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Pilot study to test the safety, tolerability and feasibility of dulaglutide during a low-energy diet for weight loss and improved glycaemic control

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ABSTRACT

Introduction Diabetes and obesity are significant public health concerns. Previous studies have demonstrated that low energy diets are effective in promoting weight loss and inducing diabetes remission. However, hunger is a potential barrier to adherence for such diets.
Dulaglutide is a glucagon-like peptide receptor agonist used in diabetes treatment. Its use is associated with weight loss, partly through increased satiety. The use of dulaglutide may improve adherence to a low energy diet through a reduction in hunger. We undertook a pilot study to assess the safety, tolerability and feasibility of this combination in individuals with obesity and type 2 diabetes.

Research design and methods We enrolled individuals with type 2 diabetes and obesity from a tertiary diabetes service in Auckland, New Zealand. Owing to their higher rates of diabetes and poorer diabetes-related health outcomes, we preferentially enrolled Māori and Pacific individuals.
Participants underwent 2 weeks of dulaglutide run-in followed by 12 weeks of the combination of dulaglutide and low energy diet. The primary endpoints were the proportion of people successfully completing the dietary intervention and the rates and types of adverse events. Secondary outcomes were changes in weight, glycaemic control, quality of life and biochemical parameters.

Results The intervention was well tolerated. Mild side effects were common during the first 2 weeks of the intervention but generally improved over the study period. Eighty-nine per cent of participants completed the 12-week dietary intervention. Participants achieved an average weight loss of 9.5 kg and a mean reduction in haemoglobin A_{1c} of 15.8 mmol/mol. Quality of life metrics were unchanged.

Conclusions We conclude that the combination of dulaglutide and a low energy diet is a feasible and well-tolerated intervention for individuals with diabetes and increased body weight. Future studies could be performed assessing this combination against a low energy diet alone.

Trial registration number This study was registered with the Australia New Zealand Clinical Trials Registry (ACTRN1262200015279p).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Diabetes and obesity are significant challenges to global healthcare systems. Low energy diets are effective tools for reducing body weight and improving glycaemic control but their widespread uptake is limited by the associated increase in hunger.

WHAT THIS STUDY ADDS

⇒ The combination of dulaglutide and a low energy diet is a well-tolerated and effective tool for weight loss and improved glycaemic controls in individuals with obesity and type 2 diabetes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this pilot study will be used to inform a randomised control trial comparing dulaglutide and a low energy diet with a low energy diet alone.

BACKGROUND

The global prevalence of obesity and type 2 diabetes mellitus (T2DM) have continued to increase in recent decades.[1] These closely linked conditions are associated with multiple adverse health outcomes, and affected individuals experience a lower quality of life and higher mortality rates.[2 3] Accordingly, the management of obesity and diabetes is one of the foremost issues facing healthcare systems.

Obesity is the most important risk factor for the development of T2DM,[4] increasing the risk of T2DM approximately 7-fold in men and 12-fold in women.[5] In people with a body mass index (BMI) greater than 50 kg/m^2, the rate of T2DM approaches 40%.[6] Weight loss is associated with improved glycaemic control, reduced cardiovascular events, improved quality of life and a reduction in mortality rates.[7] Sufficient weight loss by dietary, pharmacological or surgical means can lead to remission of T2DM.[7–9] Despite these potential benefits, only a minority of people with an increased BMI and T2DM achieve the 5% targeted weight loss recommended by the American Diabetes Association.[10 11]

Within New Zealand, Māori and Pacific people are disproportionately affected by obesity and T2DM, and face higher rates of significant diabetes-associated vascular

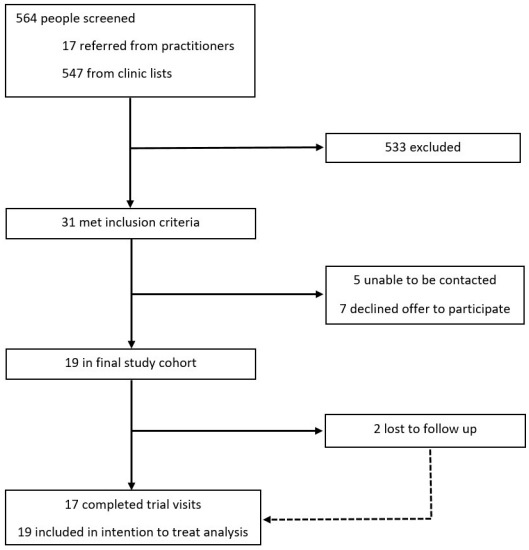

Figure 1 Cohort flow for participant enrolment.

complications.[12–16] There is interest in developing targeted interventions that might be effective in treating diabetes and obesity in these high-risk ethnic groups.

Low energy diets (LEDs) are a tool for managing obesity and diabetes. LEDs were demonstrated to be effective in the Diabetes Remission Clinical Trial, a 2018 study performed across multiple primary care centres in the UK. In the intervention arm, people with type 2 diabetes and obesity underwent total dietary replacement (TDR) with a LED of 825–853 kcal/day for 3–5 months.[8] In this group, mean body weight fell by 10.0 kg and diabetes remission was achieved in 46% of participants. This promising result was maintained on 2-year follow-up where 36% of the intervention cohort remained free of diabetes.[17] However, in real-world practice, there are barriers to the widespread adoption of LEDs in treating T2DM, including the increased hunger associated with caloric restriction.[18 19]

Dulaglutide is a once-weekly injectable glucagon-like peptide-1 receptor agonist used in the treatment of T2DM. Its use is associated with a modest reduction in body weight,[20 21] an effect which is in part mediated by increased satiety.[22–24] In New Zealand, dulaglutide is publicly funded for certain patients at high risk of cardiovascular events by the national Pharmaceutical Management Agency (PHARMAC) under Special Authority (SA) criteria.

While both LED and dulaglutide are used in treatment of T2DM, the combination has not previously been assessed. It is hypothesised that the satiety-promoting effect of dulaglutide may improve the acceptability and adherence to a LED. As such, the present study investigated whether TDR with a LED, in association with once-weekly self-administered dulaglutide, would be a feasible intervention to promote weight loss and glycaemic control without significant adverse events. The trial was designed with a particular emphasis on enrolling Māori and Pacific people.

METHODS

We conducted a single-arm, non-blinded pilot study assessing the tolerability and feasibility of the combination of dulaglutide and an LED in people with T2DM and an elevated BMI. The study was run from the tertiary diabetes service of Te Whatu Ora—Waitematā (formerly Waitematā District Health Board) based in Auckland, New Zealand.

Participant selection

Eligible participants were those with T2DM, aged 20–65 years, diagnosed with diabetes less than 6 years ago, had a BMI of 27–45 kg/m^2 and were eligible for publicly funded dulaglutide under PHARMAC SA criteria. All ethnicities were eligible, with preferential enrolment of Māori and Pacific people. Exclusion criteria were haemoglobin A_{1c} (HbA_{1c}) >108 mmol/mol, estimated glomerular filtration rate<30 mL/min/1.73 m^2, substance abuse, known malignancy, myocardial infarction or stroke in the preceding 6 months, heart failure, significant learning difficulties, diagnosed eating disorder, current treatment with anti-obesity medication, pregnancy or considering pregnancy, prior hospitalisation for depression, use of antipsychotic medication, participation in another research trial or taking a monoamine oxidase inhibitor. People who were already prescribed dulaglutide as part of routine clinical care were eligible to enter the trial.

Participants were sourced from the Te Whatu Ora—Waitematā outpatient diabetes service. Outpatient lists were systematically searched for all Māori and Pacific individuals seen by the diabetes service in the past 2 years. Furthermore, Te Whatu Ora—Waitematā diabetes practitioners were given information regarding the study and asked to refer individuals eligible to participate. Eligible individuals were then contacted by an investigator who provided information about the trial and extended an invitation to a group information session. The investigator was not involved in the routine diabetes care of any trial participant.

Study protocol

Participants were enrolled for 14 weeks; a 2-week dulaglutide 1.5 mg self-administered weekly run-in period (or continuing dulaglutide 1.5 mg weekly, if previously prescribed) without dietary modification, followed by 12 weeks of dulaglutide and LED. During the run-in, pre-existing oral hypoglycaemic agents and insulin were titrated based on baseline HbA_{1c} and capillary blood glucose recordings. Oral hypoglycaemic agents and insulin were ceased at the commencement of the LED and were reintroduced as required based on capillary blood glucose results (online supplemental appendix A).

The LED used products from the commercially available Cambridge Weight Plan. Participants underwent TDR with an allowance of 825 kcal/day using Cambridge Weight Plan products in addition to two cups of non-starchy vegetables and 2.25 L of water per day. Participants were instructed on the Cambridge Weight Plan by a diabetes dietitian with specific training in this LED. At commencement of the LED, all diabetes and blood

Table 1 Baseline participant information

Participants at enrolment (number)	19	
Ethnicity (number/percentage)		
European	2	11%
New Zealand Māori	5	26%
Pacific	10	53%
Other	2	11%
Age (years) (mean/SD)	40.2	11.0
Gender (number/percentage)		
Male	10	53%
Female	9	47%
Baseline key measurements (mean/SD)		
Weight (kg)	118.4	18.2
BMI (kg/m^2)	37.3	4.6
HbA_{1c} (mmol/mol)	70.7	21.2
Deprivation deciles (number/percentage)		
0–6	6	32%
7–8	6	32%
9–10	7	37%
Pre-existing diabetes duration (years) (mean/SD)	4	1.8

BMI, body mass index; HbA_{1c}, haemoglobin A_{1c}.

pressure-lowering medications were ceased. If required, these were reintroduced in a stepwise fashion based on prespecified guidelines (online supplemental appendices A and B). Participants continued to self-monitor capillary blood glucose once per day between trial visits. At the completion of the trial period, a dietitian supported transitioning back to normal eating.

Information sessions were offered in a group or individual format based on participant preference. These information sessions served as an initial trial visit for those who subsequently wished to enter the trial. Individuals could opt to enter the trial at this session or were able to consider the trial over subsequent days and delay or decline entry. At the initial visit, height, weight, waist and hip circumference, blood pressure, baseline blood and urine samples were collected. A pregnancy test was completed in women of childbearing age. Baseline health-related quality of life questionnaires were completed using the EuroQol 5 Dimension 5 Level (EQ-5D-5L) index (scored 0–1, with higher scores indicating better self-assessed health) and visual analogue scale (scored 0–100 with higher scores indicating better self-assessed health). Binge Eating Disorder Screener-7 questionnaires were also completed. Education on dulaglutide self-administration was provided. Following enrolment, a 2-week dulaglutide run-in period was commenced. Participants provided written informed consent prior to enrolment and all underwent the study intervention.

Participants had a total of 10 trial encounters—7 face to face and 3 by phone (online supplemental appendix C). At each contact, adverse events were determined (online supplemental appendix D) and capillary blood glucose records were reviewed. Weight, blood pressure and capillary blood glucose were measured at each face-to-face visit. In addition, the final visit included repeat measurements of waist and hip circumference as well as repeat blood and urine samples. Participants also completed a repeat EQ-5D-5L health-related quality of life questionnaire at trial completion. Ongoing diabetes medication management, including the option to continue with long-term dulaglutide, was discussed at trial exit.

Table 2 Adverse events arising during low energy diet (LED) and dulaglutide intervention phase

	Baseline		End of 2-week run-in		After 2-week LED		End of trial	
Number of participants reporting ≥1 symptom	**5**		**10**		**13**		**10**	
Symptoms reported	**N**	**%***	**N**	**%***	**N**	**%***	**N**	**%***
Nausea	2	10.5	7	36.8	3	15.8	0	0.0
Vomiting	1	5.3	1	5.3	0	0.0	0	0.0
Abdominal pain	2	10.5	4	21.1	2	10.5	0	0.0
Diarrhoea	3	15.8	5	26.3	6	31.6	0	0.0
Constipation	1	5.3	0	0.0	4	21.1	1	5.3
Dizziness	2	10.5	4	21.1	4	21.1	2	10.5
Heartburn	0	0.0	2	10.5	1	5.3	0	0.0
Headaches	2	10.5	5	26.3	3	15.8	3	15.8
Mood changes	2	10.5	3	15.8	2	10.5	1	5.3
Cold sensitivity	2	10.5	2	10.5	4	21.1	4	21.1
Hair loss	1	5.3	0	0.0	2	10.5	3	15.8
Fatigue	3	15.8	7	36.8	4	21.1	1	5.3
Total symptoms reported	21		40		35		15	

*Percentages calculated from total number of participants, not just of those reporting adverse effects.

Table 3 Enrolment and completion mean values, change in mean values and two-tailed significance

	Mean at enrolment	Mean at completion	Change in mean	P value
Weight (kg)	118.4	108.9	−9.5	<0.001
BMI (kg/m^2)	37.3	34.3	−3.0	<0.001
HbA_{1c} (mmol/mol)	70.7	54.9	−15.8	<0.001
Random blood sugar (mmol/L)	10.4	9.4	−1.0	0.403
Systolic BP (mm Hg)	139	137	-2	0.625
Diastolic BP (mm Hg)	86	84	-2	0.237
Cholesterol (mmol/L)	4.73	4.15	−0.58	0.027
Low density lipoprotein (mmol/L)	2.69	2.38	−0.31	0.162
Waist circumference (cm)	119.5	113.7	−5.8	<0.001
Hip circumference (cm)	117.8	113.1	−4.7	0.001
EQ-5D-5L—VAS	67.5	77.4	+9.9	0.073
EQ-5D-5L—Index	0.919	0.943	+0.025	0.312
Number of diabetes medications	2.47	1.32	−1.15	<0.05
Number of BP medications	0.95	0.42	−0.53	<0.05

BMI, body mass index; BP, blood pressure; EQ-5D-5L, EuroQol 5 Dimension 5 Level; HbA_{1c}, haemoglobin A_{1c}; VAS, visual analogue scale.

Deprivation was assessed using the 2018 NZDep index values for the areas where participants resided. This index assesses the deprivation of households within predefined small geographical areas, based on nine New Zealand census metrics. Deprivation data are presented as deciles for each area (scored 1–10, with 10 being the highest deprivation).[25]

Outcome measures

The primary outcome was the proportion of people who successfully completed the 12-week TDR phase. Secondary outcomes were the frequency and type of adverse events, occurrence of severe adverse events (defined as severity grade 3, or any instance of hospitalisation or death), changes in anthropometric parameters, changes in laboratory parameters, changes in EQ-5D-5L health-related quality of life scores, and the rates of discontinuation of antihypertensive and diabetes-related medications. The degree of observed weight loss, coupled with the frequency of trial discontinuation, may be used to inform sample size calculations for future trials investigating this trial combination.

Statistical analysis

Our sample size was based on the maximum number of people we could enrol within our cost and research personnel limitations. We aimed to enrol 20 participants. Baseline and adverse effect-related data were analysed via simple descriptive methods. Changes in measured characteristics of normally distributed data were compared using paired sample t-tests using baseline and final mean values. EQ-5D-5L health index values were calculated using New Zealand value set data.[26] Blood pressure-affecting medications were included in the pre-study and post-study counts even if prescribed for a non-blood pressure-related indication. Analysis was on an intention-to-treat basis, with missing data managed via a last observation carried forward single imputation method. Data were analysed using IBM SPSS Statistics for Windows, V.26.0.

RESULTS

In total, 564 people were screened for eligibility, 17 who were referred directly by their treating practitioners and 547 Māori and Pacific individuals identified from clinic list screening. Five hundred thirty-three people were excluded on review, largely due to their having a diabetes duration of more than 6 years. Of the 31 participants who met the inclusion criteria, 26 people were contactable to invite into the study. All 19 individuals who agreed to attend the information sessions elected to enter the trial. Figure 1 describes the cohort enrolment flow.

Baseline participant information is presented in table 1. The sample group was 53% male (n=10) with a mean age of 40 years. Māori and Pacific peoples made up 79% of the participants (5 Māori, 10 Pacific). Most participants were from high deprivation areas, with 68% (n=13) residing in areas with deprivation decile 7 or higher and more than one-third of participants (37%, n=7) residing in areas with deprivation decile 9 or 10. Participants had a mean pre-existing diabetes duration of 4 years and five participants were already established on dulaglutide at enrolment. Mean enrolment weight, BMI and HbA_{1c} were 118.4 kg, 37.3 kg/m^2 and 70.7 mmol/mol, respectively.

Of the 19 participants who entered the trial, 17 (89%) completed the full 14-week trial period and had results available for analysis. Two participants (11%) were lost to follow-up and no data were available regarding their reasons for discontinuation. No participants required hospitalisation or reported grade 3 adverse events of special interest (online supplemental appendix D). There was one significant event which was an episode of brief syncope while exercising in one participant. No dose adjustments were made to the prescribed dulaglutide and it was not discontinued in any participant.

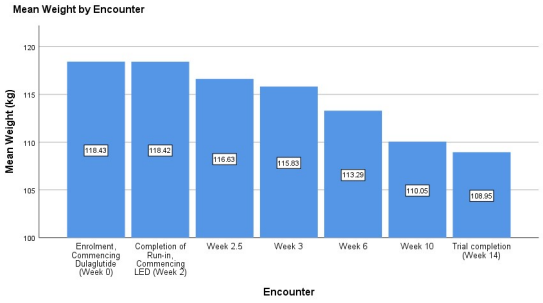

Figure 2 Mean weight (kg) by follow-up encounter. LED, Low energy diet.

At baseline, 5 participants reported a total of 21 symptoms of special interest, with diarrhoea and fatigue being the most common (both 15.8%). At completion of the dulaglutide run-in period, adverse events were reported by 10 participants, with 40 cumulative symptom reports at this stage. The most common symptoms were nausea (36.8%), fatigue (36.8%), diarrhoea (26.3%) and headaches (26.3%). No individuals required lengthening of the run-in period due to dulaglutide side effects. While the same number of participants reported symptoms at the end of the trial, the total number of symptoms reported reduced to 15. The most commonly reported adverse events at the end of the trial were cold sensitivity (21.1%), headaches (15.8%), fatigue (15.8%) and dizziness (10.5%). There were no instances of hypoglycaemia encountered. Table 2 summarises adverse events recorded during the trial.

There was no significant weight loss seen during the 2-week dulaglutide run-in (p=0.991). However, there was a significant reduction in mean weight (9.5 kg, 8.0%, p<0.05) observed by the end of the trial (table 3). Accordingly, a significant decrease in average BMI was also observed by the end of the trial (mean decrease 3.0 kg/m^2, p<0.05). Figure 2 describes the mean weight values and trend across each in-person trial visit. Figure 3 is a waterfall plot of weight change by individual participant.

Significant reduction in HbA_{1c} (15.8 mmol/mol, p<0.05) and number of diabetes medications (1.15, p<0.05) were seen by completion of the trial (table 3). No significant differences in systolic and diastolic blood pressures were demonstrated at completion (p=0.625 and 0.237, respectively) though the average number of blood pressure medications being used reduced by 0.53 (p<0.05). EQ-5D-5L index and visual analogue scores increased but these changes did not reach statistical significance. There were significant reductions in cholesterol, LDL, waist circumference and hip circumference (table 3).

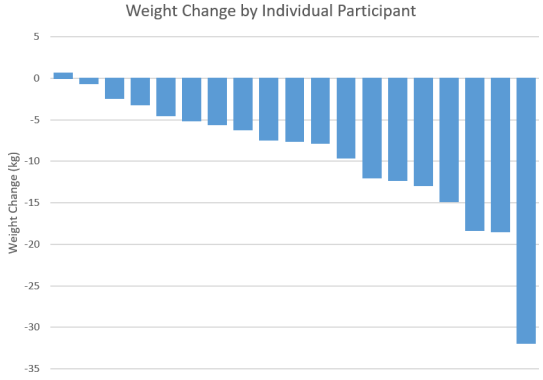

Figure 3 Waterfall plot of weight change by individual participant.

DISCUSSION

This pilot study examined the feasibility of concurrent LED and weekly dulaglutide administration as an intervention to promote weight loss and improve glycaemic control in people with obesity and T2DM of less than 6 years duration. Importantly, the pilot included individuals from high-risk ethnic groups who resided in areas of high deprivation. Our findings indicate that the combination of dulaglutide and an LED was well tolerated in this population and warrants further investigation.

The primary areas of interest for the present study were safety and tolerability endpoints. We observed a high rate of trial completion with one significant adverse event and no admissions to hospital. Minor adverse events were frequent at dulaglutide initiation but these decreased with time. Health-related quality of life did not significantly change.

In addition to these promising safety data, we also demonstrated significant reductions in body weight, with a mean weight loss of 9.5 kg over the trial period. Accordingly, significant reductions in BMI, waist circumference and hip circumference were also seen. Significant improvements in glycaemic control were demonstrated, with average HbA_{1c} falling by 15.8 mmol/mol and the average number of diabetes medications used decreasing by 1.15. While systolic and diastolic blood pressure values did not change, the average number of antihypertensive medications required saw a significant reduction.

This study has potential limitations for consideration. First, there was a small sample size with no comparator group, meaning limited conclusions may be drawn about the efficacy of individual components of the intervention. Second, only short-term follow-up data are available. Weight regain can be seen following a period of weight loss[27] and longer term follow-up would be valuable to assess the durability of the response observed. It is not known whether the continued use of dulaglutide may be protective against this. Third, we did not formally assess adherence to the LED. However, this reflects real-world practice and may increase the generalisability of our findings. Fourth, we were not able to contact two participants to ascertain their reasons for leaving the trial meaning adverse events may be under-reported. Finally, the trial protocol was inflexible with regards to culturally important food sharing and future interventions should incorporate this into their design.

The key strength of this study was the active recruitment of a high-risk population for whom effective and acceptable weight loss interventions are needed. Additionally, we have confidence in the recorded rates and types of systematic

events based on their frequent and systematic screening. We also recorded high rates of data completeness for individuals who completed the 14-week intervention.

The results of this pilot study could inform a future trial comparing the combination of dulaglutide and LED versus LED alone in people with diabetes and increased body weight.

CONCLUSION

The combination of TDR via an LED and weekly dulaglutide administration represents a novel intervention to promote weight loss and improve glycaemic control in high-risk groups with pre-existing obesity and T2DM. This pilot study has demonstrated an acceptable safety profile of this combination. Significant weight reduction and diabetes-related improvements were seen, although no inference can be drawn on any additional benefit of dulaglutide over a LED alone. These data may be used to inform larger scale clinical trials investigating this combination regimen.

Contributors CP and SY were responsible for the concept. CP, SY and JADS prepared the protocol. CP, SY and JADS arranged ethics approval. JADS and FV conducted study visits. JADS and FV analysed the data. All authors were responsible for the final manuscript. JADS is the guarantor of the data.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Ethics approval was granted by the National Health and Disability Ethics Committee (approval number 11506). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed by Lei Qian, Innoventbologics Clinical Development, Shanghai, China.

Data availability statement Data are available upon reasonable request.

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APPENDICES

APPENDIX A: Protocol for re-introduction of blood glucose lowering medications

Blood glucose levels were monitored by participants and reviewed at each trial contact. Insulin and oral hypoglycaemic agents were adjusted as outlined below. This protocol is based on guidance published by Baldry et al in 2020 (28).

Oral hypoglycaemic agents

- At the commencement of dulaglutide, sulphonylurea dose was reduced by 50% if HbA_{1c} < 75mmol/mol
- At the commencement of dulaglutide, DPP-IV inhibitors were ceased
- All oral hypoglycaemic agents were ceased at the commencement of LED
- If BSL >7mmol/L for 7 consecutive days or >10mmol/L for 3 consecutive days, agents were reintroduced in the following order:
  1. Metformin
  2. SGLT2 inhibitor
  3. Sulphonylurea, pioglitazone or basal insulin

Insulin

- At time of initiating dulaglutide, the insulin total daily dose was reduced by 20%
- At the initiation of LED, insulin was ceased
- If insulin reintroduction was required, dosing decisions were made at the discretion of the responsible investigator

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APPENDIX B: Protocol for re-introduction of blood pressure lowering medications

Antihypertensives were stopped at the initiation of the low energy diet except if prescribed for another indication. The blood pressure (BP) was measured at each face-to-face study visit. For ease, only the systolic BP was considered when making decisions regarding medication reintroduction. If the systolic BP was >165mmHg in the first two weeks of the LED or >140mmHg thereafter, antihypertensives were reintroduced according to the order of reintroduction below. Doses were increased to achieve target BP before another agent was added.

Order of reintroduction of previously used drugs

1. Angiotensin converting enzyme inhibitor
2. Angiotensin receptor blocker
3. Thiazide type
4. Spironolactone
5. Calcium channel blocker
6. Beta blocker
7. Alpha blocker
8. All other

APPENDIX C: Overview of Study Visit Protocol

Week 0	***Week 2***	***Week 2.5***	***Week 3***	***Week 4***	***Week 6***	***Week 8***	***Week 10***	***Week 11***	***Week 14***
In-person	In-person	In-person	In-person	By phone	In-person	By phone	In-person	By phone	In-person
Group or individual information session. Enrolment and consent Baseline QoL, anthropometric and laboratory measures Education and commence dulaglutide Titration of diabetes medications Cease BP medications	Completion of dulaglutide run-in Commence LED Cease remaining diabetes medications Measure weight, BP, and BSL Adverse event screen (pre-determined and/or other)	Measure weight, BP, and BSL Adverse event screen (pre-determined and/or other)	Measure weight, BP, and BSL Adverse event screen (pre-determined and/or other)	Adverse event screen (pre-determined and/or other)	Measure weight, BP, and BSL Adverse event screen (pre-determined and/or other)	Adverse event screen (pre-determined and/or other)	Measure weight, BP, and BSL Adverse event screen (pre-determined and/or other)	Adverse event screen (pre-determined and/or other)	Trial completion Adverse event screen (pre-determined and/or other) Final QoL, anthropometric, and laboratory measures Discuss ongoing diabetes medication plan (Dietitian follow-up after trial completion)
General feedback collected, respond to arising concerns, reviewing diet adherence									
Diabetes and blood pressure medication review and/or re-introduction and/or titration									

APPENDIX D: Events of special interest, medical events and hospitalisation

At each visit, adverse events were systematically screened for using the below form. All adverse events were graded 0-3 in severity.

Grading System

0 = Not present
1 = Mild (no real interference with daily activities)
2 = Moderate (occasional/minor interference with daily activities)
3 = Severe (frequent/constant/marked interference with daily activities)

Appointment	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	**0 (Group Visit)**	**2**	**2.5**	**3**	**4**	**6**	**8**	**10**	**12**	**14**
Nausea										
Vomiting										
Abdominal pain										
Diarrhoea										
Constipation										
Dizziness										
Heartburn/Indigestion										
Headache										
Mood changes										
Sensitivity to cold										
Hair loss										
Fatigue										