Effects of liraglutide on weight, satiation, and gastric functions in obesity: a randomised, placebo-controlled pilot trial

Houssam Halawi, Disha Khemani*, Deborah Eckert, Jessica O'Neill, Hoda Kadouh, Karen Grothe, Matthew M Clark, Duane D Burton, Adrian Vella, Andres Acosta, Alan R Zinsmeister, Michael Camilleri*

Summary

Background Liraglutide, a long-acting GLP-1 receptor agonist, is approved for treatment of obesity; however, the mechanisms of action of liraglutide are incompletely understood. We compared effects of liraglutide versus placebo on gastric motor functions, satiation, satiety, and weight in obese individuals over 16 weeks.

Methods We did a randomised, double-blind, placebo-controlled pilot trial at a single centre (Mayo Clinic, Rochester, MN, USA). Participants were randomly allocated (1:1) by a computer generated randomisation schedule with no stratification to receive subcutaneous liraglutide (3·0 mg) or placebo, with standardised nutritional and behavioural counselling. Allocation was concealed from participants and study investigators. Otherwise healthy, local residents aged 18–65 years with body-mass index (BMI) 30 kg/m² or higher were included. Liraglutide or placebo was escalated by 0·6 mg/day each week for 5 weeks and continued until week 16. The primary outcome was change in gastric emptying (delay relative to baseline) of solids $T_{1/2}$ (time taken for half the radiolabelled meal to empty from the stomach), measured at 5 weeks and 16 weeks in all patients who received at least one dose of study drug, with missing data imputed. Secondary outcomes included weight loss at weeks 5 and 16, satiation (volume to fullness and maximum tolerated volume), satiety, and fasting and postprandial gastric volumes at 16 weeks. This trial is registered with ClinicalTrials.gov, number NCT02647944, and is closed to new participants.

Findings Between Dec 18, 2015, and Sept 1, 2016, 40 adults were enrolled and randomly allocated (19 to the liraglutide group; 21 to the placebo group). Compared with placebo, liraglutide delayed gastric emptying of solids at 5 weeks (median 70 min [IQR 32 to 151] *vs* 4 min [–21 to 18]; p<0·0001) and 16 weeks (30·5 min [–11 to 54] *vs* –1 min [–19 to 7]; p=0·025). There was also significantly greater weight loss in the liraglutide group than in the placebo group (at 5 weeks: median 3·7 kg [IQR 2·8 to 4·8] *vs* 0·6 kg [–0·3 to 1·4], p<0·0001; at 16 weeks: 5·3 kg [5·2 to 6·8] *vs* 2·5 kg [0·1 to 4·2], p=0·0009). Satiation, as assessed by maximum tolerated volume at 16 weeks, was lower in the liraglutide group (median 750 mL [IQR 651 to 908]) compared with the placebo group (1126 mL [944–1185]; p=0·054). No significant differences were noted between groups in terms of volume to fullness, satiety, or fasting and postprandial gastric volumes at week 16. Post-hoc analysis showed that the $T_{1/2}$ of gastric emptying of solids at 5 weeks correlated with change in weight loss at week 16 with liraglutide (Rs 0·567, p=0·018). Nausea was the most common adverse event in the liraglutide group (12 of 19) compared with placebo (four of 21).

Interpretation Effects of liraglutide on weight loss are associated with delay in gastric emptying of solids; measurement of gastric emptying (eg, at 5 weeks of treatment) may be a biomarker of responsiveness and may help to select individuals for prolonged treatment with this class of drug.

Funding US National Institutes of Health grant R56-DK67071.

Lancet Gastroenterol Hepatol 2017

Published Online
September 25, 2017
http://dx.doi.org/10.1016/S2468-1253(17)30285-6

See Online/Comment
http://dx.doi.org/10.1016/S2468-1253(17)30291-1

*Contributed equally

Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER) (H Halawi MD, D Khemani MD, D Eckert BSN, J O'Neill, H Kadouh PhD, D D Burton MHA, A Acosta MD, Prof M Camilleri MD), **Department of Psychology** (K Grothe PhD, M M Clark PhD), **Division of Endocrinology** (Prof A Vella MD), **and Division of Biomedical Statistics and Informatics** (Prof A R Zinsmeister PhD), **Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA**

Correspondence to:
Prof Michael Camilleri, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA
camilleri.michael@mayo.edu

Introduction

Obesity prevalence is increasing worldwide.[1] Responses to current non-surgical treatments, including diet, exercise, and drugs, remain highly variable and are associated with high recidivism.[2,3] Obesity is associated with larger fasting gastric volume, accelerated gastric emptying of solids in a subset of individuals, and higher calorie loads to satiation (volume to fullness), suggesting that gastrointestinal traits may constitute relevant pathophysiological mechanisms in obesity and potential targets for therapy.[4] Alternatively, these gastrointestinal traits may be consequences of obesity.

Glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to be effective in reducing weight in obesity,[5] and weight loss associated with GLP-1 receptor agonists is suggested to occur through multiple mechanisms, including delay in gastric emptying, increase in satiety, increase in resting energy expenditure, and direct effects on appetite centres in the brain.[6] The short-acting GLP-1 receptor agonist exenatide (5·0 µg subcutaneously, twice daily for 30 days) caused delayed gastric emptying that resulted in lower postprandial blood glucose level and borderline weight loss.[7]

Liraglutide, a long-acting GLP-1 receptor agonist with 97% homology to the human gut-derived incretin hormone[8] GLP-1, is approved for weight management in adults with body-mass index (BMI) of 30 kg/m² or higher,

Research in context

Evidence before this study

We conducted an extensive PubMed search on the effects of GLP-1 and short-acting (eg, exenatide) or long-acting (liraglutide) GLP-1 receptor agonists on weight loss, gastric functions, and tachyphylaxis. The PubMed search was conducted between May, 2014, and September, 2015. The search terms included "GLP-1", "GLP-1 analogs", "exenatide", "liraglutide", "gastric emptying", "obesity", "type 2 diabetes mellitus", "gastric sensorimotor function", "gastric accommodation", and "tachyphylaxis", as individual terms and combinations of the terms. Publications in any language were included. The reference lists in the original articles were also scanned to ensure no important references were missed.

The long-acting GLP-1 analogue liraglutide (3·0 mg daily) is approved for treatment of obesity. The literature is inconclusive regarding the mechanism of weight loss. Despite effects of GLP-1 and analogues on gastric emptying and association with nausea, it has been claimed that tachyphylaxis reduces the potential of liraglutide to delay gastric emptying.

Added value of this study

The results from this randomised, double-blind, placebo-controlled study, using state-of-the-art methods in a single clinical research centre, show that liraglutide significantly delays gastric emptying. There is evidence of tachyphylaxis, as expected with consistent stimulation of GLP-1 receptors by a long-acting analogue, but significant delay is still observed after 3 months of treatment. Additionally, weight loss persists during this phase of tachyphylaxis, and the absolute gastric emptying $T_{1/2}$ (time taken for half the radiolabelled meal to empty from the stomach) is significantly associated with degree of weight loss.

Implications of all the available evidence

The effect on gastric emptying is a potential mechanism of weight loss observed with a long-acting GLP-1 analogue and measurement of gastric emptying (eg, at 5 weeks of treatment) may be a biomarker of responsiveness to this class of drug. This may help to select individuals for prolonged treatment or for cessation of treatment with this relatively expensive drug.

or those with BMI of 27 kg/m² or higher with obesity-related comorbidities. A large multicentre trial showed average weight loss of 8% after 6 months of treatment; notably, weight loss of more than 10% of bodyweight was observed in 33% of the participants and more than 15% of bodyweight in 14% of the participants.[9] However, the mechanisms by which liraglutide leads to weight loss remain unclear. Previous reports of effects of liraglutide on gastric emptying are inconclusive. Liraglutide (1·2 mg, 1·8 mg, or 3·0 mg daily for 3, 4, or 5 weeks),[6,10,11] delayed 1-h gastric emptying, as measured by the plasma acetaminophen method (which reflects predominantly the gastric emptying of liquids, not solids) compared with placebo. However, the 5-week trial showed no difference in the acetaminophen 5-h gastric emptying between liraglutide (1·8 mg or 3·0 mg daily) and placebo.[10] Additionally, 12 weeks of treatment with 1·2 mg liraglutide in participants with type 1 diabetes showed no difference in the rate of gastric emptying of liquids compared with placebo under hypoglycaemic conditions, which stimulate vagal function.[11] The reported differences in effects of exenatide and liraglutide on gastric emptying are potentially related to differences in methods of measurement rather than biological differences, since there are only relatively minor structural differences between exenatide and liraglutide, which are both GLP-1 analogues and exert their effects by binding to the same naturally occurring G-protein-coupled, 7-transmembrane-domain GLP-1 receptor.

There is evidence of desensitisation of GLP-1 receptors, in part due to activation of protein kinase C, when there is continuous presence of GLP-1,[12] as may occur in the context of a long-acting GLP-1 analogue such as liraglutide. In fact, the hypoglycaemic effect of GLP-1 is attenuated as the effect of GLP-1 on gastric emptying undergoes rapid tachyphylaxis at the level of vagal function.[13]

The effects of liraglutide or GLP-1 on gastric emptying were reported to abate over time, based on rat[14] (liraglutide 30, 100, or 300 µg/kg) and human[15] (GLP-1 0·8 pmol/kg · min) studies, but it is unclear whether this also applies to the 3·0 mg dose of liraglutide. Given the reported inconsistency in the effects on gastric emptying and the stronger effect on fasting glucose levels of long-acting GLP-1 receptor agonists, the hypoglycaemic effects have been attributed predominantly to insulinotropic and glucagonostatic actions.[15] Moreover, rat studies suggested that weight-lowering effects of GLP-1 receptor agonist stimulation with liraglutide are not subject to desensitisation, suggesting that regulation of appetite signals in the brain, rather than effects on gastric emptying, constitutes the main mechanism for liraglutide-induced weight loss.[14] However, exenatide and liraglutide are both associated with development of nausea, and, in previous studies of exenatide with a thiazolidinedione in patients with type 2 diabetes, weight loss was significantly greater in patients who experienced nausea.[16] Overall, these data support the hypothesis that effects of liraglutide on weight loss may be mediated, at least in part, by delaying gastric emptying.

There is also evidence that GLP-1 increases fasting and postprandial gastric volumes measured non-invasively.[17]

 Published online September 25, 2017 http://dx.doi.org/10.1016/S2468-1253(17)30285-6

However, liraglutide (0·6 mg) inhibited gastric accommodation, as measured by an intragastric balloon measurement.[18] Thus, an effect of the liraglutide on gastric accommodation (indirectly affecting appetite) could contribute to the effect of liraglutide on weight loss.

Based on the published literature, our study hypothesis was that liraglutide results in a short-lived reduction in the rate of gastric emptying, with subsequent tachyphylaxis and normalisation of gastric emptying by 16 weeks (that is, after 12 weeks on the 3·0 mg dose), with persistence of significant weight loss. Our study aim was to compare the effects of liraglutide versus placebo on gastrointestinal functions and bodyweight over 16 weeks of treatment, based on the standard dose escalation approved for weight management, up to 3·0 mg subcutaneously daily.

Methods

Study design and participants

We did a double-blind, placebo-controlled, parallel-group pilot study of once-daily, subcutaneous liraglutide or placebo for a total treatment period of 16 weeks, conducted exclusively at a single centre (Mayo Clinic, Rochester, MN, USA). The original proposal was submitted as an RO1 grant application to the US National Institutes of Health (NIH) to address the weight loss in response to liraglutide (3·0 mg), with participants stratified by rate of gastric emptying; the original sample size proposed was 180 individuals. Instead, however, the NIH recommended and funded a pilot study to appraise feasibility to conduct such a single-centre study, assess compliance and dropout rate, and obtain preliminary data on the coefficient of variation in order to plan the hypothesis-testing study. The results of this pilot study are presented here.

Overweight adults (BMI ≥27 kg/m²) with an obesity-related comorbidity and adults with obesity (BMI >30 kg/m²), aged 18–65 years residing within 125 miles of the Mayo Clinic, Rochester, MN, USA, were recruited. Participants were otherwise healthy individuals with no unstable psychiatric or medical disease or treatment that could interfere with the study conduct or interpretation. The study was approved by Mayo Clinic Institutional Review Board (IRB 15-001783), and all participants provided written informed consent. Standard US Food and Drug Administration (FDA) recommendations on use of liraglutide were followed for eligibility. Screening questionnaires appraised psychiatric symptoms,[19] alcohol use disorders,[20] eating disorders,[21] and intake of medications, whether prescribed or over the counter (except multivitamins), within 7 days of the study. Permitted concomitant medications during the study were the birth control pill, oestrogen and thyroxin replacement therapy, and any medication administered for comorbidities as long as they did not alter gastric emptying or accommodation or satiation. Specifically, statins for hyperlipidaemia, diuretics, β-adrenergic blockers, angiotensin-converting-enzyme (ACE) inhibitors and angiotensin antagonists for hypertension, and metformin for type 2 diabetes or prediabetes were permissible. In contrast, resin sequestrants for hyperlipidaemia (which may reduce gastric emptying and appetite), α2-adrenergic agonists for hypertension, other GLP-1 receptor agonists (eg, exenatide) or amylin analogues (eg, pramlintide), which delay gastric emptying, were not permissible.

Individuals with delayed gastric emptying of solids (>90th percentile according to sex) were excluded, since it was considered potentially dangerous to significantly increase the delay in gastric emptying with a GLP-1 receptor agonist. Delayed gastric emptying was defined as less than 36% emptied at 2 h and less than 87% emptied at 4 h in men and less than 31% at 2 h and less than 81% at 4 h in women.[22]

Randomisation and masking

A randomisation schedule, computer generated by the study statistician's office, was submitted to the Mayo Clinic research pharmacy. Participants were randomly assigned (1:1) to liraglutide or placebo, with no stratification factors. Allocations were concealed by the study pharmacists, who assigned patients to treatment groups and were physically separated from the clinical trials unit, where the patients were enrolled by the study coordinators. The study personnel (coordinators and technicians performing measurements, and the physicians involved in the study) did not have knowledge of the next assignment in the sequence, which could not be revealed by the research pharmacists or guessed by the study staff. Group assignments were blinded to the participants, study staff, and care providers until data were transmitted to the statistician for data lock. No formal evaluation of the success of study masking was conducted.

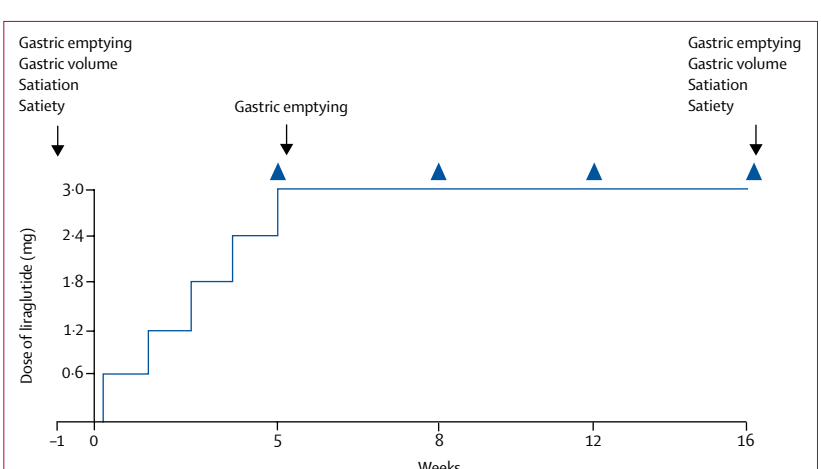

Figure 1: **Study design**
Triangles represent clinical research unit visits, which included assessment of compliance, adverse events, urine pregnancy test in women, and body weight. The liraglutide dose was escalated by 0·6 mg per week, reaching 3·0 mg at week 5.

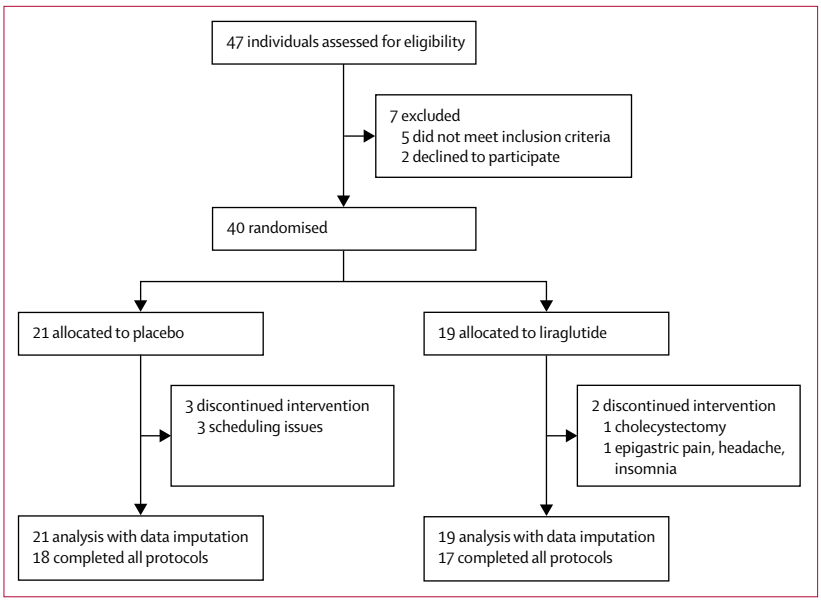

Figure 2: **Trial profile**

	Placebo (n=21)	Liraglutide (n=19)
Age (years)	37 (26–51)	42 (32–51)
Body-mass index (kg/m²)	34·6 (33·4–38·9)	37·2 (33·6–41·0)
Weight (kg)	99·1 (90·1–111·2)	103·7 (90·0–112·2)
Gastric emptying $T_{1/2}$ (min)	120 (88–138)	120 (97–145)
Gastric fasting volume (mL)	198·6 (167·0–244·2)	215·0 (163·7–251·4)
Gastric postprandial volume (mL)	701·1 (589·4–760·0)	660 (615·8–806·0)
Gastric accommodation volume (mL)	456·7 (376·7–551·8)	454·4 (408·8–582·1)
Satiation volume to fullness (mL)	660 (510–780)	600 (510–870)
Satiation maximum tolerated volume (mL)	1185·0 (948·0–1422·0)	1185·0 (829·5–1282·0)
VAS aggregate score (max 400)	187·0 (141·5–253·5)	217·0 (116·0–261·0)
Buffet meal total calories	879·0 (693·6–1018·0)	711·0 (647·0–1006·0)

Data are median (IQR). $T_{1/2}$=time for half the radiolabelled contents to empty the stomach. VAS=visual analogue scale.

Table 1: **Baseline demographics and measurements**

See Online for appendix

Procedures

All participants underwent screening visits, baseline measurements of gastrointestinal, behavioural, and psychological factors, and received the same doses and dose escalation (figure 1). Liraglutide was purchased from, or provided by, Novo Nordisk (Plainsboro, NJ, USA) and stored in the Mayo Clinic research pharmacy; all liraglutide and saline placebo supplies were dispensed from the research pharmacy. Liraglutide was administered as recommended by the FDA: initiated at 0·6 mg daily for 1 week, with instructions to increase by 0·6 mg weekly until 3·0 mg was reached (over 4 weeks). Once the maintenance dose of 3·0 mg was reached by week 5, participants returned every 4 weeks to obtain a new supply of the study drug. Similar weekly volume increments were used for placebo.

For the FDA recommended use see http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206321Orig1s000lbl.pdf

Participants received education and a pamphlet with directions for use provided by the clinical trials unit nurses not associated with the research study. All participants also received standardised dietetic and behavioural advice for weight reduction therapy (appendix pp 1, 2).

Quantitative traits of satiety by buffet meal, satiation by volume to fullness, reports (based on 100 mm visual analogue scales) of nausea, fullness, bloating and pain 30 min after ingesting the maximum tolerated volume of Ensure (Abbott Laboratories, IL, USA), gastric emptying of solids (standardised 320 kcal solid-liquid meal[22]), and fasting and postprandial gastric volumes (in response to a standard volume of 300 mL Ensure[23]) were measured at baseline and at week 16. An additional gastric emptying test was done at 5 weeks.

The methods to measure gastric emptying of solids,[22] gastric volumes,[23] satiation,[4] and satiety[4] are described in detail in the appendix (p 1). Briefly, gastric emptying of solids was assessed by scintigraphy using a 320 kcal ^{99m}Tc-radiolabelled egg, solid-liquid meal. Fasting and postprandial gastric volumes were measured by single photon emission CT (SPECT) imaging of the stomach after intravenous injection of ^{99m}Tc-pertechnetate, which is taken up by the gastric mucosa. Satiation was tested by ingestion of Ensure at a constant rate of 30 mL/min to measure volume to fullness and maximum tolerated volume. Satiety (a measure of appetite) was appraised by buffet meal consisting of standard foods of known nutrient composition. Plasma peptide YY levels were measured by radioimmunoassay that detected two molecular forms, 1-36 and 3-36.

We assessed safety and tolerability throughout the study by evaluation of adverse events, vital signs, fasting blood glucose, and physical examination. These assessments were conducted at baseline and at visits for dose escalations at weeks 2, 3, and 4, as well as follow-up visits at weeks 8, 12, and 16.

Outcomes

As a result of the change of focus recommended by NIH, the primary endpoint of this study was changed from weight loss stratified by rate of gastric emptying at baseline to comparison of the effects of liraglutide treatment on gastric emptying. Change in gastric emptying (delay relative to baseline) of solids $T_{1/2}$ (time taken for half the radiolabelled meal to empty from the stomach) was the primary endpoint, measured at 5 weeks and 16 weeks. Secondary endpoints were weight loss at week 5 and week 16, satiety by buffet meal, satiation (assessed both by volume to fullness and maximum tolerated volume), and fasting, postprandial, and accommodation gastric volumes.

Participants were assessed by the study physicians and nurses at each follow-up visit, and the following adverse events were reported: nausea, abdominal pain, diarrhoea, light-headedness, injection-site rash, and injection-site reaction.

Statistical analysis

We calculated that, for the pilot study, we would need 20 patients in each treatment group, to have 80% power (at α=0·05) to detect a difference in absolute gastric emptying $T_{1/2}$ of 27·1 min between the treatment groups based on gastric emptying $T_{1/2}$ mean (SD) of 121·7 min (29·8) published previously[22] from a study of 319 healthy volunteers. Effect sizes demonstrable with 80% power for weight loss and other quantitative traits with 20 patients per treatment group are shown in the appendix (p 2). The statistical analysis was conducted to address the hypothesis that there was a treatment effect with liraglutide compared with placebo on the study endpoints.

All available data from all randomised patients were used in the statistical analyses. Data were imputed for the participants who dropped out. For each missing data value, we imputed the average value for all patients in the study and reduced the degrees of freedom by one for each data value imputed for that endpoint.

We analysed the effects of liraglutide and placebo on gastric emptying $T_{1/2}$ of solids and lag time (time to 10% emptying) at week 5, and on gastric emptying $T_{1/2}$ of solids, lag time, gastric volumes, satiation, and satiety at week 16 of the treatment period using ANCOVA, with the corresponding baseline measurement as a covariate, using an α of 0·05. We compared the gastric emptying $T_{1/2}$ of solids at 5 and 16 weeks in participants receiving liraglutide using a paired *t* test (test for normality passed using Shapiro-Wilk test). No sensitivity analyses were performed. A post-hoc analysis assessed the relationship between change in gastric emptying and weight loss at 5 and 16 weeks.

We used Spearman correlations to assess the relationship between (absolute value of) gastric emptying $T_{1/2}$ of solids at 5 and 16 weeks and degree of weight loss on treatment. All analyses were done with SAS version 9.4.

This study is registered with ClinicalTrials.gov, number NCT02647944, and is closed to new participants.

Role of the funding source

The funding source had no involvement in the study design, in collection, analysis, and interpretation of the data, in writing the report, or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and the decision to submit for publication.

Results

47 participants were recruited between Dec 18, 2015, and Sept 1, 2016 (figure 2). Two participants withdrew before completing all the screening visits, and five participants were excluded at screening (one each due to alcohol use disorder, BMI <30 kg/m² without obesity comorbidities, and prior abdominal surgery, and two due to delayed gastric emptying). 19 participants were assigned to liraglutide and 21 to placebo. 35 participants completed the study; five participants dropped out during the study: two on liraglutide and three on placebo (appendix p 2). There was delayed dose escalation in two participants who could not tolerate the standard up titration due to nausea; these individuals were in the liraglutide group and reached the 3·0 mg dose at week 12 (of 16 weeks). Thus, all those randomised to liraglutide who completed the study were on the fully escalated dose of 3·0 mg/day.

The baseline demographics and measurements in the two treatment groups were not significantly different (table 1). The lowest BMI at baseline was

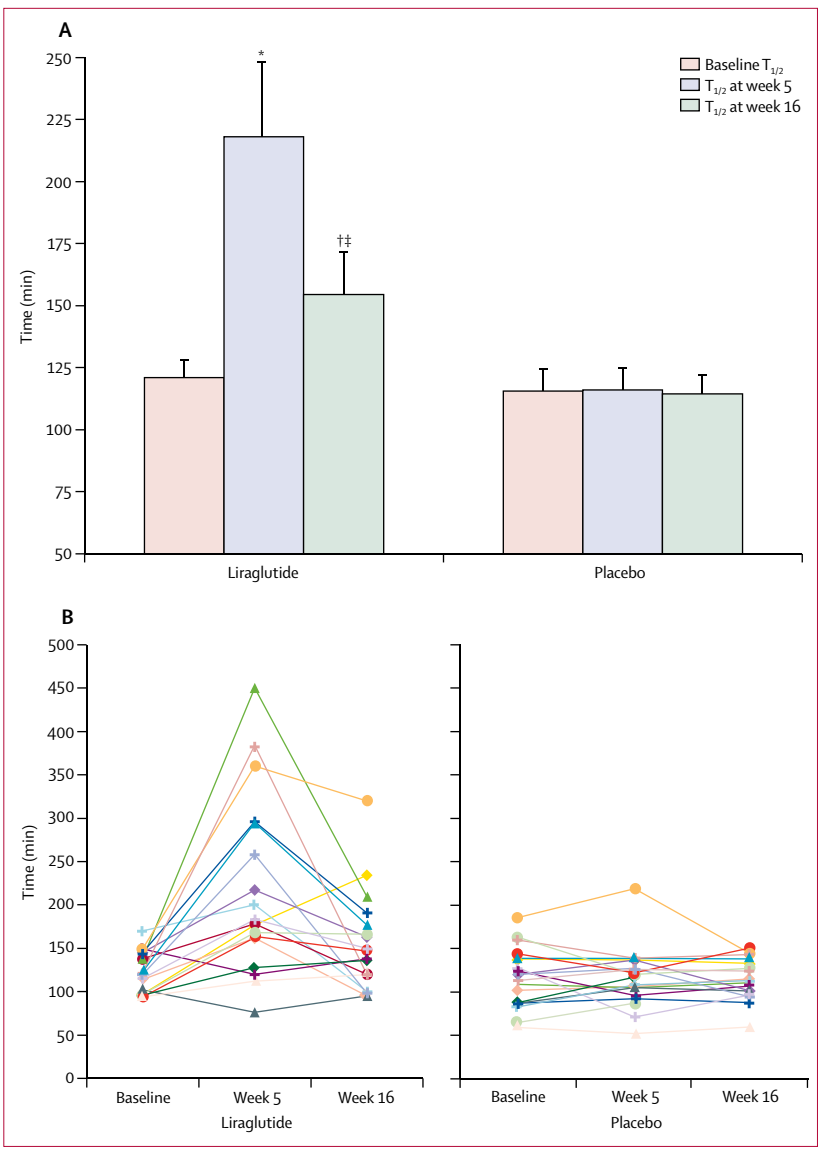

Figure 3: **Effects of liraglutide *vs* placebo on gastric emptying at baseline, 5 weeks, and 16 weeks**
Group data (A; mean [SEM]) and individual data (B). Comparisons between treatment groups were adjusted for baseline gastric emptying. A paired analysis was done to compare the 5-week and 16-week timepoints with liraglutide treatment. *p<0·0001 *vs* placebo, adjusted for baseline covariate. †p<0·021 *vs* 5 weeks liraglutide, paired analysis. ‡p<0·025 *vs* placebo, adjusted for baseline covariate.

	Placebo	Liraglutide	p value*
Weight			
Baseline (kg)	99·1 (90·4 to 111·0)	103·7 (90·0 to 112·2)	..
5 weeks (kg)	98·7 (89·4 to 110·2)	99·9 (85·2 to 108·6)	..
16 weeks (kg)	96·8 (90·1 to 106·2)	94·2 (84·2 to 103·6)	..
5 weeks *vs* baseline (kg)	0·6 (–0·3 to 1·4)	3·7 (2·8 to 4·8)	<0·0001
16 weeks *vs* baseline (kg)	2·5 (0·1 to 4·2)	5·3 (5·2 to 6·8)	0·0009*
Gastric emptying			
Baseline lag time (min)	13 (11 to 25)	14 (10 to 27)	..
Lag time at 5 weeks (min)	13 (9 to 24)	18 (13 to 47)	..
Lag time at 16 weeks (min)	14 (11 to 20)	12·5 (9·0 to 15·0)	..
Baseline $T_{1/2}$ (min)	120 (88 to 138)	120 (97 to 145)	..
$T_{1/2}$ at 5 weeks (min)	117 (96 to 137)	180 (162 to 295)	..
$T_{1/2}$ at 16 weeks (min)	113 (101 to 133)	142 (120 to 177)	..
$T_{1/2}$ 5 weeks *vs* baseline (min)	4 (–21 to 18)	70 (32 to 151)	<0·0001*
$T_{1/2}$ 16 weeks *vs* baseline (min)	–1 (–19 to 7)	30·5 (–11·0 to 54·0)	0·025*
$T_{1/2}$ 16 weeks *vs* 5 weeks (min)	4 (–4 to 8)	–47 (–105 to 8)	0·040*
Gastric emptying volumes			
Baseline gastric fasting volume (mL)	198·6 (167·0–244·2)	215·0 (163·7–251·4)	..
Baseline gastric postprandial volume (mL)	701·1 (589·4–760·0)	660·0 (615·8–806·0)	..
Baseline gastric accommodation volume (mL)	456·7 (376·7–551·8)	454·4 (408·8–582·1)	..
Gastric fasting volume at 16 weeks (mL)	192 (179–223)	231 (192–277)	0·13
Gastric postprandial volume at 16 weeks (mL)	668 (605–794)	705 (633–744)	0·68*
Gastric accommodation volume at 16 weeks (mL)	433 (408–602)	453 (378–536)	0·95*
Satiation volumes and symptoms			
Baseline satiation volume to fullness (mL)	660 (510–780)	600 (510–870)	..
Baseline satiation MTV (mL)	1185·0 (948·0–1422·0)	1185·0 (829·5–1282·0)	..
Satiation volume to fullness at 16 weeks (mL)	600 (480–720)	360 (360–600)	0·069*
Satiation MTV at 16 weeks (mL)	1126 (944–1185)	750 (651–908)	0·054
Baseline VAS aggregate score (mm)	187·0 (141·5–253·5)	217·0 (116·0–261·0)	..
VAS aggregate score at 16 weeks (mm)	203 (168–230)	218 (196–263)	0·56
VAS nausea score at 16 weeks (mm)	27 (10–50)	50 (28–60)	0·53
VAS fullness score at 16 weeks (mm)	73 (69–86)	77 (72–79)	0·75
VAS bloating score at 16 weeks (mm)	68 (41–83)	74 (42–79)	0·89
VAS pain score at 16 weeks (mm)	23 (14–50)	48 (24–65)	0·64
Satiety			
Baseline buffet meal total calories (kcal)	879·0 (694·0–1018·0)	711·0 (647·0–1006·0)	..
Buffet meal total calories at 16 weeks (kcal)	680·5 (513·0–1002·0)	554·0 (406·0–687·0)	0·27

Data are median (IQR). *Statistical analyses based on a rank transformation including imputation for missing data unless otherwise stated. For VAS, the aggregate symptom score maximum is 400; individual symptom scores maximum 100. MTV=maximum tolerated volume. VAS=visual analogue scale.

***Table 2*: Effects of liraglutide on gastric emptying and weight**

30·6 kg/m². Median baseline gastric emptying $T_{1/2}$ for the 40 participants was 118·1 min (IQR 95·5–138·5, range 59–186), which is consistent with the reported range for normal controls (median 120 min (5th–95th percentiles, 78·4–174).[22] None of the patients enrolled had type 2 diabetes.

Liraglutide had a significant effect on change (delay relative to baseline) in gastric emptying $T_{1/2}$ of solids at 5 weeks (median 70 min [IQR 32 to 151]) compared with placebo (4 min [–21 to 18]; p<0·0001; figure 3). Similarly, at 16 weeks, median change (relative to baseline) in gastric emptying $T_{1/2}$ of solids was 30·5 min (–11·0 to 54·0) in the liraglutide group, which was significantly slower than placebo (–1 min [–19 to 7]; p=0·025; figure 3). Effects of liraglutide on gastric emptying lag time are shown in table 2.

Median weight loss at 5 weeks was significantly greater for the liraglutide group (3·7 kg [2·8 to 4·8]) than for the placebo group (0·6 [–0·3 to 1·4]; p<0·0001; figure 4). Similarly, median weight loss at 16 weeks was significantly greater for the liraglutide group (5·3 kg [5·2–6·8]) than for the placebo group (2·5 kg [0·1–4·2]; p=0·0009; figure 4). In the placebo group, one outlier lost 17·1 kg during the study.

The maximum tolerated volume measure of satiation at 16 weeks was lower in the liraglutide group (median 750 mL [IQR 651–908]) compared with the placebo group (1126 mL [944–1185]; p=0·054; table 2), which is equivalent to a difference of 376 kcal (1 kcal/mL) before reaching maximal fullness.

There were no significant effects of liraglutide on fasting, postprandial, and accommodation gastric volumes or on postprandial symptoms after the satiation drink test at week 16 (table 2). Calorie intake at the 16-week buffet meal was lower with liraglutide than with placebo (median 554 kcal [IQR 406–687] *vs* 680 kcal [513–1002]), as was volume to usual fullness during nutrient drink satiation test (median 360 mL [IQR 360–600] *vs* 600 mL [480–720]), but these results were not statistically significant (table 2). There were no significant effects of liraglutide on fasting and postprandial peptide YY (appendix p 2).

In post-hoc analyses, there were direct relationships (figure 5) between gastric emptying $T_{1/2}$ of solids and weight loss, particularly between gastric emptying $T_{1/2}$ of solids at 5 weeks and 16 weeks and weight loss (expressed as change from baseline) over the 16-week period, as well as gastric emptying $T_{1/2}$ of solids at 5 weeks and weight loss at 5 weeks for the entire study cohort. Moreover, there was significant direct correlation of gastric emptying $T_{1/2}$ of solids at 5 weeks and weight loss over the 16-week period in the liraglutide treatment group (figure 5B; Rs=0·567, p=0·018). The correlation between gastric emptying $T_{1/2}$ of solids and weight loss at 16 weeks of treatment with liraglutide was not significantly different (Rs=0·277; p=0·28).

Post-hoc analysis also showed a significant correlation between change in gastric emptying $T_{1/2}$ at 5 weeks and weight loss at 5 weeks (Rs=–0·587; p<0·0001), and was borderline (Rs=–0·313; p=0·071) for the analysis at 16 weeks (appendix p 3).

One participant in each treatment group underwent uneventful cholecystectomy for acute cholecystitis associated with gallstones during the study; the patient in the placebo group chose to continue participation in the trial. Adverse effects occurring in at least three participants are shown in the appendix (p 2); only nausea was

appreciably different between groups (12 of 19 on liraglutide and four of 21 on placebo). Nausea in those taking liraglutide was reported during the follow-up visits: by three participants on one visit; four participants on two visits; two participants on three visits; one participant on four visits; and two participants on five visits. Only five participants had nausea after week 5 of treatment. Nausea in participants on placebo was reported on one occasion by three participants and on two occasions by one participant.

A post-hoc subgroup analysis of the liraglutide group comparing the participants who reported nausea at any time while on liraglutide (n=12) with those who did not experience nausea (n=6) showed no significant difference in the median gastric emptying $T_{1/2}$ at baseline, 5 weeks, or 16 weeks between the two groups.

Discussion

This randomised, controlled pilot trial has shown that, in obesity, liraglutide (3·0 mg daily) delays gastric emptying of solids, with persistent delay at 16 weeks of treatment. Additionally, the degree of weight loss was associated with the gastric emptying $T_{1/2}$ of solids, and there was reduced effect on the gastric emptying of solids with liraglutide treatment over time, demonstrated by a decrease in the delay (relative to baseline) in gastric emptying of solids at 16 weeks compared with 5 weeks. This is consistent with tachyphylaxis in the effect of liraglutide on gastric emptying of solids as previously described with GLP-1 by Nauck and colleagues,[13] although there was still significant delay in gastric emptying of solids at 16 weeks.

Previous reports showed inconclusive evidence of the effect of liraglutide on gastric emptying,[10,11,14,24] which may have reflected lower doses tested, shorter duration of treatment, heterogeneous patient groups (eg, type 1 or 2 diabetes, healthy controls, obese and non-diabetic groups), different sample sizes, insufficient statistical power to detect differences, and different methods used to assess the effect of liraglutide on gastric emptying. In fact, most previous studies relied on the acetaminophen method, which reflects predominantly the gastric emptying of liquids, since the drug dissolves in the stomach, empties with the liquid phase of the meal, and is completely absorbed in the small intestine within 5 h of ingestion. It is thus expected that the observed effect of liraglutide was evident only in the first hour after administration of the drug.[10,24,25] Others found no effect of liraglutide on gastric emptying of solids using the ^{13}C-octanoate breath test and a 969 kcal meal with 65% fat.[26] This extremely high fat and calorie content may itself considerably delay gastric emptying.[27] Another study in people with type 2 diabetes showed no effect of liraglutide (0·9 mg/day) on gastric emptying of liquids measured by the ^{13}C-acetate breath test.[28]

Our observation of tachyphylaxis in the effect of liraglutide on gastric emptying of solids probably reflects the continuous activation of the GLP-1 receptor by the long-acting GLP-1 receptor agonist, leading to tolerance.[13,15] Despite the tachyphylaxis, the rate of gastric emptying of solids remained slow compared with placebo, even at 16 weeks. Given recent evidence that liraglutide (3·0 mg) was associated with greater weight reduction compared with placebo at 16 weeks of therapy,[29] the effect on gastric emptying beyond 16 weeks deserves further study.

The absolute gastric emptying $T_{1/2}$ of solids was associated with the degree of weight loss during the first 5 weeks and the entire 16-week period. It is interesting to note that, in large multicentre studies of liraglutide,[9,29] around 50% of the average weight loss was achieved in

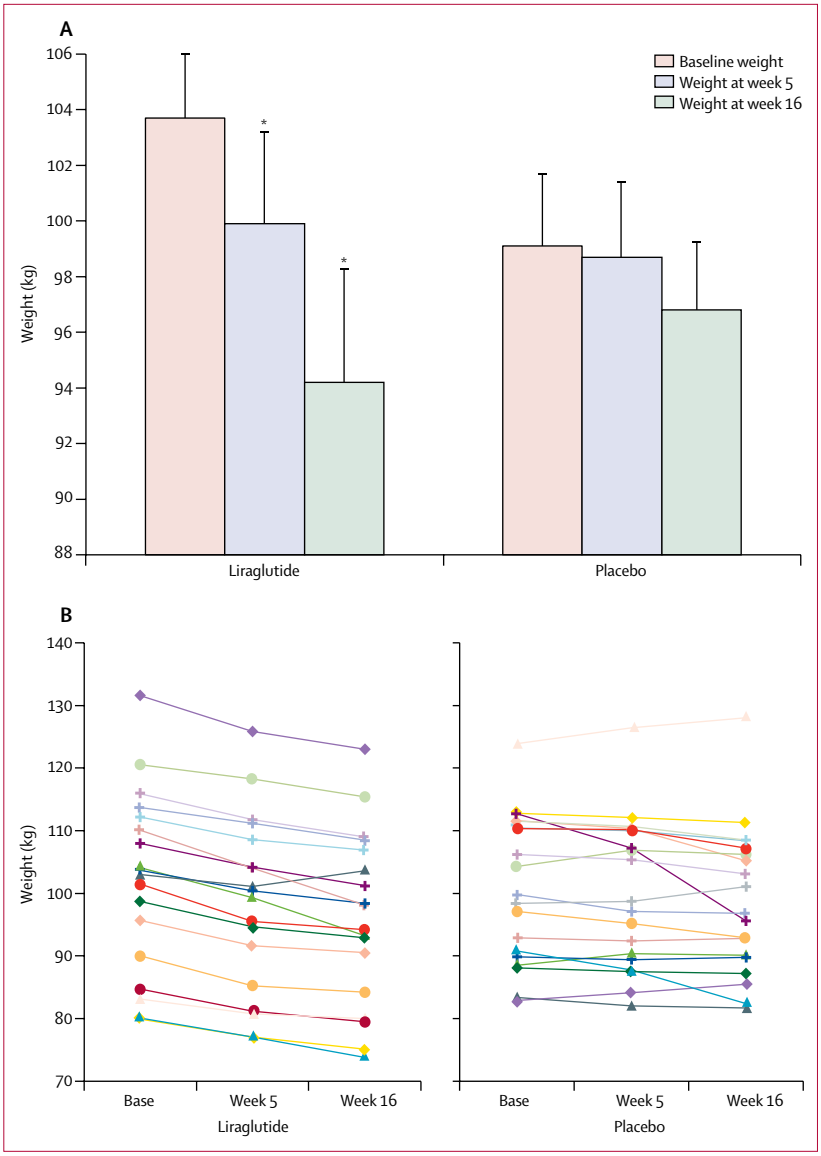

Figure 4: **Effects of liraglutide *vs* placebo on bodyweight at baseline, 5 weeks, and 16 weeks**
Group data (A; mean [SEM]) and individual data (B). Comparisons between treatment groups were adjusted for the baseline covariate. *p<0·0001 *vs* placebo, with baseline covariate. †p=0·0009 *vs* placebo, with baseline covariate.

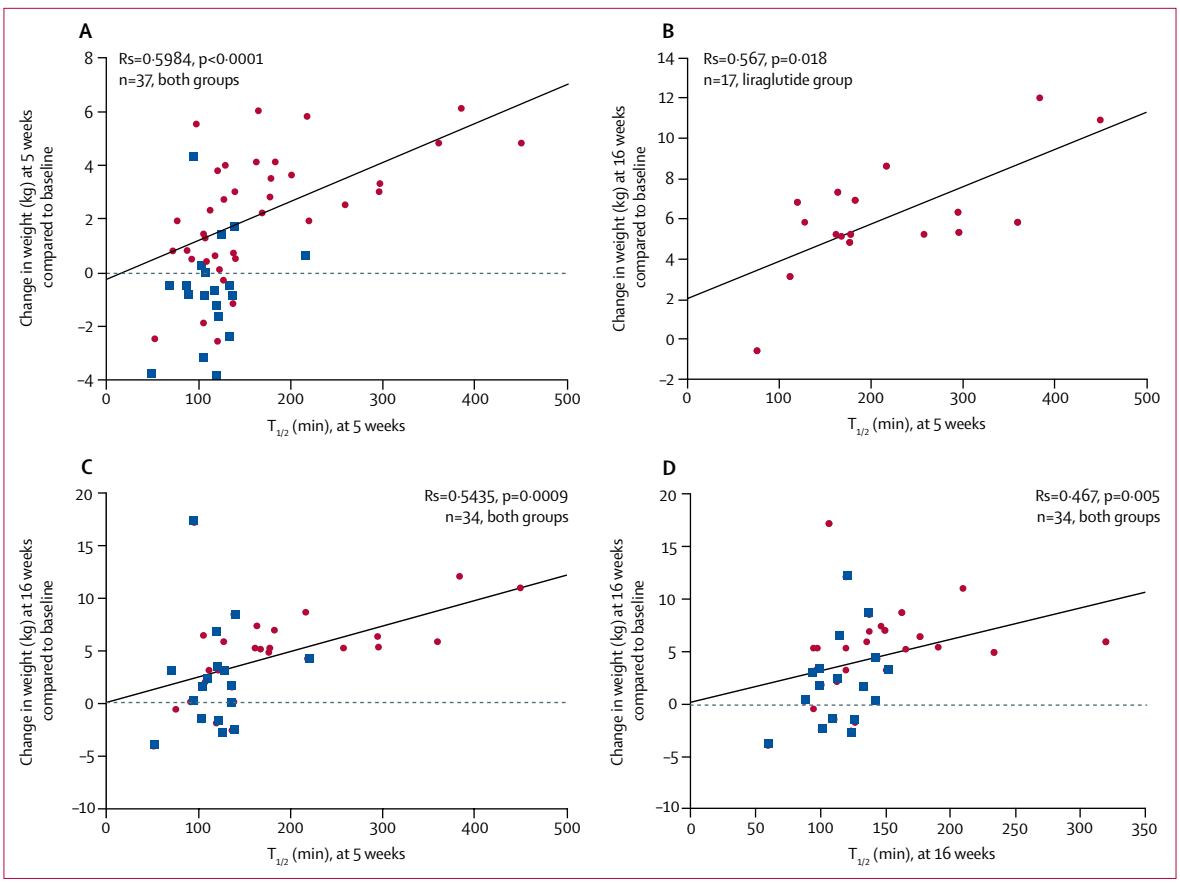

Figure 5: **Relationship of change in gastric emptying $T_{1/2}$ and weight change at 5 and 16 weeks**
(A) Relationship between weight change at 5 weeks and gastric emptying at 5 weeks. (B) Relationship between weight change at 16 weeks and gastric emptying at 5 weeks (liraglutide treatment group alone). (C) Relationship between weight change at 16 weeks and gastric emptying at 5 weeks, (D) Relationship between weight change at 16 weeks and gastric emptying at 16 weeks. Blue squares indicate placebo, red circles indicate liraglutide treatment.

the first 8 weeks of treatment, when there was unequivocal delay in gastric emptying of solids in our study. It would be interesting to assess whether effect on gastric emptying was a stronger predictor of weight loss than the occurrence or severity of nausea, although the two are certainly not independent. In our study, we recorded the occurrence of nausea as an adverse effect, but we did not quantitate the severity of nausea. Therefore, we cannot accurately appraise the impact of the presence of nausea in the 12 affected individuals, compared with the seven without reported nausea, on liraglutide. This interesting association could be addressed in future studies in which the daily severity of nausea could be quantitated with validated instruments. Data for previous dietary intake was not included in our study.

The weight-lowering effect of liraglutide potentially reflects multiple mechanisms, including delay in gastric emptying, as shown here, as well as activation of brainstem or hypothalamic GLP-1 receptors.[30] The weight-lowering effect is supported by our observation of decreased maximal tolerated volume (implying increased satiation), which, in the absence of changes in gastric volumes, would be consistent with central appetite suppression. Future studies may need to include measurements of central (eg, hypothalamic) function in response to GLP-1 receptor analogues.[30] Our observation that there were no significant differences among participants who experienced nausea and those who did not in the median gastric emptying $T_{1/2}$ at baseline and after 5 weeks and 16 weeks of liraglutide therapy suggests that nausea is not one of the mechanisms by which liraglutide causes weight loss. Nausea was observed in 12 participants who received liraglutide, but was only present in five of the 12 patients after 5 weeks of treatment.

A major strength of our study is the double-blind, randomised, placebo-controlled design with validated methods to measure quantitative traits in obese individuals with similar baseline characteristics in the two treatment groups. Although we did not formally assess masking, the individual in the placebo group who lost 17·1 kg weight was thought by the participant and the assessors to be on liraglutide. Additionally, our study confirms the previously established safety profile of liraglutide. Two participants (one per treatment group) developed acute biliary pain and underwent cholecystectomy during the course of our

study. It is unclear whether these individuals had gallstones before entering the study.

Our observation of an association between delay in gastric emptying of solids and change in weight loss cannot prove cause and effect. Future studies of gastric emptying of solids are needed to establish the duration of the effect of liraglutide on gastric emptying and to determine whether gastric emptying of solids is fully normalised over time or whether it persists. However, our data suggest that modulation of gastric emptying plays a key part in weight loss with liraglutide, especially early in the treatment course, which is a crucial phase in obesity management. The study also provides an explanation for nausea or vomiting noted in large multicentre studies.[9]

In conclusion, 12 weeks of daily administration of liraglutide, at 3·0 mg, after standard weekly dose escalation by 0·6 mg/week, combined with brief counselling led to significant weight loss, significant delay of gastric emptying of solids, and increased satiation compared with placebo. There was persistent slowing of gastric emptying of solids at 16 weeks of treatment, despite tachyphylaxis. Greater delay of gastric emptying of solids was associated with greater weight loss and seems to be a mechanism by which liraglutide results in weight loss, especially in the early phase of treatment. Although our study does not necessarily address causality, the associations between absolute gastric emptying $T_{1/2}$ (figure 5) or change in gastric emptying $T_{1/2}$, especially at 5 weeks (appendix p 3), and degree of weight loss over the 5-week and 16-week periods support the hypothesis that there is an association between effects on gastric emptying and weight loss.

Our study has provided information that is useful to plan the study to test the hypothesis addressing the weight loss in response to liraglutide stratified by rate of gastric emptying at baseline. Thus, assuming that a third of obese participants have accelerated, and two-thirds have normal, gastric emptying, we estimate that, with 56 individuals assigned to each treatment group (liraglutide or placebo), there would be 80% power (at α=0·05) to detect a difference in weight loss of 2·15 kg based on stratification by the absolute value of gastric emptying $T_{1/2}$ at baseline. Future research will appraise the role of accelerated gastric emptying as a potential biomarker for individualised therapy with agents that slow gastric emptying, such as liraglutide. One intriguing implication of this study is that measurement of gastric emptying (eg, at 5 weeks of treatment) may be a biomarker of responsiveness to this class of drug. This may help to select individuals for prolonged treatment with this relatively expensive drug or for cessation of treatment in those in whom there is no significant effect on this biomarker.

Contributors

HH and DK were responsible for patient screening and first-line care of participants in the clinical research unit. DE and JO'N were responsible for recruitment and management of participants' schedules. HK, KG, and MMC were responsible for standardisation of dietary and behavioural treatment. DDB was responsible for technical measurements of gastric functions and analysis. AV and AA were staff co-investigators, and were responsible for supervision of participants' care. ARZ was the study statistician. MC was the principal investigator, the NIH grant recipient, and was responsible for supervision of all aspects of the study.

Declaration of interests

MC reports grants (R56-DK67071) from NIH, non-financial support from Novo Nordisk, and a research grant from Elira and Kallope. MMC and DDB report grants from NIH. AV reports consulting fees paid to Mayo Clinic from Novo Nordisk, personal fees from Sanofi Aventis and VTV Therapeutics, and research grants from VTV Therapeutics, Novartis, and XOMA. All other authors report no relevant financial or personal conflicts of interest.

Acknowledgments

We thank Cindy Stanislav for excellent secretarial assistance, the nurses and staff of the Mayo Clinic Clinical Research Unit for nursing support and the care of patients, Erin Stern for research pharmacy support, and Michael Ryks and Deborah Rhoten for excellent technical support. Some of the medication supplies were provided by Novo Nordisk (Plainsboro, NJ, USA). The study was conducted in the clinical research unit (supported by Mayo Clinic Center for Clinical and Translational Science [CCaTS] grant UL1-TR000135).

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