Adjunctive Liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery: the GRAVITAS randomised controlled trial

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Background: Obesity surgery is effective for obesity and type 2 diabetes (T2DM). However, many patients do not achieve sustained diabetes remission following surgery. Liraglutide, a GLP-1 analogue, improves glycaemia and reduces body weight. Our aim was to evaluate the safety and effectiveness of Liraglutide 1·8 mg in patients with persistent or recurrent T2DM after surgery.
Methods: In this double-blind, placebo-controlled trial, adults with HbA1c >48 mmol/mol (>6·5%) at least one year after surgery were randomised 2:1 to once-daily subcutaneous Liraglutide 1·8 mg or Placebo, together with a reduced-calorie diet and increased physical activity. The primary outcome was the change in HbA1c from baseline to 26 weeks. EudraCT 2014-003923-23 and ISRCTN 13643081.
Findings: Between February 2016 and November 2018, we assigned 80 patients to receive Liraglutide (n=53) or Placebo (n=27). Seventy-one (89%) participants completed the study up to week 26 (complete-cases population). A multivariable linear regression analysis taking baseline HbA1c and type of surgery into account as covariates showed that Liraglutide was associated with a difference in HbA1c change of -13·3 mmol/mol or -1·22%, 95% CI -19·7 to -7·0, p<0·001) vs Placebo at 26 weeks. Liraglutide was associated with a difference in the change of weight of -4·23 kg [95% CI -6·81 to -1·64, p<0·001) vs Placebo. No significant influence of type of surgery was noted.
Interpretation: This is the first randomised controlled trial of adjunctive Liraglutide treatment in patients with diabetes mellitus after metabolic surgery. The results support the use of Liraglutide therapy in this clinical context.
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Introduction

Randomised controlled trials (RCTs) have demonstrated that obesity surgery, such as Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG), is substantially more effective than intensive medical care for the treatment of type 2 diabetes mellitus (T2DM) in patients with obesity. The effects of surgery are so profound that 30-63% of patients achieve diabetes remission, i.e. normoglycaemia in the absence of glucose-lowering medications[1]. Whilst many of the benefits of obesity surgery on glucose control can be attributed to weight loss, both early and longer-term substantial improvements in glycaemia also take place independent of weight loss. This has led to the concept of "metabolic surgery". However, even after surgery, 37-70% of patients do not go into diabetes remission and of those who do, 25-35% relapse at five years[2]. The STAMPEDE RCT shows only a minority of patients stay in remission (HbA1c ≤6·5% without diabetes medications) at 5 years: 30·6% for RYGB and 23·4% for VSG[3]. Therefore, the management of persistent or recurrent T2DM after metabolic surgery represents a clinical challenge as, in the absence of RCTs, current guidelines do not provide specific recommendations on the safety and efficacy of glucose-lowering medication after metabolic surgery.

The mechanisms underlying suboptimal metabolic responses to surgery are not completely understood. Risk factors for suboptimal glycaemic response to surgery include long duration of T2DM, poor glycaemic control before surgery, suboptimal weight loss and substantial weight regain amongst others[4]. In a minority of patients, anatomical factors may be responsible, such as the formation of a fistula between the gastric remnant and gastric pouch or a "candy cane" after RYGB and the widening of the neogastric tube after VSG. Hormonal factors are considered to be important determinants of the glycaemic and weight loss responses after surgery. Following RYGB and VSG, the post-prandial secretion of the gut hormone glucagon like peptide (GLP)-1 is enhanced compared to pre-operatively[5]. GLP-1 increases satiety and insulin release thus reducing both weight and glycaemia[6]. We, and others, have demonstrated that suboptimal responders in terms of weight loss after RYGB have an attenuated GLP-1 response to a standardised meal compared to optimal responders[6,7]; in a prospective study of patients having RYGB and VSG, non-remission of T2DM after surgery was associated with a smaller post-prandial rise in GLP-1[8]. However, this reduced GLP-1 post-prandial response in suboptimal responders is not always a consistent finding[9,10].

We hypothesised the GLP-1 receptor agonists (GLP-1 RAs) could bring additional glycaemic and weight loss improvements in patients who have not achieved remsission of T2DM after metabolic

surgery. We have previously shown that the acute peripheral administration of the GLP-1 RA Exendin-4 in rodent models of RYGB has additive effects to the already enhanced endogenous GLP-1 secretion as demonstrated by an additional reduction in food intake[11]. Indeed, data from retrospective non-randomised studies in humans support this hypothesis: the administration of GLP-1 RAs in patients with and without T2DM and a suboptimal response to metabolic surgery was associated with weight loss and glycaemic improvements[12-15]. This RCT was therefore designed to investigate the safety and efficacy of pharmacological administration of the GLP-1 RA Liraglutide on glycaemic control in patients with persistent or recurrent T2DM after RYGB or VSG surgery.

Methods

Study population

This was a prospective randomised double-blinded placebo-controlled clinical trial. Eighty patients with obesity and persistent or recurrent T2DM that had undergone RYGB or VSG surgery at least 12 months before randomisation were recruited from the Imperial College Healthcare NHS Trust, Guy's and St Thomas's NHS Foundation Trust, University College London Hospitals NHS Foundation Trust, St George's University Hospitals NHS Trust and Chelsea and Westminster Hospital NHS Foundation Trust. The full protocol can be accessed as a supplementary file. Key inclusion criteria included an age of 18-70 and an HbA1c >48 mmol/mol (>6·5%). Key exclusion criteria included current treatment with GLP-1 RA or dipeptidyl peptidase 4 (DPP-4) inhibitors, the presence of anatomical or endocrinological pathology causing suboptimal weight loss or weight regain (e.g. gastro-gastric fistula, hypothyroidism or Cushing's syndrome), specific contraindication to the use of GLP-1 RA, pregnancy and breastfeeding. The trial was approved by the West London Research Ethics Committee (reference 15/LO/0780) and registered in the EudraCT database (2014-003923-23) and the International Standard Randomized Controlled Trial registry (ISRCTN 13643081). Written informed consent was obtained from all patients prior to participation.

Study Treatment & Follow-up

Patients eligible for the trial entered the run-in period (trial weeks 0-2), were instructed on how to use the pen devices and self-administered Placebo once a day through a subcutaneous injection. At the end of the run-in period, the pen devices were collected and the remaining volume measured to check for patient adherence to the self-administration regime. Patients who adhered to the administration regime were then randomised at a ratio of 2:1 to either treatment with Liraglutide (Victoza®, Novo Nordisk, Crawley, UK; n=53) or Placebo (saline; n=27) via pen devices of identical appearance for a further 24 weeks. All participants, clinical study personnel and pharmacy staff were blinded to treatment assignment. The computer-generated randomisation sequence was stratified by type of surgery (RYGB or VSG). The starting dose was 0·6 mg/day (trial week 3). The dose was increased by 0·6 mg/day each week as tolerated, such that between trial week 6 and 26 all patients administered 1·8 mg/day or their maximum tolerated dose. Female participants of reproductive potential were asked to maintain effective contraception for the duration of the trial.

All assessments and interventions took place at the NIHR Imperial Clinical Research Facility at Hammersmith Hospital. Patients were assessed by an Endocrinologist and Diabetologist with a specialist interest in Obesity Medicine, and dietitian at baseline and weeks 6, 10, 18 and 26 of the trial. A psychiatrist saw all patients at baseline and on further routine visits if indicated, after signposting to relevant local services. The psychiatrist assessed and optimised patients for disordered eating behaviours and mood disturbances associated with weight gain (e.g. binge eating disorder, depression, alcohol abuse), identified at clinical interview and on questionnaires. The Obesity Medicine physician optimised patients' pharmacotherapy to remove or replace any medications associated with weight gain when clinically appropriate. The management of glucose-lowering agents (GLAs) was based on the National Institute of Health and Care Excellence (NICE) guideline NG28. The dietician assessed patients' eating behaviour and encouraged healthy eating based on the published American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery clinical practice guidelines for the perioperative nutritional, metabolic and non-surgical support of the bariatric surgery patient[16]. Patients were advised to

incorporate moderate aerobic physical activity to include a minimum of 150 minutes per week including strength training 2-3 times per week.

Outcomes

The primary outcome was the change in HbA1c from baseline at 26 weeks. Secondary outcomes included the change from baseline in body weight, systolic and diastolic blood pressure, lipid profile, number of GLAs, number of patients on insulin, insulin dose in patients taking insulin and obesity-related comorbidity score using the King's Obesity Staging Criteria[17]. This is a holistic and validated obesity staging system which incorporates the major complications of obesity.

Statistical Analyses

The trial was powered to detect a clinically significant difference in HbA1c effect of 5.5 mmol/mol (0.5% units) between the Liraglutide and Placebo groups. Assuming the change in HbA1c at 26 weeks in the Liraglutide group would be -16·4 mmol/mol (-1·5% units), and -10·9 mmol/mol (-1·0% units) in the Placebo group, with an SD of 7·3 mmol/mol (0·67% units) around the group means, we calculated a sample size of 44 completers in the Liraglutide group and 22 completers in the placebo group would provide statistical power of 80% to detect this difference at α=0·05 on the basis of perfoming a two sample t-test. Eighty patients were recruited to account for a predicted 20% drop-out rate. As part of a pre-specified analysis plan, continuous variables that were normally distributed are expressed as mean and standard deviation (SD) and 95% confidence interval (CI). The principal statistical analysis presented is a complete-cases analysis excluding patients who did not complete the final study visit at week 26. For the intention to treat (ITT) dataset analysis, imputation was done for the main clinical outcomes of the study (HbA1c, weight). Missing data was assumed to be missing at random (MAR). Where the missing value occurred at the baseline visit, available data from the screening visit was used. If the missing value occurred at the end of a time series, a Last Observation Carried Forward rule was used. Missing data within a time series was imputed using a mean imputation rule. Primary statistical comparisons were performed with a multivariable linear regression analysis for each of the following outcomes (change from baseline to week 26 of HbA1c, weight, systolic and diastolic BP, lipid parameters, King's Obesity Staging Criteria score) using the treatment assignment (Liraglutide or Placebo), baseline values of the outcome variable and type of surgery (VSG or RYGB) as covariates. Residual plots were used to check for assumptions underlying each regression analysis and were judged satisfactory. A mixed effects repeated measures linear model was used to analyse longitudinal data for weight and HbA1c for all times between baseline and 26 weeks. A unequal variance t-test was used to analyse psychological questionnaire scores. Statistical analysis was performed using GraphPad Prism 8·0·2 (GraphPad Software, Inc., California, USA) and Stata/IC 15·1 (Stata Corporation, Texas, USA). A significance level of 0·05 was used for all hypothesis testing.

Role of Funding Source

The JP Moulton Charitable Foundation funded this trial. Novo Nordisk provided the investigational medicinal product and identical placebo pens. Imperial College London acted as the Sponsor for this study. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between February 2016 and November 2018, 80 individuals were randomised at a 2:1 ratio to receive once-daily subcutaneous Liraglutide 1·8 mg or placebo for 26 weeks, as an adjunct to a calorie deficit diet and increased physical activity. Figure 1 illustrates the screening, enrolment and allocation of patients in the trial. The intention-to-treat (ITT) population comprised 53 participants in the Liraglutide group and 27 participants in the placebo group. Table 1 shows the baseline characteristics of the Liraglutide and Placebo cohorts, as well as the VSG and RYGB subgroups. There was no difference between the Liraglutide and Placebo baseline characteristics apart from the fact that HbA1c was slightly higher in the Liraglutide group. Five participants in the Liraglutide group withdrew from the trial (2 were unable to attend for further study visits, 1 withdrew after deterioration of an underlying psychiatric condition, 1 withdrew after diagnosis of a lymphoma and 1 after a reduction in estimated glomerular filtration rate [eGFR] in the context of chronic kidney disease). Four participants in the placebo group withdrew (1 due to gastro-intestinal side effects, 1 was unable to attend for further study visits, 1 died of pneumonia, 1 withdrew after deterioration of an underlying psychiatric condition). Seventy-one of the 80 patients therefore completed the trial at 26 weeks with all patients assigned to Liraglutide titrated to the full dose of 1·8 mg as per protocol. The following statistical analysis utilises these complete cases (an ITT analysis, carried out with imputation, is available in the Supplementary Appendix).

Liraglutide improves glycaemia and body weight

A multivariable linear regression analysis utilising baseline HbA1c, treatment assignment and type of surgery as covariates estimated the mean difference in the change in HbA1c at week 26 for Liraglutide vs Placebo as -13·3 mmol/mol [95% CI -19·7 to -7·0], p <0·001. As expected there was a significant association with baseline HbA1c values, but no significant effect in the change in HbA1c from type of surgery was noted (Table 2). A mixed effects repeated measures linear model was used to assess the effect of treatement and time (baseline and weeks 6, 10, 18, 26) and their interaction on HbA1c. The significant interaction term warranted separate analyses to compare the mean changes from baseline HbA1c for the Liraglutide and Placebo groups at each timepoint (Table 3). Significant improvements in HbA1c from baseline in the Liraglutide group were already apparent at week 6 (-5·85 mmol/mol [-8·16 to -3·54], p<0·001) and plateaued by week 18 (-12·1 mmol/mol [-14·5 to -9·83], p<0·001) – Figure 2A. In contrast, we noted an increase in HbA1c in the Placebo group which was statistically significant at week 18 (+4·30 mmol/mol [0·97 to 7·64], p=0·012) and week 26 (4·13 mmol/mol [0·79 to 7·47], p=0·015). The ITT analysis (Supplementary Tables 1 and 2) did not alter the conclusions with respect to HbA1c.

The multivariable linear regression analysis utilising baseline weight, treatment assignment and type of surgery as covariates estimated the mean difference in the change in weight at week 26 for Liraglutide vs Placebo as -4·23 kg [-6·81 to -1·64], p=0·002. As expected there was an association with baseline weight, but no significant effect on the change in weight from type of surgery was noted (Table 2). The mixed effects repeated measures linear model on the data from all 5 time points found that there was also a significant interaction between treatment and time. The mean changes from baseline weight for the Liraglutide and Placebo groups were then determined (Table 3). Significant improvements in weight from baseline in the Liraglutide group were already apparent at week 6 (-2·38 kg [-3·26 to -1·49], p<0·001) and this weight reduction trend continued through week 10 (-3·71 kg [-4·59 to -2·82], p<0·001), week 18 (-4·46 kg [-5·34 to -3·57], p<0·001) and week 26 (-5·26 kg [-6·15 to -4·38], p<0·001) with no apparent plateauing of effect – Figure 2B. No significant change from baseline weight was noted in the Placebo group. The ITT analysis (Supplementary Tables 1 and 2) did not alter the conclusions with respect to weight.

Figures 3A and 3B show the individual responses of each patient in the complete-cases population in terms of percentage weight change. Overall, 22/48 (46%) lost more than 5% weight on treatment with Liraglutide and only 2/23 (8·7%) with Placebo. 7/48 (15%) lost more than 10% weight with Liraglutide and 2/48 (4·2%) lost more than 15%. Figure 3C shows that the proportion of patients on Liraglutide with weight loss >5% steadily increased from 17% at week 6, 33% at week 10, 38% at

week 18, to 46% at week 26. Figure 3D shows that the proportion of patients on Liraglutide with HbA1c <48 mmol/mol (<6·5%) was 23% at week 6, increased to 35% at week 10, 48% at week 18 and fell back slightly to 42% at week 26. In contrast, only 13% of patients on Placebo were able to improve their HbA1c to <48 mmol/mol by week 26.

Other secondary endpoints

There were no statistically significant changes in blood pressure, fasting lipid parameters or King's Obesity Staging Criteria score by week 26 in either the Placebo or Liraglutide groups (Table 2). The vast majority of patients in each group stayed on the same number of oral GLAs from baseline to week 26, with the number of patients reducing their oral GLA burden generally balanced by numbers adding on GLAs (whether in the Liraglutide or Placebo groups). Two patients in the Liraglutide group (out of 15 on insulin at baseline) were able to stop insulin as opposed to 0 out of 5 in the Placebo group (Table 4).

Psychopathology, eating behaviour and quality of life were measured using validated questionnaires[18-22]. Twenty nine percent had moderate to severe depression according to the Beck's Depression Inventory (BDI II). Thirty percent scored above the clinical cut-off score (>8) for depression and 42% scored above the clinical cut-off score for anxiety (>8) on the Hospital Anxiety and Depression Scale (HADS). Seven percent showed moderate risk of hazardous alcohol use according to the Alcohol Use Disorder Inventory Test (AUDIT). There was no significant difference in the change from baseline in measures of anxiety, depression, alcohol use, eating behaviour or quality of life between Placebo and Liraglutide (Supplementary Table 3).

Safety of Liraglutide

As expected gastrointestinal disorders were the most common side-effects observed in both study arms, but were mild in severity. Two patients in the Placebo group and 4 with Liraglutide had hypoglycaemia, all such events occurred within the first 4 weeks. There were no recorded cases of acute pancreatitis, pancreatic or thyroid cancer over the 26 week study period. The incidence of adverse events gradually declined during the trial (Table 5). Four serious adverse events (SAEs) occurred during the trial. One patient in the Placebo group was diagnosed with cellulitis at the injection site but continued in the trial. One patient in the Placebo group died due to pneumonia. One patient in the Liraglutide group was diagnosed with a lymphoma <4 weeks after randomisation and withdrew from the trial. One patient in the Liraglutide group experienced a drop in eGFR on the background of chronic kidney disease and withdrew from the trial. None of these SAEs were considered related to treatment assignment.

Discussion

This is the first RCT to demonstrate that 26 weeks adjunctive treatment with Liraglutide together with dietary and psychological support is safe and effective in improving glycaemia and weight loss in patients with persistent or recurrent T2DM following RYGB or VSG surgery. Liraglutide was well tolerated; adverse effects observed were in line with previous clinical experience[23]. The characteristics of our cohort were representative of patients with persistent or recurrent T2DM commonly seen after metabolic surgery. Whilst considered suboptimal responders in terms of glycaemia, it should be noted that the mean postoperative weight loss was satisfactory and consistent with that observed in RCTs of metabolic surgery[3]. The heterogeneity of our cohort in terms of glycaemic and weight loss response to surgery reflects the pragmatic nature of this RCT and enhances its potential for translation to routine clinical practice.

Our results are consistent with our findings in rodents in which the acute peripheral administration of Exendin-4 in rodent models of RYGB had similar effects in the reduction in food intake both in RYGB and sham-operated rats[11], and with the few retrospective studies in which GLP-1 RAs were used in patients with persistent or recurrent T2DM, suboptimal weight loss or weight regain after metabolic surgery[12-15]. It is interesting that the impact of the tested doses of Liraglutide on glucose and weight reduction in our cohort was almost identical to that observed in patients with T2DM who have not had metabolic surgery previously[23]. An explanation for this could be that the GLP-1 secretion

after metabolic surgery is enhanced only in response to eating and fasting levels post-surgery are similar to pre-surgery levels[24]. Administration of exogenous GLP-1 in the form of Liraglutide 1·8 mg increases fasting levels, conferring additional advantages in terms of appetite suppression, weight reduction and consequent improvements in insulin sensitivity, alongside increases in insulin secretion after eating.

In addition to metformin and GLP-1 RAs there are alternative GLAs that could potentially be used after metabolic surgery for patients with persistent/recurrent T2DM based on their mechanism of action. These include DPP-4 and Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors. Only a relatively small number of our patients were taking SGLT-2 inhibitors (Table 1) and these were not altered during the course of the trial. Patients on DPP-4 inhibitors were excluded as these could interact with Liraglutide. There is only one placebo-controlled RCT to our knowledge that examined the effect of a 4 week course of Sitagliptin after RYGB which demonstrated significantly decreased postprandial glucose levels during a mixed meal tolerance test[25]. The CARAT placebo-controlled RCT was also planned to examine the effect on Canagliflozin in post metabolic surgery patients with persistent T2DM[26] but this trial appears to have been terminated without results (ClinicalTrials.Org NCT02912455). It is conceivable that the combination of surgery and medicine may have additive, if not synergistic, effects on glucose control and even cardiovascular protection[27], but recommendations for their use will crucially depend on demonstration of their efficacy in future RCTs.

In our patient cohort, we observed a substantial psychological burden in terms of anxiety and depression, but not alcohol use disorder. This is similar to recent data from the LABS-2 longitudinal study where high BDI scores were associated with weight regain after RYGB[28]. It is not possible to determine the direction of causality from this data: psychological morbidity could be contributing to suboptimal weight loss and glycaemic improvement or *vice versa* the suboptimal weight loss and diabetes relapse could be a cause of distress, anxiety and depression. Health related quality of life measures and measures of disordered eating were comparable with other studies of patients after bariatric surgery[29,30]. Eating behaviour appears to become healthier in terms of reduced preference and reward from palatable food after RYGB and VSG surgery[31]. As this cohort of patients had weight loss in line with expected outcomes from bariatric surgery, there was no reason to expect disordered eating in this group. The finding of unchanged psychiatric morbidity and disordered eating at 26 weeks suggests that Liraglutide did not lead to any worsening nor improvement in psychiatric morbidity. The finding of weight stability in the Placebo group underscore the importance of psychological and nutritional monitoring and support to patients, not just before, but also after metabolic surgery. This stabilisation is indeed a positive finding considering the trajectory of weight gain frequently observed in this cohort of patients.

Limitations of the trial include the short follow-up period of 26 weeks. Our data suggests that the weight loss trend did not appear to plateau within the 26 week follow-up period. The weight loss effect with Liraglutide 1·8 mg in the LEADER trial plateaued beyond 6 months[32] and therefore a longer trial will be necessary to understand if there is a similar pattern of weight loss in this patient group. Second, there were a smaller number of participants that had previously undergone VSG, which could be explained by the tendency amongst surgeons and physicians in our units to offer RYGB to patients with T2DM. Third, patients were given Liraglutide at a maximum dose of 1·8 mg per day as per its license for the treatment of T2DM. In an audit in patients given Liraglutide 3·0 mg (licensed for the treatment of obesity) we showed that in a cohort of 188 post-surgical patients that this was associated with a median reduction of body weight of 6·4%[33] suggesting that the higher dose is effective and safe in this group of patients.

In conclusion, this RCT provides evidence for the efficacy and safety of the GLP-1 RA Liraglutide as an adjunct to dietary and psychological support for patients with persistent or recurrent T2DM after metabolic surgery. Patients with a range of baseline characteristics were included thus making our findings applicable to a wide population base. Our results highlight the importance of multimodal interventions for this complex group of patients and suggest that surgical, medical, psychological and nutritional therapies may have an additive, if not synergistic, impact in suboptimal responders to

metabolic surgery[27]. Trials with longer follow-up and exploring the use of the higher doses used for obesity treatment could provide more evidence for the long-term efficacy and safety of the combination of metabolic surgery with GLP-1 RAs.

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Contributors

TT, ADM, BP-P, AA, AP, SS and SRB contributed to study design, statistical analysis, data interpretation, drafting and review of the manuscript. ADM, BP-P, AK, MA, WA, ERM contributed to the running of the study, data collection and analysis. HC, RLB, BM, OK, VG, AA recruited patients to the study. TT is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

ADM has received honoraria for presentations and advisory board contribution by Novo Nordisk, Boehringer Ingelheim, AstraZeneca, Johnson & Johnson and research grant funding from Fractyl. AA has received honoraria for presentations by WL Gore and MSD. RLB has received support from Novo Nordisk, Fractyl, Ethicon, Nestle, Medscape. OK has received honoraria for academic and advisory board contributions from Johnson & Johnson and Medtronic.

Research in context

Evidence before this study

A Pubmed search was carried out on 24 Feb 2019 using the terms “bariatric surgery”, “metabolic surgery”, “Roux-en-Y gastric bypass”, “sleeve gastrectomy”, “GLP-1”, “GLP-1 analogues”, “GLP-1 agonists”, “Liraglutide”, “Dulaglutide”, “Exenatide”, “Lixisenatide”, “Albiglutide”, “diabetes mellitus”. Abstracts were reviewed to locate original research publications describing the effect of GLP-1 analogues on patients with suboptimal responses to bariatric surgery in terms of inadequate weight loss or inadequate resolution of diabetes. Five publications describe uncontrolled retrospective analyses of such patients in cohorts ranging from 15 to 33 patients, utilising Liraglutide at up to 3 mg daily, and all publications suggested that adjunctive treatment with Liraglutide was effective at reducing body weight and improving glycaemia in this context. No randomised controlled trials for GLP-1 RA in this clinical context were identified.

Added value of this study

To our knowledge, this is the first placebo-controlled randomised placebo-controlled trial for GLP-1 analogues as adjunctive treatment for persistent or recurrent diabetes mellitus after bariatric surgery. We demonstrate that Liraglutide 1·8 mg is effective at improving glycaemia and reducing body weight in comparison to placebo, and this clinical effect was comparable to previous studies on Liraglutide in patients with diabetes and obesity. Importantly, the treatment was safe and well tolerated, with comparable rates of adverse effects to previous studies of Liraglutide 1·8 mg.

Implications of all the available evidence

The overall evidence supports the use of Liraglutide as an adjunctive treatment in patients who have inadequate resolution of diabetes after metabolic surgery.

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Table 1. Baseline characteristics of ITT cohort. Data presented as mean (SD) except where indicated. HOMA, homeostasis model assessment; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides. GLAs, glucose lowering agents.

	Total cohort		**Vertical Sleeve Gastrectomy**		**Roux-en-Y gastric bypass**	
	Placebo n=27	Liraglutide n=53	Placebo n=8	Liraglutide n=11	Placebo n=19	Liraglutide n=42
Female (n, %)	14 (51·9%)	33 (62·2%)	3 (37·5%)	6 (54·5%)	11 (57·9%)	27 (64·3%)
Age (years)	57·2 (8·1)	54·8 (9·4)	56·3 (4·8)	58·4 (9·3)	57·6 (9·3)	53·9 (9·3)
Diabetes duration (years)	19·6 (8·0)	16·4 (7·0)	17·4 (7·2)	16·2 (7·4)	20·5 (8·3)	16·4 (7·0)
Time since surgery (years)	3·8 (2·4)	3·8 (2·0)	3·4 (1·8)	4·9 (1·8)	3·9 (2·7)	4·0 (2·1)
HbA1c (mmol/mol)	57·7 (8·2)	63·3 (15·2)	60·9 (12·3)	59·6 (18·0)	56·3 (5·7)	64·3 (14·5)
HbA1c (% units)	7·4 (0·75)	7·9 (1·39)	7·7 (1·13)	7·6 (1·65)	7·3 (0·52)	8·0 (1·33)
Fasting glucose (mmol/L)	7·5 (2·9)	8·2 (3·2)	7·4 (1·9)	8·1 (4·3)	7·5 (3·2)	8·2 (2·9)
Fasting insulin (mIU/L)	7·3 (1·7)	9·2 (9·0)	13·5 (4·8)	9·5 (10·9)	8·1 (5·9)	9·1 (8·4)
HOMA2%S	96·1 (50·2)	124·1 (81·7)	61·9 (28·8)	137·1 (113·6)	117·2 (49·6)	119·2 (67·9)
Weight (kg)	103·5 (27·0)	100·7 (20·7)	111·6 (37·4)	114·0 (23·2)	100·1 (21·6)	97·2 (18·7)
Body Mass Index (kg/m^2)	37·0 (7·7)	36·1 (7·8)	38·1 (10·3)	40·1 (8·4)	36·5 (6·6)	35·1 (7·4)
Pre-operative weight (kg)	130·8 (29·7)	127·8 (25·7)	135·5 (43·8)	132·1 (29·0)	128·8 (22·7)	126·8 (25·1)
Nadir weight after surgery kg)	92·8 (19·6)	89·0 (18·7)	95·3 (22·8)	104·3 (21·7)	91·8 (18·7)	85·3 (16·2)
Percentage weight loss after surgery at screening	-20·3 (12·9)	-20·9 (10·0)	-16·5 (11·7)	-13·9 (4·1)	-21·8 (13·4)	-22·6 (10·3)
Weight regain from nadir to screening (kg)	10·8 (12·6)	11·5 (8·8)	16·4 (19·0)	9·3 (5·7)	8·4 (8·4)	12·0 (9·4)
King´s Obesity Staging Criteria score	10·4 (3·9)	11·2 (3·9)	11·0 (4·5)	12·5 (3·9)	10·2 (3·7)	10·8 (3·9)
No. of patients/% on oral GLAs						
None	5/19%	13/25%	1/13%	3/27%	4/21%	10/24%
1 GLA	15/56%	30/57%	5/63%	5/45%	10/53%	25/60%
2 GLAs	6/22%	8/15%	2/25%	2/18%	4/21%	6/14%
3 GLAs	1/4%	2/4%	0	1/9%	1/5%	1/2%
Median no. of GLAs [IQR]	1 [1, 1·5]	1 [1, 1]	1 [1, 1·3]	1 [0·5, 1·5]	1 [1, 1·5]	1 [1, 1]
No. of patients/% on types of oral GLAs						
Metformin	21/78%	38/72%	7/89%	8/73%	14/74%	30/71%
Sulphonylureas	2/7%	4/8%	0	1/9%	2/11%	3/7%
SGLT-2 inhibitors	7/26%	2/4%	2/25%	1/9%	5/26%	1/2%
Number of patients/% on insulin	6/22%	15/28%	1/13%	1/9%	5/26%	14/33%

Blood pressure (mmHg) Systolic Diastolic	 137·5 (16·8) 72·3 (10·3)	 127·9 (15·7) 73·8 (12·2)	 132·1 (12·7) 80·9 (8·1)	 126·3 (12·8) 72·5 (10·4)	 139·8 (18·0) 68·6 (9·0)	 128·3 (16·5) 74·2 (12·8)
Heart rate (beats per minute)	72·8 (12·5)	77·6 (11·6)	79·6 (17·1)	76·2 (12·5)	70·0 (9·1)	78·2 (11·7)
Cholesterol (mmol/L) Total LDL cholesterol HDL cholesterol	 4·2 (1·2) 2·2 (0·9) 1·3 (0·4)	 4·5 (1·0) 2·5 (0·8) 1·3 (0·3)	 4·7 (1·6) 2·5 (1·1) 1·2 (0·3)	 4·8 (1·0) 2·8 (0·6) 1·3 (0·3)	 4·0 (1·0) 2·0 (0·8) 1·4 (0·5)	 4·4 (1·0) 2·4 (0·9) 1·3 (0·3)
Triglycerides (mmol/L)	1·5 (1·1)	1·8 (2·2)	2·3 (1·7)	1·6 (1·2)	1·2 (0·7)	1·8 (2·3)

Table 2. Results of multivariable linear regression analyses of the change from baseline to 26 weeks in clinical outcome variables in complete-cases population. Covariates were baseline values of the outcome variable, treatment assignment (Liraglutide vs Placebo) and type of surgery (VSG vs RYGB). Coefficients for each covariate listed. Significant p-values <0·05 highlighted in bold. LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides.

	Baseline value			**Treatment (Liraglutide vs Placebo)**			**Type of Surgery (VSG vs RYGB)**		
Primary endpoint	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
HbA1c (mmol/mol)	0·70	0·48 to 0·91	**<0·001**	-13·3	-19·7 to -7·0	**<0·001**	-4·67	-11·4 to 2.0	0·169
HbA1c (% units)	0·06	0·04 to 0·08		-1·22	-1·80 to -0·64		-0·43	-1·04 to 0·18	
Secondary endpoints									
Weight (kg)	0·95	0·89 to 1·00	**<0·001**	-4·23	-6·81 to -1·64	**0·002**	-2·04	-5·00 to 0·93	0·175
SBP (mmHg)	0·65	0·47 to 0·84	**<0·001**	2·14	-4·52 to 8·80	0·523	-3·99	-10·80 to 2·81	0·246
DBP (mmHg)	0·51	0·33 to 0·70	**<0·001**	2·88	-1·67 to 7·44	0·211	-1·41	-6·36 to 3·55	0·573
Total Cholesterol (mmol/L)	0·58	0·42 to 0·75	**<0·001**	-0·03	-0·41 to 0·35	0·879	-0·36	-0·77 to 0·05	0·087
LDL cholesterol (mmol/L)	0·73	0·55 to 0·92	**<0·001**	0·04	-0·29 to 0·37	0·815	-0·23	-0·58 to 0·13	0·213
HDL cholesterol (mmol/L)	0·89	0·74 to 1·03	**<0·001**	0·03	-0·08 to 0·15	0·545	-0·03	-0·15 to 0·09	0·622
Triglycerides (mmol/L)	0·18	0·10 to 0·25	**<0·001**	-0·26	-0·56 to 0·04	0·089	-0·29	-0·61 to 0·04	0·081
King's Obesity Staging Criteria score	0·84	0·70 to 0·98	**<0·001**	0·23	-0·87 to 1·32	0·682	-0·66	-1·86 to 0·53	0·273

Table 3. Mixed model repeated measures analysis of changes from baseline in HbA1c and body weight with time in complete-cases population. Mean changes from baseline (contrast) displayed with 95% confidence interval (CI). Significant p-values <0·05 noted in bold.

HbA1c (mmol/mol)	**Placebo**			**Liraglutide**		
Week vs baseline	**Contrast**	**95% CI**	**p-value**	**Contrast**	**95% CI**	**p-value**
6	2·08	-1·25 to 5·43	0·221	-5·85	-8·16 to -3·54	**<0·001**
10	2·13	-1·21 to 5·47	0·211	-10·7	-12·98 to -8·36	**<0·001**
18	4·30	0·97 to 7·64	**0·012**	-12·1	-14·5 to -9·83	**<0·001**
26	4·13	0·79 to 7·47	**0·015**	-11·4	-13·7 to -9·1	**<0·001**
Body Weight (kg)						
Week vs baseline	**Contrast**	**95% CI**	**p-value**	**Contrast**	**95% CI**	**p-value**
6	0·38	-0·90 to 1·66	0·557	-2·38	-3·26 to -1·49	**<0·001**
10	-0·33	-1·60 to 0·95	0·612	-3·71	-4·59 to -2·82	**<0·001**
18	-0·32	-1·60 to 0·96	0·622	-4·46	-5·34 to -3·57	**<0·001**
26	-0·87	-2·14 to 0·41	0·185	-5·26	-6·15 to -4·38	**<0·001**

Table 4. Changes in diabetes treatment at week 26 in complete-cases population. GLAs, glucose lowering agents.

	Placebo	Liraglutide
Patients categorised by change in no. of GLAs		
-1 (reduced by 1)	1	1
Unchanged	21	45
+1 (increased by 1)	1	2
Patients stopping insulin/no. on insulin at baseline	0/5	2/15
Median change in total daily dose insulin (units) [Range]	1 [0 to 10]	-4 [-69 to 0]

Table 5. Adverse events in ITT population. Adverse events (grouped by their system organ class) and serious adverse events that occurred up to and including week 26 among individuals in the safety-analysis set are included and are presented by their preferred terms from the Medical Dictionary for Regulatory Activities. Events are included if they had an onset date on or after the first day that the study drug was administered and no later than 14 days after the last day the study drug was administered.

	Vertical Sleeve Gastrectomy				**RYGB**			
	Placebo n=8		Liraglutide n=11		Placebo n=19		Liraglutide n=42	
	Early <4 weeks	Late >4 weeks	Early <4 weeks	Late >4 weeks	Early <4 weeks	Late >4 weeks	Early <4 weeks	Late >4 weeks
Total number of adverse events	12	5	7	1	12	11	26	3
Gastrointestinal								
Nausea	4	2	1	0	5	1	9	0
Diarrhoea	0	0	0	1	1	1	1	0
Constipation	2	0	3	0	1	0	0	0
Vomiting	0	0	0	0	1	1	0	0
Abdominal pain	1	0	0	0	1	0	0	0
Gastro-oesophageal reflux	0	0	0	0	0	0	2	0
Flatulence	0	0	0	0	0	1	0	0
General								
Fatigue	0	1	0	0	0	2	0	0
Headache	0	0	1	0	0	1	1	0
Injection site haematoma	3	0	0	0	0	0	0	0
Peripheral oedema	0	0	0	0	0	1	1	1
Hypoglycaemia	0	0	0	0	1	1	2	1
Infections								
Influenza	0	1	0	0	0	0	1	0
Gastroenteritis	0	1	0	0	0	0	0	0
Urinary tract infection	0	0	0	0	0	0	1	0
Metabolic and nutritional								
Decreased appetite	2	0	2	0	0	0	3	0
Hypoglycaemia	0	0	0	0	2	0	4	0
Serious adverse events								
Cellulitis	0	0	0	0	0	1	0	0
Progression of chronic kidney disease	0	0	0	0	0	0	0	1
Lymphoma	0	0	0	0	0	0	1	0
Death	0	0	0	0	0	1	0	0

Figure 1. **CONSORT Diagram** showing numbers of patients screened, randomised, assignment to groups and withdrawals.

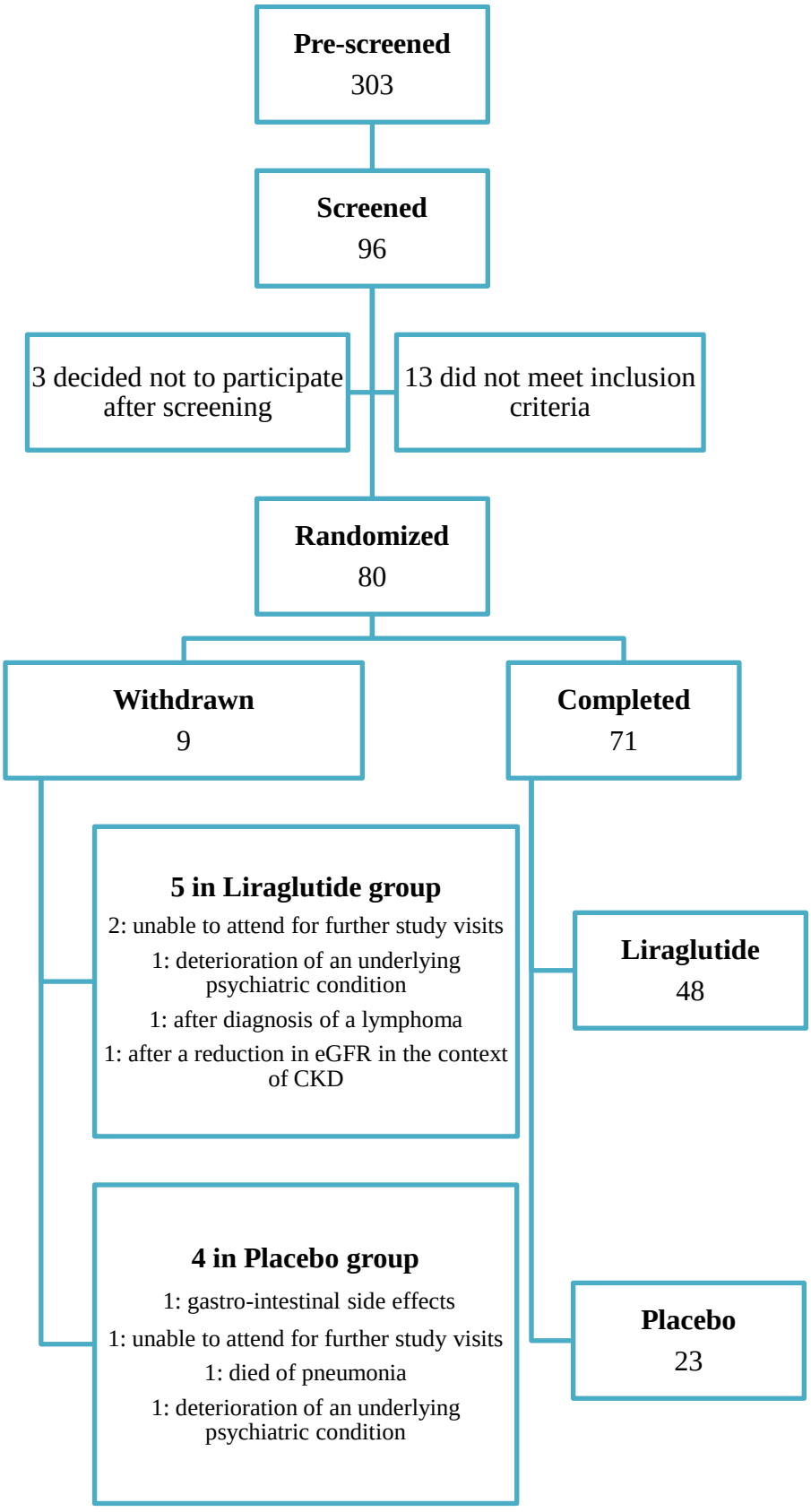


Figure 2: Effects of Liraglutide and Placebo over time on (A) glycated haemoglobin and (B) body weight in complete-cases population. Means ± 95% CI plotted. * 0.01<p<0·05; *** p <0·001 for change from baseline (mixed model repeated measures analysis, with type of surgery taken into account as covariate).

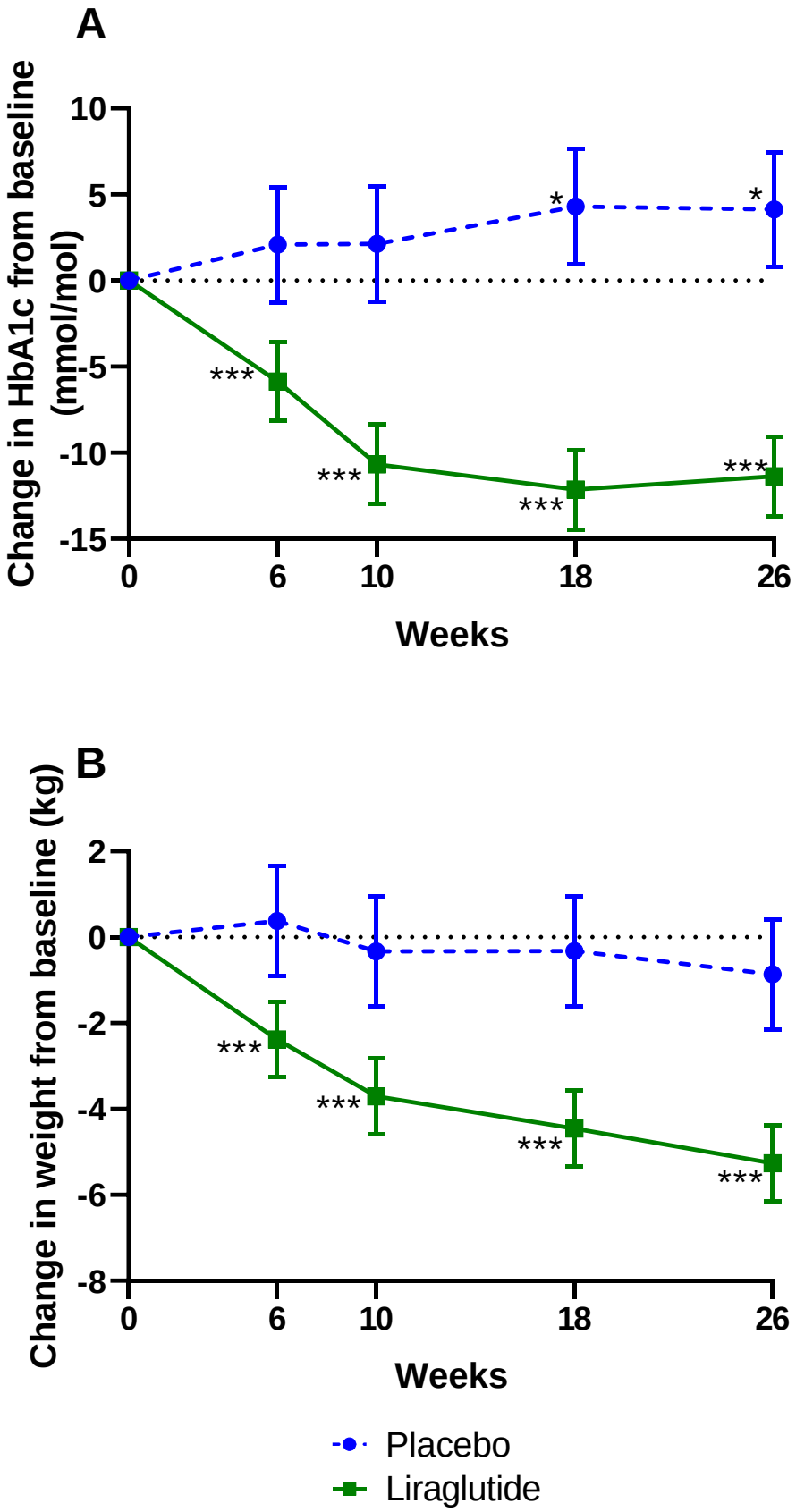
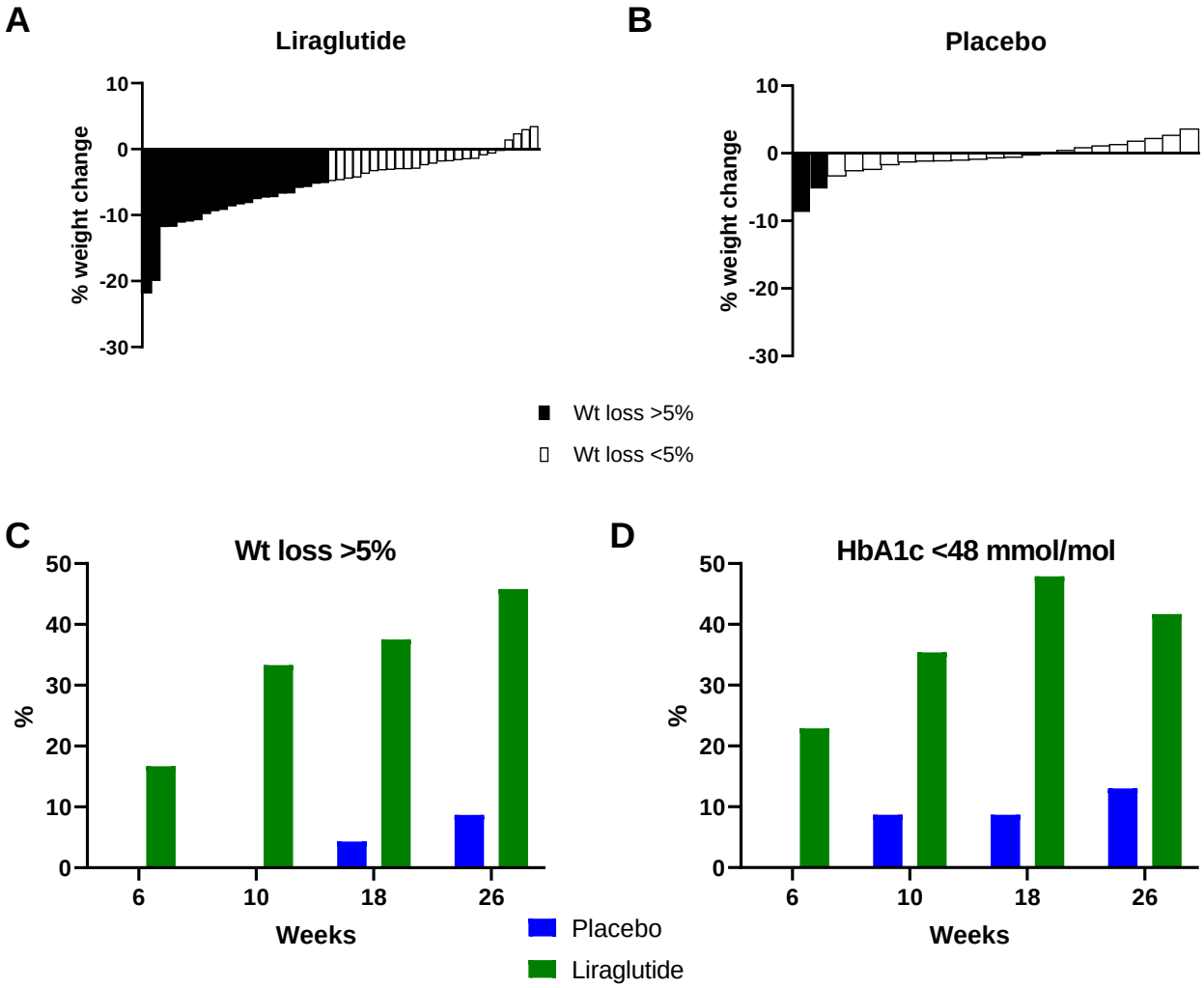


Figure 3: Weight loss and glycaemic improvement responses in complete-cases population. Waterfall plot showing percentage weight loss responses at 26 weeks in (A) Liraglutide and (B) Placebo. Percentage response rates of Placebo and Liraglutide groups in terms of (C) weight loss >5% and (D) HbA1c <48 mmol/mol at the 6, 10, 18, 26 week timepoints.



Supplementary data

Supplementary Table 1. Results of multivariable linear regression analyses of the change from baseline to 26 weeks in clinical outcome variables in ITT population. Covariates were baseline values of the outcome variable, treatment assignment (Liraglutide vs Placebo) and type of surgery (VSG vs RYGB) included as covariates. Coefficients for each covariate listed. Significant p-values <0·05 highlighted in bold. LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides.

	Baseline value			**Treatment (Liraglutide vs Placebo)**			**Type of Surgery (VSG vs RYGB)**		
Primary endpoint	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
HbA1c (mmol/mol)	0·68	0·48 to 0·88	**<0·001**	-11·5	-17·3 to -5·8	**<0·001**	-3·96	-10·2 to 2.2	0·210
HbA1c (% units)	0·06	0·04 to 0·08		-1·05	-1·58 to -0·53		-0·36	-0·93 to 0·20	
Secondary endpoints									
Weight (kg)	0·96	0·91 to 1·02	**<0·001**	-3·94	-6·34 to -1·54	**0·002**	-1·35	-4·11 to 1·40	0·333
SBP (mmHg)	0·61	0·43 to 0·78	**<0·001**	2·32	-3·71 to 8·35	0·446	-4·98	-11·44 to 1·48	0·129
DBP (mmHg)	0·51	0·34 to 0·69	**<0·001**	1·93	-2·30 to 6·16	0·367	-0·63	-5·36 to 4·10	0·792
Total Cholesterol (mmol/L)	0·62	0·46 to 0·77	**<0·001**	-0·02	-0·36 to 0·32	0·916	-0·39	-0·77 to 0·00	**0·049**
LDL cholesterol (mmol/L)	0·75	0·58 to 0·93	**<0·001**	0·02	-0·27 to 0·32	0·870	-0·25	-0·58 to 0·08	0·213
HDL cholesterol (mmol/L)	0·91	0·77 to 1·04	**<0·001**	0·04	-0·06 to 0·15	0·430	-0·05	-0·17 to 0·06	0·622
Triglycerides (mmol/L)	0·18	0·12 to 0·25	**<0·001**	-0·18	-0·46 to 0·09	0·191	-0·26	-0·56 to 0·04	0·093
King's Obesity Staging Criteria score	0·89	0·77 to 1·01	**<0·001**	0·01	-0·98 to 1·00	0·985	-0·48	-1·60 to 0·64	0·394

Supplementary Table 2. Mixed model repeated measures analysis of changes in HbA1c and Body Weight over time in ITT population. Mean changes from baseline (contrast) displayed with 95% confidence interval (CI). Significant p-values <0·05 noted in bold.

HbA1c (mmol/mol)	**Placebo**			**Liraglutide**		
Week vs baseline	**Contrast**	**95% CI**	**p-value**	**Contrast**	**95% CI**	**p-value**
6	1·93	-1·08 to 4.93	0·209	-5·35	-7·50 to -3·21	**<0.001**
10	1·59	-1·41 to 4·60	0·299	-9·75	-11·9 to -7·61	**<0.001**
18	3·44	0·44 to 6·45	**0·025**	-11·1	-13·2 to -8·93	**<0.001**
26	3·30	0·29 to 6·30	**0·032**	-10·3	-12·5 to -8·23	**<0.001**
Body Weight (kg)						
Week vs baseline	**Contrast**	**95% CI**	**p-value**	**Contrast**	**95% CI**	**p-value**
6	0·26	-0·90 to 1·42	0·664	-2·19	-3·02 to -1·36	**<0.001**
10	-0·50	-1·66 to 0·66	0·399	-3·49	-4·31 to -2·66	**<0.001**
18	-0·49	-1·65 to 0·67	0·406	-4·18	-5·00 to -3·35	**<0.001**
26	-0·95	-2·12 to 0·21	0·107	-4·91	-5·74 to -4·08	**<0.001**

Supplementary Table 3. Changes in health-related quality of life measures and measures of disordered eating between baseline and week 26. Data presented as mean (SD) except where indicated. Unpaired unequal variances t-test used to compare treatment effects between Placebo and Liraglutide. Significant p-values <0.05 highlighted in bold. DEBQ= Dutch Eating Behaviour Questionnaire; BIS/BAS= Behavioural Avoidance/Inhibition scales. BAS_drive= pursuit of desired goals / fun seeking= desire for new rewards and impulsive approach to potential rewards / responsiveness= anticipation or occurrence of reward; BIS = anticipation of punishment; AUDIT=Alcohol Use Disorders Identification Test; HADS= Hospital Anxiety and Depression Scale; BDI_II= Beck Depression Inventory-II questionnaire; EDE= Eating Disorder Examination Questionnaire; SF36=36-Item Short Form Health Survey; TFEQ= Three-Factor Eating Questionnaire; TAS= Toronto Alexithymia Scale; IWQOL= Impact of Weight on Quality of Life questionnaire.

	Baseline			**Change at week 26**		**Mean treatment difference, Liraglutide vs Placebo (95% CI)**	**p**
	Score	**Number of patients**	**%**	**Placebo n=21**	**Liraglutide n=45**		
DEBQ_restrained eating subscale	2·7 (0·9)			0·4 (1·5)	0·9 (1·0)	0·5 (-0·1 to 1·2)	0·116
DEBQ_emotional eating subscale	2·5 (1·1)			0·9 (1·0)	0·6 (0·9)	-0·2 (-0·7 to 0·2)	0·318
DEBQ_external eating subscale	2·7 (0·6)			0·7 (0·6)	0·8 (0·5)	0·1 (-1·0 to 0·3)	0·619
Power of Food scale	2·5 (1·1)			0·8 (0·7)	0·6 (0·6)	-0·2 (-0·5 to 0·0)	0·287
BIS/BAS_total	62·3 (10·2)			2·6 (9·3)	-0·9 (7·7)	-3·4 (-7·8 to 0·9)	0·119
BAS_drive subscale	11·2 (3·0)			0·3 (2·6)	0·5 (1·8)	0·2 (-1·1 to 1·3)	0·772
BAS_ fun seeking subscale	11·5 (2·3)			0·9 (2·4)	0·7 (2·5)	-0·2 (-1·5 to 1·4)	0·795
BAS_reward responsiveness	16·0 (2·8)			0·9 (3·0)	0·93 (2·2)	0·1 (-1·4 to 1·6)	0·919
BIS Scale	20·2 (3·9)			0·7 (3·0)	-0·1 (5·4)	-0·8 (-3·3 to 1·8)	0·549
Alcohol_AUDIT	2·6 (3·9)			0·9 (3·1)	0·7 (3·0)	-0·1 (-1·8 to 1·5)	0·879
No harmful/hazardous use (<8)		70	93				
Harmful/hazardous use (>8)		5	7				
HADS_anxiety subscale	7·5 (4·4)			1·8 (3·1)	0·4 (3·3)	-1·5 (-3·2 to 0·3)	0·098
No anxiety (<8)		44	58				
Clinical cut-off for anxiety (8-11)		19	25				
Significant anxiety (>11)		13	17				
HADS_depression subscale	5·5 (4·7)			1·2 (2·7)	1·0 (3·1)	-0·3 (-1·8 to 1·3)	0·741
No depression (<8)		53	70				
Clinical cut off for depression (8-11)		14	18				
Significant depression (>11)		9	12				
BDI_II	14·8 (11·4)			-0·8 (6·4)	-0·8 (7·9)	0·0 (-4·0 to 3·9)	0·985
No depression (0-13)		42	55·3				
Mild depression (14-19)		11	14·5				
Moderate depression (20-28)		11	14·5				
Severe depression (29-63)		11	14·5				
Clinically significant depression (moderate to severe)		22	28·9				
EDE-Q_restraint subscale	1·6 (1·5)			0·8 (1·5)	1·1 (1·8)	0·4 (-0·6 to 1·2)	0·506
EDE-Q_weight concern subscale	2·8 (1·7)			0·8 (1·2)	0·4 (1·2)	-0·4 (-1·0 to 0·2)	0·204
EDE-Q _eating concern subscale	1·6 (1·7)			0·8 (1·3)	0·4 (1·6)	-0·4 (-1·2 to 0·4)	0·373
EDE-Q _shape concerns subscale	3·2 (2·0)			0·9 (1·4)	0·4 (2·0)	-0·5 (-1·4 to 0·5)	0·308

EDE-Q _global score	2·3 (1·4)			0·8 (0·9)	0·6 (1·1)	-0·2 (-0·8 to 0·3)	0·381
SF36_physical functioning subscale	59·1 (34·0)			4·8 (24·4)	2·7 (25·5)	-2·1 (-15·4 to 11·2)	0·754
SF36_limitations subscale	61·2 (45·2)			-4·8 (40·0)	9·4 (48·6)	14·2 (-10·1 to 38·5)	0·248
SF36_emotional role functioning subscale	64·7 (43·2)			-4·8 (30·4)	1·5 (40·3)	6·3 (-13·5 to 26·0)	0·530
SF36_vitality subscale	45·8 (23·5)			2·9 (16·5)	3·1 (24·0)	0·3 (-11·3 to 11·8)	0·965
SF36_emotional wellbeing subscale	65·8 (24·5)			-0·4 (15·8)	0·2 (19·3)	0·6 (-9·1 to 10·2)	0·908
SF36_social role functioning subscale	66·0 (31·5)			3·0 (24·9)	-2·6 (25·0)	-5·5 (-18·7 to 7·6)	0·402
SF36_bodily pain subscale	61·3 (31·2)			-2·4 (32·7)	-5·8 (28·7)	-3·4 (-19·2 to 12·4)	0·667
SF36_general health perception	43·7 (20·8)			0·2 (14·4)	6·4 (21·1)	6·2 (-4·0 to 16·4)	0·227
TFEQ_cognitive restraint subscale	8·9 (4·0)			0·5 (3·2)	0·1 (4·5)	-0·4 (-2·5 to 1·8)	0·732
TFEQ_disinhibition subscale	6·3 (3·1)			-0·5 (2·9)	-1·5 (2·5)	-1·0 (-2·4 to 0·4)	0·140
TFEQ_hunger subscale	5·3 (3·6)			-1·0 (3·0)	-2·0 (3·2)	-0·9 (-2·6 to 0·7)	0·260
TAS_20	47·3 (15·1)			3·0 (17·4)	2·6 (18·1)	-0·4 (-9·8 to 9·1)	0·940
IWQOL_physical impact subscale	26·2 (14·7)			-4·8 (7·7)	-1·1 (16·7)	3·7 (-4·0 to 11·3)	0·341
IWQOL_self esteem subscale	18·3 (10·5)			-0·5 (6·5)	-1·7 (10·6)	-1·2 (-6·2 to 3·8)	0·637
IWQOL_sexual life subscale	10·3 (6·4)			-1·3 (3·5)	-0·5 (6·7)	0·8 (-2·3 to 3·9)	0·587
IWQOL_public distress subscale	11·5 (7·1)			-1·6 (4·2)	-1·0 (7·3)	0·6 (-2·8 to 4·0)	0·731
IWQOL_work problems subscale	8·1 (5·5)			-0·3 (3·5)	-1·0 (5·8)	-0·8 (-3·5 to 2·0)	0·579
IWQOL_Total	75·3 (40·5)			-8·4 (19·3)	-5·3 (44·5)	3·2 (-17·1 to 23·5)	0·757