorkshire, UK) and plasma insulin by microparticle enzyme immunoassay (EIA) (Eitest, 1000 IU/mL) with an intra-assay coefficient of variation (CV) of 6.6%. Total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride (TG) concentrations were measured using a colorimetric method. LDL cholesterol was calculated with the Friedewald formula [23]. HDL cholesterol was defined as low if < 40 mg/dL (1.0 mmol/L).

The HOMA-IR index [24], which is calculated by multiplying fasting plasma insulin (FPI) by fasting plasma glucose (FPG), then dividing it by 408 (160 \times 25.4).

Data were presented as numbers and percentages, and continuous data as the mean \pm standard deviation (SD); categorical data were analyzed using chi-squared test or Fisher's exact test, and continuous data were analyzed using analysis of variance (ANOVA). Changes in continuous variables at 1 year are expressed in both absolute terms and percentages relative to baseline. ANOVA was used to test differences across the three groups, and pairwise post-hoc comparisons were performed by Tukey's test. Changes over time in weight, BMI, LBM and FM were analyzed by means of a linear mixed-effects model, and the carry-forward method was used for missing data. All analyses were considered statistically significant, and all analyses were performed with RStudio open-source software.

The study population (73% male) were grouped into three study arms (Fig. 1). The chi-squared test indicated a significant ($P = 0.025$) imbalance in the allocations between the three groups. In addition, at the time of enrolment, statin drugs were being used by 12/25 patients in the SG group vs 6/25 patients in the ILM and 7/25 in the ILM + liraglutide group. There was no difference observed in total and LDL cholesterol (Table I).

The study was terminated due to the detection of T2D, geographical distance and the cost of liraglutide. In addition, 10 subjects (four in the ILM group and six in the ILM + liraglutide group) dropped out of the study because the intervention was too rigid, while two patients in the ILM + liraglutide group left the study because they considered the drug too expensive.

l two because they were relocated for work. However, because data from at least two follow-up visits were available (Fig. 2), all recruited

Composition

Year follow-up was 975.16 ± 106.27 kcal/day, corresponding to 10.95 ± 1.74 kcal/kg body weight, whereas the caloric intakes in the two me
 t significantly different in the three arms, baseline weight in the SG group (133.5 ± 18.58 kg) was significantly higher than in the other two
 de groups, respectively; $P < 0.001$ for both pairwise comparisons), most likely due to the greater number of men in the surgical group. Patie
 65.26 ± 11.39) than the other two groups [ILM and ILM + liraglutide = 45.16 ± 6.06 kg and 55.76 ± 10.92 kg, respectively ($P < 0.001$ vs b
 nificantly higher in the SG than in the other two groups (Table I). Values at baseline and for all the recorded variables at 1 year, as well as
 s a good reflection of the absolute variations in anthropometric parameters.

ble I) was recorded in the SG group ($-32.15 \pm 4.11\%$), and the smallest weight decrement was recorded in the ILM patients (-14.12 ± 5.09
 $23.65 \pm 8.03\%$ ($P < 0.001$ for ILM vs ILM + liraglutide; $P < 0.001$ for ILM vs SG; and $P < 0.001$ for SG vs ILM + liraglutide). Using a mix
 group than in the ILM group (β interaction term for time \times treatment = -0.56 ; $P < 0.001$). Likewise, BMI was more decreased over time in b
 treatment = -0.62 ± 0.04 and -0.32 ± 0.05 ($P < 0.001$ for both respectively)].

ents was significantly different from the trend in the ILM group (β for time \times treatment = -0.49 , $P < 0.001$). Results for the FM absolute Δ
 groups.

of BMI, body weight, LBM and FM in the three groups. Changes in BMI (kg/m^2) and weight (kg) over time are depicted in Fig. S1 (see sup

MA-IR

l three groups: -6.87 ± 2.34 , -17.85 ± 7.88 and -11.08 ± 9.88 in the ILM, ILM + liraglutide and SG groups, respectively (ILM + liraglutid
 ng insulin decreased more in the ILM + liraglutide and SG groups than in the ILM group ($P < 0.001$ for both pairwise comparisons). Simila
 groups with significantly larger decrements seen with ILM + liraglutide ($P < 0.001$) and with SG ($P < 0.001$) than with ILM (-34.05 ± 8.4
 ps, respectively).

ILM, 7 (20%) in the ILM + liraglutide and 15 (43%) in the SG group— had impaired fasting glucose (IFG) at baseline, defined by the Ame
 ients (82.86%) normalized their baseline glycaemia at 1 year to values < 100 mg/dL, while fully normalized fasting glycaemia was observe
 /15) of the SG subjects.

groups were recorded for total, LDL and HDL cholesterol and TG at baseline (Table I). TG decreased over time in all three groups, with the greatest decrease in the SG group: $-23.48 \pm 12.34\%$, $-31.08 \pm 17.84\%$ and $-14.12 \pm 27.04\%$ in the ILM, ILM + liraglutide and SG groups, respectively, with a significant difference ($P = 0.02$). Total and LDL cholesterol also decreased in all patients. The average changes in total cholesterol were -9.76 ± 5.18 , -15.01 ± 11.46 and -10.5 ± 11.1 in the ILM, ILM + liraglutide and SG groups, respectively, with a significant difference ($P = 0.003$) between the ILM and SG groups. LDL cholesterol was reduced by -10.5 ± 11.1 , -22.3 ± 14.4 and -10.5 ± 11.1 in the ILM, ILM + liraglutide and SG groups, respectively, with a significant difference ($P = 0.04$) again between ILM and SG groups. On the other hand, while HDL cholesterol increased by 9.62 ± 5.18 in the ILM and ILM + liraglutide groups, it decreased in the SG group ($-1.58 \pm 31.26\%$), with significant post-hoc associations between ILM + liraglutide vs ILM ($P = 0.02$) and

no significant differences among them, and a similar DBP decrease was observed in the ILM and ILM + liraglutide groups (the post-hoc comparison was not significant).

One patient in the ILM + liraglutide group experienced severe nausea and vomiting within 1 to 3 months of enrolment, while two patients were referred for constipation. In addition, one patient in the ILM + liraglutide group experienced severe constipation within 1 to 3 months of enrolment.

Discussion

The sample size necessary to demonstrate non-inferiority [25] of 3-mg liraglutide treatment compared with SG was calculated. Assuming a non-inferiority margin of 4% SD for SG and 8% SD for liraglutide—the sample size necessary to demonstrate non-inferiority of liraglutide compared with SG had to include 88 subjects. Allowing for an attrition rate of 20%, the total number of subjects to be enrolled in a randomised controlled trial comparing liraglutide 3 mg/day to an ILM programme was 110.

Adding liraglutide 3 mg/day to an ILM programme results in a remarkable BMI change at 1 year, albeit lower than that achieved with SG. While SG reduced BMI by 24% and ILM reduced it by 14%. Thus, liraglutide as an add-on therapy to ILM almost doubled the effect of dietary restriction and physical activity.

The loss of 11.6 kg of LBM due to rapid weight loss, low protein intakes and virtually no physical exercise, whereas LBM was considerably better preserved in the ILM + liraglutide and ILM groups, respectively), which followed a high-protein diet and intensive physical activity. However, the percentage of LBM reduction was much higher than that observed in a 1-year RCT [13] wherein the mean change in body weight with liraglutide 3 mg was, compared with the lifestyle-modification approaches involved. Indeed, while the 1-year RCT diet was restricted to 500 kcal/day and patients were given only a restricted physical-activity programme [13], in our pilot series, subjects followed a VLCD for 1 month and a strict 12 kcal/kg body weight high-protein, high-fat, low-carbohydrate diet and a physical-activity programme.

markable compared with other appetite-suppressing drugs. After 4 weeks of a VLCD, sibutramine maintained a 1-year weight loss of $-5.2 \pm 1.2\%$. In our present study, those receiving ILM + liraglutide 3 mg lost 26.25 ± 10.65 kg over the same period of time.

Saxenda 16 mg plus sustained-release bupropion 360 mg/day led to a weight reduction of $-5.0 \pm 0.3\%$ ($P < 0.0001$ vs placebo) whereas, in our study [5]. In fact, the latter treatment led to considerably better results than phentermine/topiramate 7.5 mg/46 mg and 15 mg/92 mg by mouth, which was compared with 1.2% with placebo ($P < 0.0001$ for both phentermine plus topiramate doses) [27].

100% in the surgical arm and 84% in the two medical arms. Liraglutide caused gastrointestinal side-effects in two out of 25 patients, while phentermine/topiramate did not.

Weight loss was significantly lower in the ILM + liraglutide group than in the two other groups. Insulin resistance, as evaluated by HOMA-IR, was reduced in the ILM group. Circulating TG fell by 31% in the ILM + liraglutide group, while the reduction was by 23% and 14% in the ILM and SG groups.

While a decrease in LDL cholesterol was observed in the SG arm (-22%), the most pronounced increase of HDL cholesterol (27%) was in those receiving ILM + liraglutide. Also, it was noted that, unlike other authors [28], our SG patients showed no improvement in HDL cholesterol, possibly as a consequence of the lack of lifestyle counselling was offered to our surgical patients to more closely simulate what actually happens in real life after bariatric surgery. Although bariatric weight-loss surgery, the vast majority of patients fail to do them.

Weight loss was significantly greater in the ILM + liraglutide group than in the two other study arms, whereas DBP was significantly reduced only in the ILM + liraglutide group. Overall, weight loss was associated with a net reduction in costs.

The net cost of SG in Italy is €5681, while the cost of Saxenda is €4320 ($\text{€}360/\text{month} \times 12$) per year, with a net difference of €1361 in favour of SG. There are as yet no data on long-term (≥ 5 years) 3-mg liraglutide weight-loss effects.

The lack of randomization methodology, which may have generated selection bias. Indeed, there was an imbalance between the number of women allocated to the ILM + liraglutide arm and the SG arm. However, our study design did most likely reflect the preferences of men and women, and of the wealthy and non-wealthy, for either medical or surgical treatment of obesity. The ILM + liraglutide arm because they either preferred a less-invasive approach to obesity than men or were more willing to pay the high cost of the treatment through the National Health Service (SSN). Other limitations were the short duration of our trial (1 year) and that it was a single-centre study.

Our study did not include cut-off values for dyslipidaemia and arterial blood pressure. Eligible patients were enrolled as they were, with no effort to exclude those with cardiovascular disease. While this had no direct implication for the primary study endpoint, it may have influenced secondary outcome measures.

The reasons for patients choosing bariatric surgery over medical treatment with liraglutide in designing drug and bariatric surgery trials are multiple. Apart from common obstacles such as approval from ethics committees and the high cost of bariatric surgery with bariatric surgery in a country where the latter is fully covered by the SSN, while the former is totally paid for by the patients themselves. The reasons for choosing bariatric operations and with liraglutide injections were explained, many of our patients decided to go with liraglutide. Thus, a well-designed RCT comparing placebo and/or ILM + SG could offer new insights into possible alternatives to bariatric surgery, particularly for those who are either unwilling or unable to undergo surgery.

It is worth noting that, at least over the short term, injectable liraglutide at a dose of 3.0 mg once daily in association with a drastically restricted caloric intake achieved a weight loss around twice that achieved with ILM alone and only 25% less than with SG. In addition, the sample size necessary for an RCT to detect a difference between 3.0 mg daily and SG was calculated to be 110 (55 in each arm). Such a randomized study appears to be necessary in light of the gender-biased nature of bariatric surgery and also has the potential to expand our medical options for treating morbid obesity in addition to bariatric surgery. Indeed, the effect of liraglutide in our present study was similar to that observed in a previous 1-year RCT [13], probably because of our more stringent dietary regimen and the associated intensive physical-activity programme.

ly. EC, MR and LLA acquired the data. The data analysis was done by SP and ADG. Interpretation of the data was by EC, GM, MR, SP, RSB and AB made a critical revision. All authors approved the final version of the manuscript. EC, GM and SP ensured that questions related to the manuscript were investigated and resolved.

t.

external funds of the Catholic University and by a grant from Deutsche Forschungsgemeinschaft (DFG) to GM, SRB and ALB (IRTG 2251).

associated with this article can be found at <http://www.sciencedirect.com> at doi:.....

controlling the global obesity epidemic. Available: <http://www.who.int/nutrition/topics/obesity/en/>.

Block G, Lewington S, Sherliker P, Clarke R, Clarke R, Emberson J, et al. Body-mass index and cause-specific mortality in 900 000 adults: prospective cohort study. *Lancet* 2010; 375: 1047–55.

Whitman JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010; 363: 221–32.

Wong S, Cummings S, Stiles S, et al. American Heart Association Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Statement from the American Heart Association. *Circulation* 2011; 123: 1683–701.

10. J. Impact of morbid obesity on medical expenditures in adults. *Int J Obes (Lond)* 2005; 29: 334–9.

11. Guidelines for severe obesity. Consensus Development Conference Panel. *Ann Intern Med* 1991; 115:956-61.

12. Benchmarking best practices in weight loss surgery. *Curr Probl Surg* 2010; 47:79-174.

13. Larsson K, Larsson B, Wedel H, et al. Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2012; 366: 1032–41.

14. Guidone C, Iaconelli A, Leccesi L, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012; 366: 1032–41.

Guidone C, Iaconelli A, Nanni G, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: a randomized trial. *Lancet* 2015; 386:964-73.

Shikama K, Brethauer SA, Navaneethan SD, et al. STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes--3-year outcomes. *N Engl J Med* 2012; 367:1377-85.

Bariatric surgery. [Accessed August 8, 2009]; American Society for Metabolic & Bariatric Surgery. Available at:

[http://www.asmb.org/asmbs_fs_surgery.pdf](#). [Ref list]

Wainwright N, Halpern A, Krempf M, et al. SCALE Obesity and Prediabetes NN8022-1839 Study Group. A Randomized, Controlled Trial of 3.0% Liraglutide in Type 2 Diabetes. *N Engl J Med* 2017; 376:709-22.

Wainwright N, Lau DC, Van Gaal L, et al. SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes: a randomised, double-blind trial. *Lancet* 2017; 389:1399-409.

Very low calorie diet (VLCD) followed by a randomized trial of corset treatment for obesity in primary care. *Scand J Prim Health Care* 2010; 28:10-15.

Effect of normal-fat diets, either medium or high in protein, on body weight in overweight subjects: a randomised 1-year trial. *Int J Obes Relat Metab Disord* 2007; 31:1033-40.

Wittert GA, Keogh JB, et al. The satiating effect of dietary protein is unrelated to postprandial ghrelin secretion. *J Clin Endocrinol Metab* 2005; 93:1033-40.

Minian A, Brethauer S, Schauer P. Recent national trends in the surgical treatment of obesity: sleeve gastrectomy dominates. *Surg Obes Relat Disord* 2011; 7:1033-40.

Green RT, Vijgen SM, Engelfriet PM. Cost-effectiveness of a low-calorie diet and orlistat for obese persons: modelling long-term health gain. *Health Econ Law Pol* 2011; 1:1033-40.

Proton C, Thomas F, Leutenegger E. Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the effect of a low-calorie diet. *Int J Obes Relat Metab Disord* 2007; 31:1033-40.

North KG, Adamson A, Sniehotta FF, et al. The Diabetes Remission Clinical Trial (DiRECT): protocol for a cluster randomized trial. *BMC Fam Pract* 2017; 18:1-10.

Skellern WL, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med. Sci. Sports Exerc* 2002; 34:1033-40.

Wainwright N, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med. Sci. Sports Exerc* 2002; 34:1033-40.

Wainwright N, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med. Sci. Sports Exerc* 2002; 34:1033-40.

Wainwright N, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med. Sci. Sports Exerc* 2002; 34:1033-40.

Wainwright N, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med. Sci. Sports Exerc* 2002; 34:1033-40.

Wainwright N, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med. Sci. Sports Exerc* 2002; 34:1033-40.

Wainwright N, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med. Sci. Sports Exerc* 2002; 34:1033-40.

ve lifestyle modification; VLCD: very low-calorie diet; LCD: low-calorie diet; SG: sleeve gastrectomy.

ment and outcomes.

from baseline in body mass index (BMI; kg/m²), body weight, lean body mass (LBM) and fat mass (FM) in the three study arms. Data are n
ve gastrectomy.

llow-up, expressed as the percent delta (% Δ) and absolute Δ in the three study treatment groups

	ILM + liraglutide 3 mg		Sleeve gastrectomy (SG)				
	(n = 25)		(n = 25)				
	M: 5 (20)	F: 20 (80)	M: 14 (56)	F: 11 (44)	<i>P</i> = 0.025*		
	Tukey's HSD test						
	ILM vs ILM + liraglutide		ILM vs SG		ILM + liraglutide vs SG		
	Mean	SD	Mean	SD	<i>P</i>	<i>P</i>	<i>P</i>
3 (52)	46.2	17.35	42.7	11.74	0.548	0.989	0.632
6.65	40.77	5.20	42.88	5.46	0.48	0.05	0.25
1.16	31.05	4.36	28.98	2.96	0.03	<0.001	0.15
1.09	-23.65	8.03	-32.15	4.11	<0.001	<0.001	<0.001
1.98	-9.75	3.69	-13.91	3.13	<0.001	<0.001	<0.001
4.21	109.65	19.06	133.5	18.58	0.93	<0.001	<0.001
6.62	83.4	14.81	90.07	9.62	0.006	0.30	0.22
1.09	-23.65	8.03	-32.15	4.11	<0.001	<0.001	<0.001
1.59	-26.25	10.65	-43.43	10.47	<0.001	<0.001	<0.001
1.36	53.89	11.65	68.23	14.54	0.002	0.84	<0.001
0.82	45.61	10.95	56.61	9.98	<0.001	0.51	0.001
1.26	-15.26	9.03	-16.05	8.24	0.03	0.008	0.90

.86	-8.28	5.71	-11.62	7.44	0.49	0.005	0.10
.06	55.76	10.92	65.26	11.39	< 0.001	< 0.001	0.002
.82	39.4	9.06	34.12	8.83	0.36	0.70	0.08
8.6	-28.36	15.13	-47.59	10.65	0.06	< 0.001	< 0.001
.78	-16.36	9.38	-31.15	9.21	0.005	< 0.001	< 0.001
.46	5.44	0.54	5.63	0.45	0.08	0.67	0.38
0.3	4.39	0.42	4.99	0.47	< 0.001	0.08	< 0.001
.34	-17.85	7.88	-11.08	9.88	< 0.001	0.15	0.01
.14	-0.97	0.46	-0.64	0.58	< 0.001	0.13	0.04
3.9	173.86	89.28	196.24	89.02	0.99	0.49	0.57
2.63	52.03	18.21	59.86	17.53	< 0.001	< 0.001	0.39
.49	-65.07	15.99	-64.16	15.58	< 0.001	< 0.001	0.97
2.46	-129.36	84.21	-136.37	78.64	< 0.001	< 0.001	0.93
.36	6.3	3.49	7.33	3.24	0.93	0.68	0.47
.84	1.55	0.59	2.01	0.67	< 0.001	< 0.001	0.09
3.4	-71.19	14.36	-68.38	13.38	< 0.001	< 0.001	0.73
.95	-5.02	3.23	-5.33	2.86	0.001	< 0.001	0.91
.64	1.96	0.50	1.54	0.78	0.001	< 0.001	0.06
.41	1.31	0.41	1.27	0.69	0.002	< 0.001	0.96
2.34	-31.08	17.84	-14.12	27.04	0.48	0.28	0.02
.54	-0.63	0.43	-0.27	0.46	0.99	0.03	0.04
.52	5.87	1.26	4.56	0.68	0.24	0.001	< 0.001
.27	4.82	0.68	3.48	0.67	0.99	< 0.001	< 0.001
.18	-15.01	11.46	-22.43	17.02	0.39	0.003	0.13
.31	-0.99	0.92	-1.07	0.84	0.13	0.04	0.92
.14	0.98	0.1	1.1	0.32	0.04	0.85	0.16
0.1	1.26	0.19	1.02	0.27	0.91	0.002	< 0.001
1.6	27.44	11.16	-1.58	31.26	0.02	0.19	< 0.001
0.1	0.27	0.12	-0.07	0.36	0.06	0.03	< 0.001
.51	3.99	1.11	2.8	0.56	< 0.001	0.2	< 0.001

38	2.97	0.65	1.9	0.6	0.39	<0.001	<0.001
1.1	-22.3	14.4	-29.4	25.22	0.12	0.002	0.42
35	-1.02	0.82	-0.9	0.73	0.1	0.02	0.85
4.2	81.6	8	81.6	10.27	0.24	0.24	0.99
63	79.6	6.6	81.2	5.64	0.77	0.95	0.56
25	-2.15	5.88	0.79	12.74	0.51	0.06	0.44
86	-2	4.78	-0.4	10.29	0.5	0.14	0.69
07	125.8	15.72	130.6	14.74	0.01	0.3	0.41
22	122.2	11.19	124.6	10.3	0.02	0.19	0.64
32	-2.42	5.25	-3.83	9.89	0.64	0.97	0.74
64	-3.6	7.57	-6	13.23	0.67	0.99	0.64

(post-study value - baseline value)/baseline value × 100;

Female; HSD: honest significant difference; HOMA-IR: homoeostasis model of assessment of insulin resistance; HDL/LDL: high-density/low-density lipoprotein

index (BMI) and body weight in patients in the three study arms. ILM: intensive lifestyle modification; SG: sleeve gastrectomy.