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Effect of the glucagon-like peptide-1 receptor agonist liraglutide, compared to caloric restriction, on appetite, dietary intake, body fat distribution and cardiometabolic biomarkers: A randomized trial in adults with obesity and prediabetes

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Abstract

Aims: To investigate the hypothesis that weight loss with the glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide alone would lead to a greater reduction in the proportion of fat to lean tissue mass when compared to caloric restriction (CR) alone, as well as when compared to treatment with sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, that also enhances GLP-1 activity - to determine the independent effects of each treatment.

Methods: A total of 88 adults with obesity and prediabetes were randomized to 14 weeks of intervention with CR (−390 kcal/d), liraglutide (1.8 mg/d), or the dipeptidyl peptidase-4 inhibitor sitagliptin (100 mg/d) as a weight-neutral comparator. Changes between groups in appetite and hunger ratings measured via visual analogue scales, dietary intakes, body weight, body composition via dual energy x-ray absorptiometry, and resting energy expenditure via indirect calorimetry were assessed using the Kruskal-Wallis test or Pearson's chi-squared test.

Results: Weight loss ≥5% of baseline body weight occurred in 44% of participants in the CR group, 22% of the liraglutide group and 5% of the sitagliptin group ($p = 0.02$). The ratio of fat to lean mass decreased by 6.5% in the CR group, 2.2% in the liraglutide group, and 0% in the

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AUTHOR CONTRIBUTIONS

Study concept, study design, and funding: Heidi J. Silver, Nancy J. Brown, and Kevin D. Niswender. Protocol implementation: Heidi J. Silver, Dianna Olson, Dustin Mayfield, Patricia Wright, Mona Mashayekhi, James M. Luther, and Nancy J. Brown. Data acquisition and database entry: Dianna Olson, Dustin Mayfield, Patricia Wright, Mona Mashayekhi, James M. Luther, and Nancy J. Brown. Statistical analysis: Hui Nian and Heidi J. Silver. Manuscript development: Heidi J. Silver, Mona Mashayekhi, John R. Koethe, James M. Luther, and Nancy J. Brown. Manuscript revisions and final draft: Heidi J. Silver, Hui Nian, Mona Mashayekhi, John R. Koethe, Kevin D. Niswender, James M. Luther, and Nancy J. Brown.

CONFLICT OF INTEREST

Nancy J. Brown serves as a consultant for Pharvaris Gmbh and CinCor Pharma and serves as a member of the scientific advisory boards of Bio Estar and Alnylam Pharmaceuticals.

sitagliptin group ($p = 0.02$). Visceral fat reduced by 9.5% in the CR group, 4.8% in the liraglutide group, and 0% in the sitagliptin group ($p = 0.04$). A spontaneous reduction in dietary simple carbohydrates in the CR group was associated with improved homeostatic model assessment of insulin resistance score (HOMA-IR).

Conclusions: Although both liraglutide and CR are valuable strategies for cardiometabolic risk reduction, CR was associated with greater weight loss and more favourable improvements in body composition than treatment with liraglutide alone. Differences in the response to each of these interventions enables patients to be stratified to the most optimal intervention for their personal risk factors.

1 | INTRODUCTION

More than two in five people in the United States aged ≥18 years have obesity and more than 110 million today have prediabetes.[1] Both obesity and prediabetes are high-risk disease states that often precede the development of type 2 diabetes (T2D).[2] As approximately 5% to 10% of people with prediabetes progress to T2D annually, it is estimated that 70% of people with prediabetes will eventually develop T2D.[3] Interventions to prevent or delay progression to T2D that focus on reducing caloric intake and increasing physical activity provide significantly greater weight loss than usual care recommendations.[4] Moreover, systematic reviews show that diet intervention has the greatest impact on preventing progression to T2D, with a 36% reduction in relative risk on average.[4,5] While long-term maintenance of weight loss is possible, gradual weight regain occurs in up to 80% of intentional weight losers.[6] Increased appetite, dysregulated satiety, food preferences and the reward value of food contribute to vulnerability to weight regain.[7] Weight loss and weight loss maintenance can be more successful with pharmacological agents as adjunctive therapy to caloric restriction (CR), with or without increased physical activity.

The glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide is a long-acting analogue of glucagon-like peptide-1 (GLP-1), an incretin hormone that induces insulin secretion in response to enteral nutrient absorption.[8] Administered at a dose of 1.8 to 3.0 mg/d for 20 weeks, liraglutide reduces the prevalence of prediabetes by over 80% in adults with obesity.[9] Doses of 1.8 and 3.0 mg/d similarly affect gastric emptying, postprandial glucagon, glucose, insulin and C-peptide levels in adults with obesity and no prediabetes or T2D.[10] Moreover, a dose of 3.0 mg/d administered to adults with obesity for 16 weeks significantly increases visual analogue scale (VAS) ratings for fullness and reduces ratings for prospective food consumption and desire to eat foods that are sweet, salty, savoury or fatty.[11] Thus, both appetite suppression and delayed gastric emptying contribute to weight loss with liraglutide treatment.

The regional distribution of body fat, such as central adiposity, is robustly associated with cardiometabolic risk.[12,13] It is unclear whether the effects of GLP-1RAs on body composition or the distribution of body fat differ from the changes that occur with CR. In adults who have overweight or obesity, liraglutide at 3.0 mg/d significantly reduces the percentage of body fat and truncal fat with no significant change in lean tissue mass.[11] Moreover, liraglutide at 1.8 mg/d administered to adults with obesity and prediabetes

significantly reduces visceral adipose tissue (VAT) when participants achieve a target weight loss of 7% from baseline weight.[14] Reduced VAT with liraglutide administration has also been observed in adults with obesity and T2D.[15,16] Many studies show that excess visceral fat deposition correlates robustly with insulin resistance and incident prediabetes and T2D.[17–20]

The purpose of the present study was to determine the effects of liraglutide (at a dose of 1.8 mg/d) in comparison to modest CR on appetite, dietary intake, weight loss, and body fat distribution in adults with obesity and prediabetes. We hypothesized that weight loss with liraglutide would result in a greater reduction in the proportion of fat to lean tissue mass when compared to CR as well as when compared to treatment with sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor that also enhances GLP-1 activity but does not promote weight loss. We further hypothesized that weight loss with liraglutide treatment would be associated with reduced appetite that yields reduced energy intake, whereas weight loss with CR would be a direct effect of reduced energy intake.

2 | METHODS

2.1 | Participants

The study was approved by the Vanderbilt University Medical Center Institutional Review Board (IRB#170213) and registered at ClinicalTrials. gov (NCT03101930). Recruitment methods have been described in a prior publication.[21] All participants signed written informed consent and all methods were conducted in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Eligibility criteria included age 18–65 years, having a body mass index (BMI) ≥30 kg/m^2, and having prediabetes as defined by American Diabetes Association criteria (impaired fasting serum glucose level 100–125 mg/dL, impaired glucose tolerance as 140–199 mg/dL at 2 hours after 75-g oral glucose challenge, or fasting serum glycated haemoglobin level of 5.7%–6.4%). Potential participants were excluded if they were pregnant or lactating, had type 1 or 2 diabetes, resistant hypertension, a history of pancreatitis, significant cardiovascular disease, asthma with regular inhaler use, impaired kidney (glomerular filtration rate <60 mL) or liver function, gastrointestinal malabsorption, family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma, self-reported weight change >2 kg within 6 months of enrolment, or history of alcohol or illicit drug abuse.

2.2 | Study design

This study was a prospective, randomized, parallel-group intervention trial (Figure 1). Baseline screening visits were conducted at the Vanderbilt Clinical Research Center (VCRC). As the primary outcome of the study was endothelial function (reported previously[21]), enrolled participants underwent a 6-week run-in period for medical management of cardiovascular risk factors (hypertension and dyslipidaemia) based on United States Preventative Services Task Force guidelines and those with a calculated 10-year cardiovascular risk ≥10% were advised to begin low-dose (81 mg/d) aspirin.[22] After completion of the run-in period, participants had initial metabolic testing visits at the VCRC and were randomly assigned in a 2:1:1 ratio to receive liraglutide, sitagliptin, or CR.

The study was originally powered for the primary outcome of improvement in endothelial function as measured by flow-mediated dilatation.[21] Post hoc calculation using the present sample size for the outcome of weight change showed 80% power to detect a significant difference in mean weight change of 2 kg or greater between groups based on one-way ANOVA with a type 1 error rate of 0.05.

2.3 | Drug treatment

Assignment to study drugs was double-blinded. Participants randomized to the liraglutide group were provided with prefilled FlexPen devices (Novo Nordisk, Bagsvaerd, Denmark) and oral placebo. Liraglutide dosing started with 0.6 mg/d for study week 1, escalated to 1.2 mg/d for study week 2, and was then maintained at 1.8 mg/d for 14 weeks (study weeks 3–16). The sitagliptin group received an oral dose of 100 mg/d (Merck & Co., Inc., United States) and a FlexPen placebo. Participants were instructed to administer the subcutaneous medication every evening between 9:00 PM and 10:00 PM and to consume the oral medication each morning at 7:00 AM. Neither of these groups received diet intervention. All other study procedures and measurements as performed by study nurses were identical between treatment groups.

2.4 | Diet treatment

Participants in the CR group were provided with a daily caloric goal to achieve an energy deficit of 390 kcal below resting energy expenditure (REE) determined from indirect calorimetry. The energy deficit target was determined a priori, based on findings from previous studies showing that liraglutide at a dose of 1.8 mg/d would achieve weight loss of approximately 0.27 kg/week.[23–26] Initial meetings with the study registered dietitian provided the caloric goal and targeted instructions on reducing caloric intake by counting calories, controlling portion sizes, choosing reduced energy food ingredient substitutions, allowing foods that constitute “empty” calories, provision of sample menus for meals and snacks to achieve the caloric goal, provision of The CalorieKing® calorie, fat and carbohydrate counter book, and daily food intake logs to review with the dietitian at follow-up visits, which occurred every 2 weeks. No instruction was provided regarding macronutrient composition of the diet or other dietary guidance.

2.5 | Diet assessment

Dietary intakes were assessed for all three groups by averaging three 24-hour diet recalls obtained within 10 days of the baseline and final testing visits that included two nonconsecutive weekdays and one weekend day. All assessments were performed by one trained research dietitian at the Vanderbilt Diet, Body Composition, and Human Metabolism Core using the validated US Department of Agriculture (USDA) five-step multi-pass methodology, a standardized script, measuring utensils, and computer-generated prompts.[27] Dietary data were directly entered into Nutrition Data System for Research software (NDS-R, version 2018, Nutrition Coordinating Center, Minneapolis, Minnesota). The NDS-R database includes >18 000 foods and ingredients, which generates values for 174 nutrients, nutrient ratios and other food components.

2.6 | Appetite and food preference assessment

Participants rated appetite and food preferences while in the overnight fasted state at their metabolic testing visits. Appetite was rated on 100-mm VASs which have been validated for assessment of hunger, satisfaction, fullness, and prospective food consumption.[28,29] VASs were also used for participant rating of desire to consume sweet, salty, savoury and fatty foods. The repeat reliability of the VAS has been established and its use has not influenced prospective ingestive behaviour.[30] Higher ratings indicate stronger sensations for appetite and food preference factors.

2.7 | Body composition

Whole and regional body composition were acquired via dual energy x-ray absorptiometry on a Lunar iDXA scanner (GE Healthcare, Chicago, Illlinois). The scanner was phantom calibrated daily prior to data acquisition to ensure instrument reliability. Scans were acquired by one research technician certified in densitometry. Scans were analysed using enCORE software (version 13.6, GE Healthcare) and the android region of interest for quantification of VAT mass was automatically determined by the device software.

2.8 | Indirect calorimetry

Resting energy expenditure was measured in the supine position using a Parvo TrueOne 2400 portable metabolic cart system (ParvoMedics, Sandy, Utah) in a temperature-controlled room. Upon placing a ventilated plexiglass hood over the participant's head and connecting it to the metabolic cart by expiration-gas tubing, calorimetry measures proceeded for 25 to 30 minutes, with the first 5 to 10 minutes eliminated from analysis. Before use, the system was calibrated to room air and a gas tank of 16% O_2 and 1% CO_2. Whole-body rates of O_2 consumption and CO_2 production were determined from measured expired volume and the differences in O_2 and CO_2 concentration between inspired and expired air. Ventilation is measured by a mass flow meter, oxygen concentration by a paramagnetic O_2 analyser, and CO_2 by an infrared analyser. REE and substrate oxidation were calculated automatically using the Weir equation and the methods of Frayn.[31,32]

2.9 | Cardiometabolic biomarkers

Plasma glucose was measured at the VCRC bedside using a YSI glucose analyser (YSI Life Sciences, Yellow Springs, Ohio). Plasma insulin was measured at the Vanderbilt Hormone Assay & Analytic Services Core via radioimmunoassay. Homeostatic model assessment of insulin resistance (HOMA-IR) score was calculated from measured glucose and insulin levels as [fasting glucose (mg/dL) × fasting insulin (mU/mL)]/405.[33] Lipid profiles were measured at the Vanderbilt Department of Pathology Diagnostic Laboratory via selective enzyme hydrolysis.

2.10 | Statistical methods and data analysis

Within-group changes were assessed using Wilcoxon signed-rank tests. Between-group comparisons were performed using the Kruskal-Wallis test or Pearson's chi-squared test. Pairwise comparisons were conducted using the Wilcoxon rank-sum test when the Kruskal-Wallis test was significant. Spearman's rank correlations were used to assess relationships

between changes in independent variables and cardiometabolic biomarkers. In the tables, continuous variables are presented as mean and standard deviation and categorical variables are presented as frequency and proportion. Statistical analyses were performed with a type I error rate of 5% using SPSS version 28.0 (IBM, Montauk, New York) and R software version 4.0.2. (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

A full description of study enrollment, randomization, retention, and participant characteristics has been published previously.[21] Of the 88 participants who were randomized to treatment groups (44 to liraglutide, 22 to sitagliptin, 22 to CR) and completed the study, 68% were female, 83% self-identified as White, and the mean age was 50.3 ± 10.8 years. At baseline, the mean BMI was 39.0 ± 6.0 kg/m^2, with 33% having Class I obesity (BMI 30.0–34.9 kg/m^2), 34% Class II obesity (BMI 35.0–39.9 kg/m^2), and 33% Class III obesity (BMI ≥40.0 kg/m^2). The mean fasting glucose level was 97.4 ± 10.4 mg/dL, insulin level was 22.3 ± 12.8 μU/mL, HbA1c concentration was 5.7 ± 0.3%, triglyceride (TG) level was 121.5 ± 56.5 mg/dL, HDL cholesterol level was 46.7 ± 10.3 mg/dL, and TG/HDL cholesterol ratio was 2.9 ± 1.7.

3.1 | Effects of treatment on weight and body composition

Weight loss ≥5% of baseline body weight occurred in 44% of participants in the CR group, 22% of participants in the liraglutide group, and 5% of participants in the sitagliptin group ($p = 0.02$). The amount of weight loss was significantly different among the three groups (difference CR vs. liraglutide: −2.8 kg [95% confidence interval {CI} −1.2, −4.8], $p = 0.01$; CR vs. sitagliptin: −3.5 kg [95% CI −0.1, −6.9], $p = 0.006$; liraglutide vs. sitagliptin: −1.7 kg [95% CI −0.3, −3.7], $p = 0.01$). Both the CR and liraglutide groups had significant reductions in total fat mass (difference CR vs. liraglutide: −2.3 kg [95% CI −0.4, −4.2], p = 0.04) and percent body fat (−1.3% [95% CI −0.3, −2.3], $p = 0.01$), whereas fat mass increased over the intervention period in the sitagliptin group (Table 1). There were no significant changes in lean tissue mass in the CR or sitagliptin groups. Although not significantly different from the other two groups, loss of lean mass occurred within the liraglutide group ($p = 0.007$). Thus, the change in the proportion of fat to lean mass differed among groups ($p = 0.02$), with the reduction in the fat to lean mass ratio greatest in the CR group (difference CR vs. liraglutide: −0.05 [95% CI −0.01, −0.09], $p = 0.04$; CR vs. sitagliptin: −0.07 [95% CI −0.01, −0.12], $p = 0.006$; liraglutide vs. sitagliptin: −0.02 [95% CI −0.02, 0.07], $p = 0.40$).

Overall, the reduction in the fat to lean mass ratio in the liraglutide group was significantly associated with reduced truncal fat, reduced proportion of android to gynoid fat, and reduced visceral fat ($r = 0.72$, $p < 0.001$; $r = 0.71$, $p < 0.001$; $r = 0.43$, $p = 0.02$, respectively). As with the liraglutide group, the reduction in the proportion of fat to lean mass in the CR group was significantly associated with reduced truncal fat ($r = 0.77$, $p = 0.005$). The reduction in the percentage of fat in the truncal region differed significantly among the three groups (difference CR vs. liraglutide: −1.5% [95% CI −0.4, −2.7], $p = 0.007$; CR vs sitagliptin: −2.6% [95% CI −1.0, −4.1], $p < 0.001$; liraglutide vs. sitagliptin: −0.7% [95% CI −0.2, 0.4],

$p = 0.29$). Consequently, visceral fat reduced by 4.8% in the liraglutide group, 9.5% in the CR group, and 0.1% in the sitagliptin group ($p = 0.05$).

3.2 | Effects of treatment on REE and substrate oxidation

Despite significant loss of body weight and fat mass in the liraglutide and CR groups, the reductions in REE were minor (<100 kcal/d), with no significant difference among treatment groups ($p = 0.50$; Table 2). Similarly, no significant changes were detected in respiratory quotients ($p = 0.97$) or substrate oxidation rates, which averaged 50% carbohydrate, 30% fat and 20% protein kcal/d.

3.3 | Effects of treatment on dietary intakes

Energy and macronutrient intakes were similar among the three groups at baseline, with participants reporting an average of 2138.9 ± 851.5 kcal/d, which comprised 37.9 ± 8.3% fat kcal, 44.2 ± 10.2% carbohydrate kcal and 15.2 ± 4.7% protein kcal. Among all participants, energy intakes reduced on average by 300.0 ± 891.8 kcal/d ($p = 0.007$) over the study intervention period. No significant differences were observed among treatment groups for the change in the amount of food consumed, the reduction in energy intakes, the change in percent of calories as fat, or the type of fat consumed (Table 3). However, the change in the percentage of calories from carbohydrates as well as the intake of total and added sugars differed significantly among groups. The CR group significantly reduced consumption of dietary carbohydrates (−68.1 ± 124.1 g/d, $p = 0.04$). The intake of total sugars and added sugars decreased significantly more with CR compared to liraglutide and sitagliptin (total sugars: difference CR vs. liraglutide: −29.5 g [95% CI −5.0, −54.8], $p = 0.02$; CR vs. sitagliptin: −25.1 g [95% CI −25.9, −75.2], $p = 0.02$; liraglutide vs sitagliptin: −9.9 g [95% CI −14.4, 34.2], $p = 0.42$; added sugars: CR vs. liraglutide: −31.1 g [95% CI −9.7, −52.5], $p = 0.005$; CR vs. sitagliptin: −23.0 g [95% CI −67.4, −21.4], $p = 0.005$; liraglutide vs sitagliptin: −5.6 g [95% CI −42.9, 31.6], $p = 0.43$). Consequently, total dietary glycaemic load reduced 30.4% in the CR group compared to 12.4% in the liraglutide group ($p = 0.07$). In the CR group, the reductions in the consumption of added sugars and dietary glycaemic load were significantly associated with reduced HOMA-IR score ($r = 0.60$, $p = 0.04$; $r = 0.73$, $p = 0.007$, respectively). HOMA-IR score decreased by 35.4% in the CR group (from 3.3 ± 0.9 to 2.2 ± 0.6, $p = 0.02$) and by 30.8% in the liraglutide group (from 3.5 ± 0.6 to 2.5 ± 0.5, $p = 0.03$), and increased in the sitagliptin group (from 2.9 ± 0.7 to 4.9 ± 1.2, $p = 0.10$). Concomitant with the reduction in dietary carbohydrates, the percentage of calories from dietary protein increased. The increase in protein intakes was most significant in the CR group (difference CR vs. liraglutide: 4.0% kcal [95% CI 0.3, 7.7], $p = 0.03$; CR vs. sitagliptin 5.4% kcal [1.7, 12.6], $p = 0.03$; liraglutide vs. sitaglipitin: 1.4% kcal [95% CI −2.3, 4.9], $p = 0.46$).

3.4 | Effects of treatment on appetite and food preferences

Participants in the sitagliptin and CR groups reported greater hunger at the end of the intervention period, with no change in hunger ratings in the liraglutide group (Table 4). Increased hunger in the CR group was associated with decreased fullness ($r = 0.71$, $p = 0.006$). In contrast, participants in the liraglutide group rated their feeling of fullness higher ($p = 0.003$) and their rating of how much they could consume lower ($p = 0.02$) at the end

of the intervention period. The increase in fullness rating was significantly associated with the increase in the rating of feeling satisfied ($r = 0.47$, $p = 0.007$). Overall, the changes from baseline to end of study in participants' ratings of feeling hungry, feeling satisfied, feeling full, or how much participants perceived they could consume at their next meal were not significantly different among treatment groups. Likewise, the changes in participants' desire for sweet or savoury foods were not significantly different among groups. There was a tendency toward a significantly greater reduction in the desire for fatty and salty foods with participants in the CR group compared to the liraglutide and sitagliptin groups.

4 | DISCUSSION

Obesity and prediabetes are serious and widespread risk factors for development of T2D. Effective approaches to reduce T2D risk that are safe, well tolerated, and economical are much needed as T2D is now prevalent in over 500 million adults worldwide.[34] Most previous studies investigating the effects of the GLP-1RA liraglutide on appetite, body weight, body composition and energy expenditure in adults with overweight/obesity and prediabetes have combined liraglutide treatment with CR or lifestyle modification. A novel aspect of the present study is that we randomized adults with obesity and prediabetes to CR versus liraglutide or the DPP-4 inhibitor sitagliptin as a weight-neutral comparator, which enabled the independent effects of each treatment to be determined. While all three treatments decreased energy intakes, significant weight loss occurred in the CR and liraglutide groups. Notably, there was a significant loss of lean body mass in the liraglutide group but not the CR group, such that the reduction in the overall ratio of fat to lean mass was greater in the latter, even though overall weight loss was also greater in the CR group. It is possible that the greater preservation of lean mass during weight loss observed in the CR group was driven by curtailment of proteolysis, which would be attenuated from increased protein consumption, as demonstrated in randomized controlled trials with healthy normal-weight adults.[35] In a 40-week trial in persons with obesity and normoglycaemia, liraglutide dosed at 3 mg/d in conjunction with CR of 500 kcal/d reduced the proportion of fat to lean tissue by 7.2%,[36] indicating a low amount for the fraction of weight loss as lean tissue.

A second major finding was that weight loss and improvements in the proportion of body fat to lean mass in the liraglutide and CR groups were not accompanied by significant changes in REE. It is plausible that the improvements in body composition that occurred in the liraglutide and CR groups prevented the degree of reduction in REE more typically observed with weight loss.[37] It is well established that decreases in resting metabolism are directly proportional to the loss of fat-free mass. Experiencing reduced REE after weight loss is often thought to increase propensity for weight regain. Thus, preserving REE is a potential therapeutic target to ensure the continued cardiometabolic benefits of weight loss.

Notably, the improvements observed in the ratio of fat to lean mass associated with significantly reduced percentage of fat in the truncal region, improved android to gynoid fat mass ratio, and meaningful reductions in visceral fat mass, which decreased by 9.5% in the CR group and 4.8% in the liraglutide group. The degree of reduced VAT in the liraglutide group was equivalent to prior treatment with liraglutide in adults with T2D,

despite the fact that the present cohort would be expected to have better glycaemic status, and thus, lower baseline amount of VAT mass.[38,39] The relative percent change in VAT detected in the liraglutide group appears to be consistent with changes observed in adults with normoglycaemia when accounting for differences in intervention duration.[36] Since accumulation of VAT is an independent predictor for development of T2D,[40] as well as atherogenic dyslipidaemia and carotid plaques,[41,42] reduced VAT mass in both the liraglutide and CR groups suggests reduced cardiovascular risk after 14 weeks of intervention. This may be especially important in people with obesity, in whom storage of excess energy intake as TGs in subcutaneous fat transitions to a dysfunctional adiposity characterized by accumulation of ectopic fat in the visceral depot, organs, and skeletal muscle.[43] An additional indicator of reduced cardiovascular risk was the improvement in HOMA-IR score, which decreased most significantly in the CR group and was associated with the reductions in simple carbohydrate intake and total dietary glycaemic load.

Indeed, the most notable change in food intakes during the intervention period was a spontaneous reduction in the percentage of energy from dietary carbohydrates, including total and added sugars, in the CR group. The emphasis on limiting carbohydrate intake advocated currently in the popular media, along with the proliferation of low-carbohydrate food products being marketed, probably contributed to this voluntary modification in dietary macronutrient composition. Interestingly, the CR group experienced the most weight loss during the intervention period. This finding may be a function of the short-term duration (14 weeks) of the study as limiting carbohydrate intake induces an initial rapid weight loss that becomes equivalent to the amount of weight loss with low-fat diets at 12 months of intervention.[44] Both a recent Cochrane review and a systematic review of systematic reviews confirm that there is no difference in long-term weight loss with low-carbohydrate versus low-fat diets.[45,46] Importantly, the reduction in dietary carbohydrates and total glycaemic load was significantly associated with reduced insulin resistance, as detected by the change in HOMA-IR score. While it is expected that reduced carbohydrate intake would also induce depletion of glycogen stores and a metabolic shift to increased fat oxidation to meet energy needs, we observed no significant changes in macronutrient oxidation via indirect calorimetry in any of the treatment groups. Additionally, no significant changes were detected from baseline to study end in respiratory quotient.

With CR, the objective is to modify the extrinsic food reward environment by adopting strategies such as replacing high-caloric-density with low-caloric-density food items, reducing portion sizes, incorporating “calorie-free” foods, meal/menu planning, crafting grocery shopping lists, using calorie-counting applications, and keeping a daily record of food intake. In contrast, GLP-1RA pharmacological agents such as liraglutide target altering an individual’s intrinsic food reward environment by reducing appetite and hunger while increasing satiation at meals and satiety between meals. Prior evidence in adults with obesity as well as those with obesity and T2D have consistently shown improvements in visual analogue scale ratings of appetite-related factors with liraglutide treatment of 1.8 and 3.0 mg/d.[10,47,48] It is thought that these effects occur by activating GLP-1 receptors expressed on glutamatergic neurons in the hypothalamus.[49] In the present study of obesity and prediabetes, similar increased sensations of satiation and satiety were observed with liraglutide treatment as participants rated their feeling of fullness higher and prospective

consumption lower at intervention end. In addition to effects on appetite, one study of obesity treatment with semaglutide, a GLP-1 analogue similar in structure to liraglutide, showed reduction in the preference for fatty foods.[50] Although no significant differences among groups for food preferences were detected in the present study, there was a relative reduction in preference for fatty and salty foods reported by the CR group. It is interesting that the direction of change for food preferences differed among the groups, with ratings for desire for sweet and fatty foods increased in the liraglutide group. In contrast, more sensitive tools such as functional brain imaging provide evidence that GLP-1 receptor activation may reduce anticipatory food reward and food cravings.[51]

The main limitation of the present study is the relatively small sample sizes in each treatment group, which may have prevented the identification of additional significant differences between groups. Additionally, the length of the intervention period was moderate, which prevents the durability of the findings from being determined. Further, the dose of liraglutide provided (1.8 mg/d), chosen based on published cardiovascular benefits, may have limited the amount of weight and body fat loss achieved. Finally, we recognize that diet assessment methodology is constrained by the potential for under- or over-reporting. To limit possible bias, we train our study participants on portion size estimation and utilize the validated USDA multi-pass methodology along with NDS-R software-generated prompts.[52,53] The strengths of the study include: randomization to pharmaceutical versus dietary intervention; the inclusion of a sitagliptin group to assess the effects of increasing GLP-1 without weight loss; double blinding of drug treatment; the thoroughness of cardiometabolic phenotyping; and the validity and reliability of the methods used to assess diet, appetite, body composition and energy expenditure factors.

In conclusion, the results of this study show that liraglutide or CR are valuable strategies for treatment of adults with obesity and prediabetes to reduce body weight and improve body composition, both of which contribute to moderating cardiometabolic risk. However, the improvement in body weight and body composition was greater with CR than treatment with liraglutide alone. Further, the difference in response to treatment regarding a readily available biomarker of insulin resistance, HOMA-IR score, affords useful information to enable healthcare providers to stratify patients to the most optimal intervention for their personal risk factors. Future investigation might be designed to further elucidate which individuals would derive the greatest benefit from either approach. It might also be beneficial to compare the cost-effectiveness of pharmaceutical versus dietary approaches in the treatment of prediabetes.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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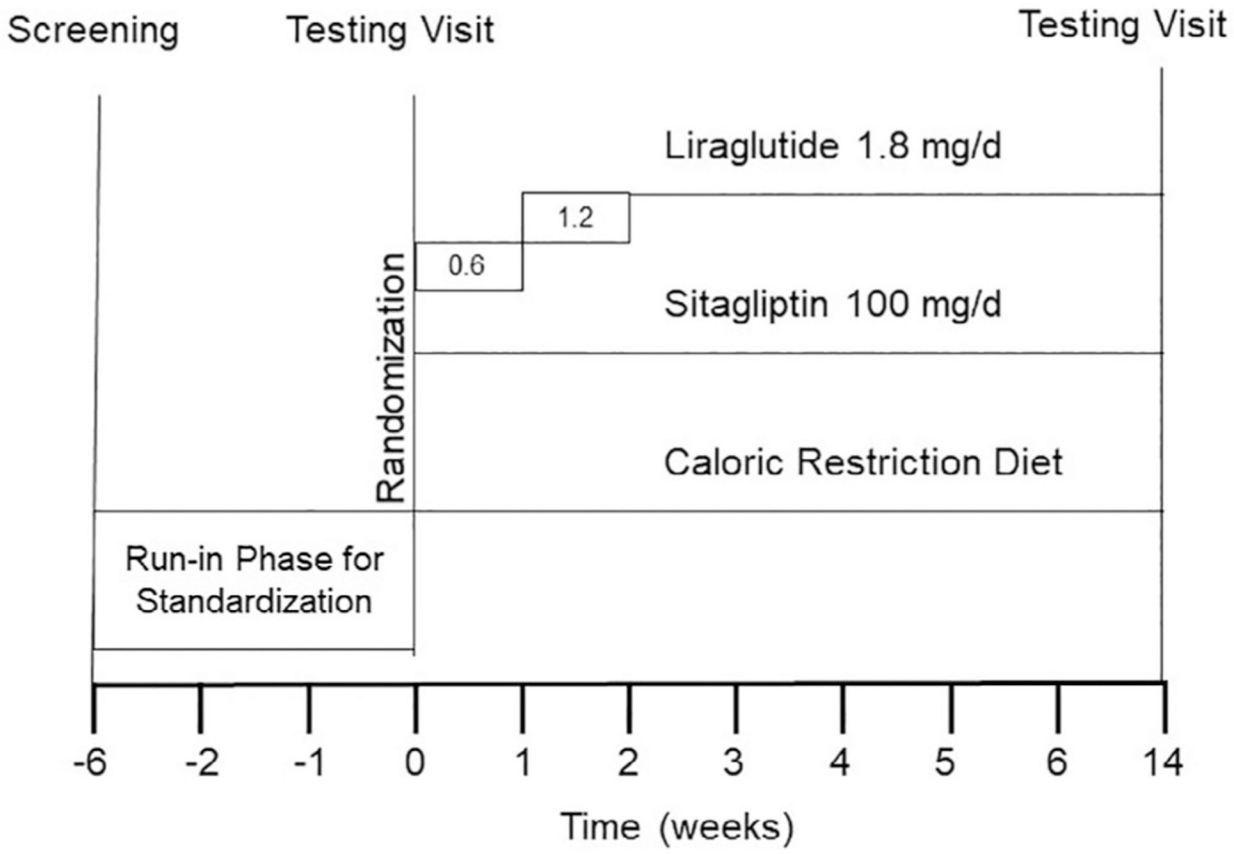

FIGURE 1.
Study design

TABLE 1

Changes in weight and body composition by treatment group

Variable	Liraglutide, *N* = 44	Sitagliptin, *N* = 22	Caloric restriction, *N* = 22	*p* value*
Weight, kg				0.01
Baseline	108.5 ± 21.6	112.4 ± 22.8	109.9 ± 16.9	
Final	106.3 ± 22.5	112.1 ± 23.4	105.2 ± 18.2	
Change	−2.5 ± 3.6^{a,b}	−0.1 ± 2.7^{a,c}	−4.4 ± 5.9^{b,c}	
BMI, kg/m^2				0.006
Baseline	38.6 ± 6.1	39.6 ± 5.7	38.4 ± 5.7	
Final	38.2 ± 6.3	39.6 ± 6.1	37.3 ± 5.6	
Change	−0.9 ± 1.3^{a,b}	0.0 ± 1.0^{a,c}	−1.6 ± 2.1^{b,c}	
Total fat mass, g				0.004
Baseline	49.4 ± 12.7	49.8 ± 14.2	49.5 ± 14.4	
Final	47.1 ± 13.6	51.5 ± 13.2	47.2 ± 14.6	
Change	−1.5 ±2.4^{b}	1.5 ± 2.3^{c}	−3.9 ± 4.1^{b,c}	
Total lean mass, g				0.90
Baseline	53.6 ± 9.3	57.5 ± 13.9	56.0 ± 9.7	
Final	52.8 ± 9.8	56.9 ± 13.7	56.7 ± 9.6	
Change	−0.8 ± 1.5	−0.5 ± 1.4	0.7 ± 2.0	
Fat mass/lean mass ratio				0.02
Baseline	0.93 ± 0.22	0.93 ± 0.16	0.92 ± 0.29	
Final	0.91 ± 0.21	0.93 ± 0.17	0.86 ± 0.28	
Change	−0.02 ± 0.04^{b}	0.00 ± 0.06^{c}	−0.06 ± 0.07^{b,c}	
Android/gynoid ratio				0.52
Baseline	0.67 ± 0.15	0.67 ± 0.13	0.65 ± 0.17	
Final	0.69 ± 0.18	0.65 ± 0.12	0.64 ± 0.16	
Change	0.01 ± 0.11	−0.01 ± 0.05	−0.02 ± 0.04	
Visceral adipose tissue, g				0.05
Baseline	2.1 ± 0.9	2.5 ± 1.6	2.1 ± 0.9	
Final	2.0 ± 1.1	2.5 ± 1.6	1.8 ± 0.8	
Change	−0.1 ± 0.3	0.0 ± 0.2	−0.2 ± 0.3	

Variable	Liraglutide, *N* = 44	Sitagliptin, *N* = 22	Caloric restriction, *N* = 22	*p* value*
Total body fat, %				0.02
Baseline	47.1 ± 5.8	45.8 ± 7.5	46.8 ± 6.7	
Final	47.1 ± 5.7	47.6 ± 4.6	45.2 ± 7.8	
Change	−0.1 ± 1.2[b]	0.1 ± 1.4[c]	−1.7 ± 1.9[b,c]	
Trunk fat, %				0.01
Baseline	52.1 ± 5.3	51.0 ± 6.7	51.5 ± 5.3	
Final	51.5 ± 5.6	52.5 ± 4.6	49.2 ± 6.4	
Change	−0.8 ± 1.5[b]	0.1 ± 1.4[c]	−2.3 ± 2.4[b,c]	

Abbreviation: BMI, body mass index.

[a]Mean change is significantly different between liraglutide and sitagliptin.

[b]Between liraglutide and caloric restriction.

[c]Between sitagliptin and caloric restriction.

*p value for the difference in mean change among the three groups determined by Kruskal-Wallis test.

TABLE 2

Changes in resting energy expenditure and substrate oxidation by treatment arm

Variable	Liraglutide *N* = 44	Sitagliptin *N* = 22	Caloric restriction *N* = 22	*p* value*
REE, kcal				0.50
Baseline	1755.4 ± 353.5	1853.7 ± 394.1	1833.2 ± 396.1	
Final	1670.9 ± 329.2	1711.9 ± 452.0	1767.3 ± 402.6	
Change	−76.6 ± 249.5	−85.9 ± 146.2	−91.2 ± 245.7	
RQ, VCO2/VO2				0.97
Baseline	0.82 ± 0.06	0.81 ± 0.06	0.81 ± 0.04	
Final	0.81 ± 0.05	0.81 ± 0.05	0.80 ± 0.06	
Change	0.00 ± 0.07	0.00 ± 0.07	0.00 ± 0.05	
Fat, % REE kcal				0.85
Baseline	50.6 ± 15.3	49.8 ± 15.0	52.1 ± 11.8	
Final	48.9 ± 15.9	50.3 ± 15.6	53.4 ± 19.3	
Change	−0.1 ± 19.4	1.4 ± 19.1	0.2 ± 15.2	
Carbohydrate, % REE kcal				0.90
Baseline	30.2 ± 15.6	31.5 ± 15.5	29.3 ± 12.3	
Final	31.7 ± 15.9	30.1 ± 14.4	27.9 ± 18.4	
Change	0.1 ± 20.0	−1.5 ± 18.5	−0.3 ± 13.7	
Protein, % REE kcal				0.62
Baseline	20.0 ± 5.8	18.9 ± 3.9	19.0 ± 3.6	
Final	19.4 ± 3.9	19.5 ± 5.5	18.6 ± 4.8	
Change	−0.8 ± 5.1	0.1 ± 2.3	−0.1 ± 2.8	

Abbreviations: REE, resting energy expenditure; RQ, respiratory quotient; VCO2, volume of carbon dioxide production; VO2, volume of oxygen consumption.

** p* value for the difference in change among the three groups determined by Kruskal-Wallis test.

TABLE 3

Changes in dietary intakes by treatment group

Variable	Liraglutide, *N* = 44	Sitagliptin, *N* = 22	Caloric restriction, *N* = 22	*p* value*
Amount of food, g				0.50
Baseline	3267.3 ± 1315.4	3618.4 ± 1694.4	3161.2 ± 1154.7	
Final	3041.4 ± 1274.6	3049.1 ± 1232.8	3217.8 ± 1637.8	
Change	−317.9 ± 1479.5	−662.8 ± 1823.6	122.9 ± 2093.7	
Energy, kcal				0.90
Baseline	2191.6 ± 904.6	2000.3 ± 766.9	2037.4 ± 715.4	
Final	2015.1 ± 783.8	1828.7 ± 859.3	1669.2 ± 413.6	
Change	−293.8 ± 1018.3	−242.4 ± 668.4	−373.6 ± 870.0	
Fat, %kcal				0.57
Baseline	37.5 ± 8.7	38.3 ± 7.4	36.9 ± 7.9	
Final	36.4 ± 8.2	37.4 ± 8.5	38.8 ± 7.0	
Change	−1.2 ± 11.8	−1.4 ± 8.7	2.2 ± 9.3	
Carbohydrate, %kcal				0.18
Baseline	44.9 ± 10.0	44.0 ± 9.9	44.1 ± 10.1	
Final	44.5 ± 9.0	45.4 ± 9.7	37.7 ± 7.2	
Change	−0.2 ± 12.8	2.4 ± 11.6	−6.4 ± 13.9	
Protein, %kcal				0.10
Baseline	15.0 ± 4.4	15.5 ± 4.2	16.0 ± 5.8	
Final	17.1 ± 5.5	15.7 ± 4.4	21.1 ± 8.6	
Change	1.8 ± 6.4	0.2 ± 5.1	5.1 ± 11.6	
Saturated fat, g				0.51
Baseline	32.0 ± 19.4	30.2 ± 13.0	29.0 ± 14.7	
Final	27.1 ± 15.3	24.4 ± 13.4	21.1 ± 7.3	
Change	−6.6 ± 23.8	−6.8 ± 11.8	−7.9 ± 12.6	
Monounsaturated fat, g				0.92
Baseline	34.1 ± 18.4	31.4 ± 13.3	28.1 ± 12.2	
Final	27.9 ± 15.2	26.5 ± 12.7	27.5 ± 10.6	
Change	−6.3 ± 25.1	−4.9 ± 15.1	−0.6 ± 14.3	

Variable	Liraglutide, *N* = 44	Sitagliptin, *N* = 22	Caloric restriction, *N* = 22	*p* value*
Polyunsaturated fat, g				0.61
Baseline	21.4 ± 10.5	18.0 ± 8.3	18.6 ± 9.1	
Final	18.5 ± 10.6	19.9 ± 14.7	17.2 ± 7.2	
Change	−2.9 ± 14.1	1.9 ± 16.4	−1.4 ± 13.2	
Total sugars, g				0.04
Baseline	107.0 ± 58.1	98.9 ± 75.8	88.7 ± 60.6	
Final	94.8 ± 50.8	81.6 ± 63.3	57.3 ± 20.2	
Change	−12.2 ± 53.3[a,b]	−17.4 ± 53.6[b,c]	−31.4 ± 61.9[a c]	
Added sugars, g				0.02
Baseline	80.5 ± 57.9	65.7 ± 89.5	62.0 ± 56.7	
Final	69.7 ± 47.7	56.4 ± 73.1	29.0 ± 21.5	
Change	− 9.6 ± 48.2[a,b]	−9.0 ± 45.3[b c]	−30.5 ± 56.8[a,c]	
Glycaemic load				0.20
Baseline	137.6 ± 54.3	124.7 ± 81.2	125.4 ± 66.7	
Final	121.2 ± 50.3	111.9 ± 83.2	88.8 ± 32.5	
Change	−16.4 ± 57.7	−12.7 ± 50.5	−36.6 ± 76.5	

*p value for the difference in change among the three groups determined by Kruskal-Wallis test.

[a]Mean change is significantly different between liraglutide and sitagliptin.

[b]Between liraglutide and caloric restriction.

[c]Between sitagliptin and caloric restriction.

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TABLE 4

Changes in appetite and food preference items by treatment group

Variable	Liraglutide, *N* = 44	Sitagliptin, *N* = 22	Caloric restriction, *N* = 22	*p* value*
Hunger				0.18
Baseline	5.2 ± 2.4	4.2 ± 2.2	3.9 ± 3.2	
Final	5.2 ± 2.5	5.7 ± 2.9	5.7 ± 2.7	
Change	0.1 ± 2.3	1.5 ± 2.9	1.8 ± 2.6	
Satisfied				0.22
Baseline	2.3 ± 2.3	3.0 ±2.1	2.5 ± 1.9	
Final	3.0 ± 2.3	2.7 ± 1.8	3.3 ± 2.4	
Change	0.7 ± 2.1	−0.3 ± 2.2	0.8 ± 2.6	
Fullness				0.33
Baseline	1.4 ± 1.8	2.4 ± 2.2	2.6 ± 2.5	
Final	2.9 ± 2.5	2.7 ± 1.7	2.4 ± 2.3	
Change	1.4 ± 2.4	0.3 ± 2.0	−0.2 ± 3.0	
Prospective consumption				0.15
Baseline	6.6 ± 2.1	4.9 ± 2.0	6.4 ± 2.3	
Final	5.6 ± 2.3	5.6 ± 2.4	6.1 ± 2.4	
Change	−0.9 ± 2.5	0.7 ± 2.7	−0.3 ± 2.3	
Desire for sweet foods				0.47
Baseline	5.5 ± 3.2	6.2 ± 2.8	7.2 ± 3.2	
Final	6.1 ± 2.8	5.6 ± 2.8	6.5 ± 3.1	
Change	0.6 ± 3.2	−0.6 ± 3.3	−0.8 ± 3.3	
Desire for salty foods				0.09
Baseline	4.7 ± 3.1	5.4 ± 2.6	5.2 ± 3.3	
Final	4.8 ± 2.8	5.9 ±2.6	3.8 ± 2.9	
Change	0.1 ± 3.0	0.4 ± 2.0	−1.4 ± 3.1	
Desire for savoury foods				0.84
Baseline	3.9 ± 2.7	4.0 ± 2.9	4.6 ± 3.5	
Final	3.8 ± 2.4	4.0 ± 2.7	3.9 ± 2.8	
Change	−0.2 ± 2.7	0.0 ± 3.2	−0.7 ± 1.4	

Variable	Liraglutide, $N = 44$	Sitagliptin, $N = 22$	Caloric restriction, $N = 22$	p value*
Desire for fatty foods				0.05
Baseline	5.5 ± 2.9	6.6 ± 2.6	5.6 ± 3.1	
Final	5.9 ± 2.6	6.2 ± 2.9	4.7 ± 2.7	
Change	0.4 ± 2.3	−0.4 ± 1.9	−0.9 ± 2.8	

* p value for the difference in change among the three groups determined by Kruskal-Wallis test.