A very-low-calorie diet (VLCD) intervention for the management of prediabetes and early Type 2 diabetes mellitus in a multi-ethnic cohort in Aotearoa New Zealand: The PROGRESS NZ feasibility study

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ABSTRACT

Background and Objectives: Very-low calorie diets (VLCD) achieve weight loss and remission of Type 2 diabetes (T2DM), but efficacy and acceptability in non-European populations is less clear. This feasibility study examines the impact of 10% weight loss through VLCD on metabolic and body composition outcomes in a multi-ethnic cohort of Aotearoa New Zealand (AoNZ) men with prediabetes/early T2DM, and VLCD tolerability/cultural acceptability. **Methods and Study Design:** Participants followed a VLCD intervention (mean energy 3033kJ/day) until achievement of 10% weight loss. OGTT, hyperinsulinaemic isoglycaemic clamp with stable isotopes, hood calorimetry and DXA were undertaken before and after intervention. Qualitative data on VLCD tolerability/cultural acceptability were collected. **Results:** Fifteen participants were enrolled; nine achieved 10% weight loss. In this group, mean HbA1c reduced by 4.8mmol/mol (2.4-7.1) and reverted to normoglycaemia in n=5/9; mean body weight reduced by 12.0 kg (11.0-13.1) and whole-body glucose disposal improved by 1.5 mg kgFFM-1 min-1 (0.7-2.2). Blood pressure and fasting triglycerides improved significantly. No changes in hepatic glucose metabolism were found. In all participants who attended completion testing, HbA1c reduced by 3.4mmol/mol (SD 3.5) and total weight by 9.0kg (SD 5.7). The intervention was highly tolerable/culturally acceptable however challenges with fulfilment of cultural obligations were described. **Conclusions:** Results support VLCD use in AoNZ however further work to investigate ethnic differences in physiological response to VLCDs and to optimise protocols for multi-ethnic populations are required.

Key Words: VLCD, very-low calorie diet, Type 2 diabetes, prediabetes, New Zealand

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a leading cause of morbidity and mortality worldwide. In the Western Pacific region, an estimated 206 million individuals are living with diabetes.[1] In Aotearoa New Zealand (AoNZ), rates of T2DM and associated complications are highest amongst Māori, Pacific and South Asian populations.[2] NZ Māori, the Indigenous tangata whenua [people of the land] of AoNZ, are nearly three times as likely to develop T2DM than NZ European peoples; have greater micro- and macro-vascular complications, with onset at a younger age; and have two times greater rates of cardiovascular and all-cause mortality.[3,4] Likewise, Pacific and South Asian people have greater rates of prediabetes and progression to T2DM than the NZ European population.[5] The drivers of inequities in outcomes for

individuals with T2DM are many; interventions which seek to reduce these disparities are urgently required.

Lifestyle interventions may slow progression of prediabetes to T2DM and improve outcomes in established T2DM.[6] However, lifestyle interventions based on 'Western' dietary and exercise concepts may be less effective in non-European populations,[7] and may not take into account the socio-cultural context of health and wellbeing for Indigenous populations.[8] There is increasing interest in the use of very low-calorie diets (VLCD) for diabetes management. The DiRECT study reported remission of T2DM in 86% of participants who lost 15kg body weight, and 46% of all participants at 12 months after VLCD use.[9]

A major limitation of VLCD research is lack of ethnic diversity amongst participants. Over 98% of participants in the DiRECT study were of European ethnicity. Generalisability to more diverse populations, including those in the Western Pacific, is largely unknown. Limited small studies report improvements in glycaemic control after VLCD use in non-European participants;[10-12] very few have explored cultural acceptability or tolerability. In one study from Barbados, cultural expectations in social situations and negative associations with rapid weight loss were identified as barriers to successful VLCD implementation in individuals with T2DM.[11]

To date, no published reports explore the feasibility of a VLCD intervention in the multi-ethnic AoNZ context. The PROGRESS NZ study was designed to assess the efficacy and feasibility of a VLCD intervention in NZ Māori, Pacific, South Asian and European New Zealanders with prediabetes and early T2DM. The specific aims of this study were to explore metabolic responses to a VLCD after achievement of 10% weight loss, and to explore the tolerability and cultural acceptability of the intervention, to inform the design and power calculations for larger-scale research in this area.

MATERIALS AND METHODS

Trial design

The PROGRESS NZ study was a cohort study assessing the effects of a VLCD Optifast diet in a multi-ethnic group of New Zealand men with prediabetes or early T2DM. The impact of 10% weight loss, through VLCD, on in-depth markers of glucose metabolism and body composition was assessed. Measurements were taken at baseline and after achievement of 5% and 10% weight loss. Tolerability, adherence and cultural acceptability of the intervention was assessed.

Data collection was performed at the Centre for Translational Physiology (Whaiaroaro Whakawhiti), University of Otago, Wellington after obtainment of full written informed consent. The study was approved by the Central Health and Disability Ethics Committee (Ethics reference 16/CEN/143) and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000146392).

Study participants

Males aged 18 to 65 years, with a BMI of ≥27kg/m^2 and a diagnosis of prediabetes or early T2DM were recruited. Early T2DM was defined as T2DM within 5 years of diagnosis, untreated with oral/subcutaneous medication or insulin. An HbA1c between 41-60mmol/mol within the preceding three months was required for inclusion. Participants were included if they self-identified as NZ Māori, Pacific, South Asian, or NZ European and had at least three grandparents of same ethnicity.

Exclusion criteria included diagnosis of unstable cardio-respiratory disease or obstructive sleep apnoea. Use of glucocorticoids for longer than 7 days in the preceding three months; weight change of >5kg within the preceding three months or individuals unable to partake in any protocol component were also exclusions.

Intervention

All participants underwent a VLCD using Optifast (Nestlé Health Science, Switzerland) meal replacement shakes (total energy 2523 – 2987 kJ; protein 57.6-60 g; carbohydrate 54.6–70.2 g, fibre 10.8-14.4 g per day) plus two cups of non-starchy vegetables and one teaspoon of olive/canola oil. Participants were provided with all shakes, alongside instructions and vegetable recipe suggestions, culturally tailored to their ethnic backgrounds. Shakes were purchased by the investigators; no funding was provided by Nestlé.

Participants were contacted weekly during the diet for a semi-structured telephone interview to record experience and monitor weight. Side-effects were documented and small dietary adjustments were made as required, including increased fibre intake and water consumption to alleviate constipation. Participants weighed themselves weekly at home to calculate percentage weight loss from baseline. Achievement of 5% and 10% weight loss was validated using research facility scales prior to study investigations.

Clinical assessments and measurements

Participants presented to the research facility on five occasions (Figure 1) with two visits at baseline, one after 5% weight loss achieved and two after 10% weight loss achieved. Individuals who remained in the study but failed to reach target 10% weight loss were invited to attend for completion testing. Visits occurred after a 10-hour overnight fast; participants were instructed to avoid unusual exercise or alcohol for 24-hours prior.

Body composition

Height (m), weight (kg), BMI (kg/m^2), waist circumference (WC, cm), hip circumference (HC, cm) and blood pressure (mmHg) were recorded. Total fat and lean mass and estimated visceral adipose tissue (VAT) were assessed by dual-energy x-ray absorptiometry (DXA; Hologic Horizon A (Malborough, USA)). All measurements were completed at baseline and after 10% weight loss, with weight and BMI also recorded after 5% weight loss.

Hood calorimetry

Resting energy expenditure was measured via indirect calorimetry (Promethion (Sable Systems, USA)) at baseline and after 10% weight loss.

Glucose metabolism assessments

A hyperinsulinaemic isoglycaemic clamp (HIC) with [6'6'-2H2]-glucose isotope enrichment for assessment of whole-body and hepatic insulin sensitivity was undertaken at baseline and after 10% weight loss. An 18 g cannula was inserted in the right antecubital fossa for glucose infusions and a 20-22 g cannula in the dorsum of the left hand for phlebotomy. This hand was placed in a 50°C hand warmer to arterialise blood. Two baseline samples were taken for fasting plasma glucose and insulin, ten minutes apart. A bolus of 10% [6'6'-2H2]-glucose solution was administered intravenously (volume 0.6 x fasting plasma glucose (mmol/L)) followed by a 270-min continuous infusion of 10% dextrose, 2% enriched with [6'6'-2H2]-glucose at a rate of 0.04mg kg-1 min-1 for isotope enrichment. Blood samples for plasma glucose, insulin and [6'6'-2H2]-glucose were taken at 10-minute intervals from -40 min until 0min for basal isotope analysis. Following 150 minutes of enrichment, a primed continuous insulin infusion (40 mU m-2 BSA min-1) was administered for 120 min for assessment of whole-body and hepatic insulin sensitivity. Body surface area (BSA) was calculated using the Mosteller equation. A variable rate infusion of 10% dextrose with 2% isotope enrichment was administered to 'clamp' whole blood glucose at the fasting glucose concentration (isoglycaemia) with infusion rate determined by bedside whole blood glucose concentration

measured every five minutes. Blood samples were taken at 0, 60, 80, 100 and 120 min for plasma glucose and insulin, and at 0, 100, 110 and 120 min for [6'6'-2H2]-glucose.

Participants completed an oral glucose tolerance test (OGTT) at baseline and after achievement of 5% and 10% weight loss. Baseline blood samples were taken for plasma glucose and insulin, fasting lipids and HbA1c. After ingestion of a 75g Carbotest liquid glucose solution (Fronine, Thermo Fisher Scientific, Victoria, Australia), blood samples were taken at 30, 60, 90 and 120 min for plasma insulin and glucose.

Physical activity

An International Physical Activity Questionnaire (IPAQ long form) was undertaken at baseline and after 10% weight loss to estimate physical activity.[13]

Adherence

Self-reported compliance with the VLCD was measured through quantification of Optifast sachets consumed per week, and days of ingestion of non-prescribed foods per week. Urinary ketones were measured at each study visit.

Qualitative data

Participants were invited to complete a questionnaire regarding study experiences (REDCap, Vanderbilt, USA). VLCD tolerability and cultural acceptability was assessed via Visual Analogue Scales (VAS), marked from 0-100. Free-field boxes invited participants to provide additional information and suggest improvements. Questionnaires were completed during study visits on a research iPad with technical assistance provided as required.

Sample analysis

Whole blood HbA1c and lipids were analysed using a point-of-care analyser (cobas b 101, Roche Diagnostics, Basel, Switzerland). Urinary ketones were measured by urine ketone dipstick (Ketostix, Bayer Leverkusen, Germany).

Plasma glucose was analysed by hexokinase method using a Roche c311 chemistry analyser (Roche Diagnostics, Basel, Switzerland). Plasma insulin, adiponectin and leptin were analysed by solid-phase sandwich ELISAs (R&D Systems, Minneapolis, USA). [6'6'-2H2]-glucose was analysed by gas chromatography – mass spectrometry (GCMS) using an Aligent 5975C inert XL EI/CI MSD GCMS System (Aligent Technologies, Wokingham, UK) at the

School of Biosciences at the University of Surrey, UK. All other analyses were undertaken at the University of Otago, Wellington.

Calculations

Whole-body insulin sensitivity (M value) was calculated during the final 30 min of the HIC as described by DeFronzo et al.[14] M value was expressed per kg fat free mass (mg kgFFM-1 min-1) with correction for glucose space. To account for differences in fasting plasma glucose across the study, the glucose metabolic clearance rate (MCR) was calculated by dividing the M value by mean plasma glucose during the final 30 min of the clamp (M/(Glucosemean x 0.18). The modified Steele's equation was used to calculate total rate of glucose appearance (total Ra; μmol kgFFM-1 min-1).[15-16] Endogenous glucose production (EGP) was calculated from Ra at baseline (Endo RaBL, μmol kgFFM-1 min-1) and by the subtraction of the glucose infusion rate from total Ra during the final 30 min of the clamp (Endo RaClamp, μmol kgFFM-1 min-1). Hepatic insulin sensitivity was expressed as percentage suppression of EGP during the final 30 min of the HIC as compared to baseline.

The Matsuda Index was from OGTT results as described by Matsuda et al.[17] Insulinogenic index (IGI) was calculated using the formula ((I_30-I_0))/((G_30- G_0)*18. Disposition index (DI) was calculated as the product of the Matsuda Index and IGI.18 HOMA2-IR and HOMA2-β were calculated using the Diabetes Trials Unit, University of Oxford calculator (HOMA Calculator, v2.2.3, Oxford, UK).

Statistical analyses

Quantitative data are presented for those who achieved 10% weight loss (10%WL group) and for all participants. For participants in the 10%WL group, continuous outcome measures were compared by a paired t-test. Logarithm transformation was used for analysis of known non-normally distributed variables (fasting insulin; fasting triglycerides; HOMA2-IR). For all other variables, estimation was based on t-tests on the scale of measurement. Comparisons are shown with 95% confidence intervals for point estimates.

Qualitative data are presented for all participants. Questionnaire data were analysed using a combination of descriptive statistics and thematic analysis.

All statistical analyses were undertaken using RStudio v 4.0.5 (RStudio, PBC, Boston, USA).

RESULTS

Recruitment

A flow-chart of participant recruitment is shown in Figure 2. One hundred and nineteen individuals completed an online Expression of Interest (EOI). Where ethnicity information was available (n= 80/119), 19% identified as NZ Māori, 19% as Pacific, 21% as South Asian and 37% as European, and 4% of other ethnicity. Of the 119 EOIs, 25 individuals were eligible for inclusion. Ten declined study involvement after screening: seven were unable to make the time commitments; one had family commitments; one felt the investigations were too invasive and one was vegan and unable to have Optifast.

Fifteen participants were enrolled and had baseline study visits. An OGTT was undertaken in all 15, however one participant was excluded from some OGTT analysis due to sample degradation affecting plasma insulin results. All 15 participants commenced the VLCD with planned assessment at 5% and 10% weight loss; one participant withdrew from the study within two weeks due to family commitments.

Ten participants (71%) achieved 5% weight loss; four participants (29%) described difficulties with adherence and did not achieve target weight loss. All 10 participants proceeded to the 5% weight loss OGTT however one participant was excluded from some analysis due to sample degradation affecting plasma insulin results. One participant withdrew after the 5% weight loss visit due to a medical event.

Nine participants (69%) achieved 10% weight loss (10%WL). All completed the post-VLCD investigations. The four participants (31%) who failed to reach 10% weight loss and remained in the study attended completion testing.

Stable isotope data were available for 5/9 participants in the 10%WL group; data for the other four were not included due to challenges with infusate mixing or failure to achieve isotope steady-state during sample collection.

Participants

Baseline characteristics of study participants are described in Table 1. 10% weight loss was achieved in 3/5 NZ European, 4/5 South Asian, 1/1 NZ Māori and 1/4 Pacific participants. Mean baseline HbA1c was lower in the 10%WL group than for all participants.

10%WL group

Impact of the VLCD on glucose metabolic outcomes

Impact of the VLCD on metabolic outcomes is described in Table 3. Of note, in the 10%WL group, whole-body insulin sensitivity improved with a mean change in M value of 1.5 mg kgFFM-1 min-1 (95% CI 0.7, 2.2; p=0.002) and MCR of 1.5 mL kgFFM-1 min-1 (95% CI 0.3, 2.7; *p*=0.02). Where stable isotope testing data were available, there were no statistically significant differences in basal EGP (EndoRaBL) or percentage suppression EGP (Table 4).

HbA1c reduced by a mean of 4.8 mmol/mol (95% CI 2.4, 7.1; *p*=0.002). HbA1c reverted to the normoglycaemic range (≤40 mmol/mol) in 5/9 (56%) and improved into or within the prediabetes range for the remainder. Fasting insulin reduced after 5% and 10% weight loss. No statistically significant difference in fasting plasma glucose was seen. Matsuda Index and HOMA2-IR improved with 5% and 10% weight loss.

Impact of the VLCD on body composition

The impact of the VLCD on body composition is described in Table 5. Of note, total body weight reduced by a mean of 7.5 kg (95% CI 5.8, 9.2; *p*=6.16E-06) after 5% weight loss and 12.0 kg (95% CI 11.0, 13.1; *p*=4.68E-09) after 10% weight loss. BMI reduced by a mean of 2.3 kg/m^2 (95% CI 1.9, 3.4; *p*=0.004) after 5% and 3.9 kg/m^2 (95% CI 3.5, 4.3; *p*=2.7E-08) after 10% weight loss.

Impact of the VLCD on other metabolic outcomes

The impact of the VLCD on other metabolic outcomes is described in Table 3. Of note, there was a statistically significant reduction in systolic BP of 12.4 mmHg (95% CI 5.3, 19.6, *p*=0.01). Fasting triglycerides reduced significantly.

All participants

All data are presented as mean (SD) and are depicted in Tables 3 and 5. In all participants who proceeded to end of intervention testing, including those who did not achieve 10% weight loss, mean HbA1c reduced by 3.4 (3.5) mmol/mol. HbA1c improved for all bar one participant. M value increased by 1.3 mg kgFFM-1 min-1.

Total weight reduced by 9.0 (5.7) kg and BMI by 2.9 (1.9) kg/m^2. Systolic BP reduced by 10.9 (7.9) mmHg and fasting triglycerides reduced by 0.5 (0.6) mmol/L.

Adherence

Time to 5% and 10% weight loss visit for those who did and did not achieve weight loss targets are described in Table 2.

Adherence is described in Table 6. The 10%WL group self-reported ingestion of a mean (SD) of 21.6 (4.2) Optifast sachets/weeks compared to 19.1 (6.4) for all participants. Sachet ingestion was higher in the first four weeks of the diet as compared with the final four weeks of the diet. The 10%WL group ingested non-prescribed foods on a mean (SD) of 2.6 (1.3) days per week as compared to 3.1 (1.3) for all participants. Ingestion of non-prescribed foods was lower during the first four weeks of the diet as compared with the final four weeks of the diet.

Adverse effects

The total prevalence of self-reported adverse effects is described in Table 7, calculated as a proportion of total participants. Adverse effects were more common in the first four weeks than the final four weeks of the intervention and were more common in the 10%WL group.

Tolerability and Cultural Acceptability of the VLCD intervention

Tolerability and cultural acceptability of the VLCD dietary intervention was determined by VAS. Mean (SD) tolerability was 83.6% (31.7) with cultural acceptability 89.0% (20.7).

Several participants described experiencing symptoms in the first week of the diet. For most, symptoms resolved as they continued the intervention. “At first the diet was quite difficult as my body adjusted…I then enjoyed the shakes and found it sustainable”. Some participants described improvements in overall wellbeing during the VLCD. “I felt balanced internally. I had more energy. I slept better. I dealt with work-related stress better.”

Some participants identified difficulties with the VLCD in their day-to-day lives. Using the shakes while travelling or on the road for work was difficult, whilst others mentioned challenges during social situations.

Whilst the diet was deemed culturally acceptable, some participants experienced an impact on ability to fulfil cultural obligations. One Pacific participant observed that “Some cultural events required me as a community leader to sit on the front table. Food was presented to me…it is disrespectful not to eat that food. In those circumstances it was awkward.” The NZ Māori participant noted “I avoided going to the marae [meeting house] because I was concerned I would overeat. Tell people not to go to the marae!”

Participants suggested areas for improvement to the protocol. Some suggestions focused on improving the taste and variety of allowable foods. For others, provision of shakers to prepare the drinks was requested. Some participants cited constipation as a major area for improvement. Greater support with compliance and emotional wellbeing whilst on the diet was identified by one participant: "Provide more guidance on how to bounce back from setbacks".

DISCUSSION

In this multi-ethnic cohort of New Zealanders with prediabetes and early T2DM, 10% weight loss with VLCD use was achievable, culturally acceptable and associated with favourable improvements in metabolic and body composition parameters. Improvements were sustained when including participants who did not achieve target weight loss.

Glucose metabolism

Achievement of 10% weight loss was associated with a nearly 5mmol/mol reduction in HbA1c. Whilst a greater reduction in HbA1c of 9.3 mmol/mol was noted in the DiRECT study, results are not directly comparable due to the higher baseline HbA1c and 12-month follow-up in that cohort.9 To our knowledge, only one study has assessed HbA1c after VLCD in prediabetes or impaired fasting glucose.[19] In that study, HbA1c improved by only 2.1 mmol/mol after an 8-week VLCD, but mean baseline HbA1c was 36.7 mmol/mol, a lower HbA1c than the threshold for diagnosing prediabetes in AoNZ. Findings in the present study are comparable to the only other published study employing a VLCD in an AoNZ cohort. Chong et al (2020) reported a reduction in HbA1c of 4.9mmol/mol after mean weight loss of 7.2 kg in participants with non-alcoholic fatty liver disease who followed a brief VLCD prior to inulin or metronidazole supplementation.[20]

The reduction in HbA1c of 4.8 mmol/mol in the 10%WL group and of 3.4mmol/mol in all participants is clinically significant. The Diabetes Prevention Program Outcomes Study demonstrated a 56% reduction in risk of developing T2DM amongst participants who reverted to normoglycaemia, compared with those with persistent prediabetes.[21] Reversion to normoglycaemia occurred in 5/9 (56%) of the 10% WL group and improved within the prediabetes range for the remainder. These results, if reproduced in a larger sample, suggest VLCD as a viable option for the reversal of prediabetes and prevention of T2DM and its complications in AoNZ populations.

Whole body insulin sensitivity and MCR glucose improved significantly for the 10%WL group. In contrast, whilst data are only available in a subset of participants, no significant improvement in hepatic insulin sensitivity, determined by percentage suppression of EGP, was seen.

Studies investigating physiological changes in glucose metabolism after VLCD use consistently demonstrate early and significant reductions in basal EGP, in cohorts with,[22-24] and without diabetes.[25] In the Counterpoint study, a rapid increase in insulin suppressibility of hepatic glucose output from 43±4% to 74±5% after 8 days of a VLCD was described.[22] After continuation of the diet for eight weeks, improvements in hepatic insulin sensitivity remained and additional improvements in first-phase and maximal insulin secretion were described.

Absence of significant alteration in hepatic insulin sensitivity in the present work is therefore of interest, correlating with the lack of improvement in fasting glucose. Due to the sample size, no real conclusions about changes in hepatic insulin sensitivity post VLCD in this population can be reached. Nevertheless, if a true finding, the possible physiological explanations are worth exploring in the context of the ethnic diversity of the AoNZ populations. All VLCD studies undertaking assessment of EGP have involved cohorts with T2DM; these participants may have had greater capacity for improvement in hepatic insulin sensitivity due to more advanced derangements in hepatic glucose metabolism. However, baseline EndoRa in the present study was slightly greater than that described in the Counterpoint study in participants with T2DM.[22]

The relatively similar EGP in this cohort with prediabetes to published T2DM cohorts may be explainable in part by the significant representation of South Asian participants. Basal EGP and hepatic fat are demonstrated to be greater in South Asian than European populations across the glycaemic spectrum.26,27 Whether there are ethnic differences in EGP amongst NZ Māori and Pacific populations is unknown. It is possible that the multi-ethnic background of our cohort contributed to a reduced hepatic response to the VLCD. The impact of VLCDs on EGP in South Asian populations is poorly understood. The feasibility of a 3-5 month VLCD in a South Asian population with T2DM in the UK was recently explored.[12] Diabetes remission rates were comparable to that of the DiRECT European cohort, however rates of reduction in liver fat were slightly lower. In Bakker et al (2015), South Asian and European participants underwent an 8-day VLCD intervention. South Asian participants had greater hepatic insulin resistance at baseline, and whilst EGP improved to a similar extent in both groups, overall hepatic resistance remained higher in the South Asian cohort.[27] The significance of this on hepatic insulin sensitivity after a longer VLCD intervention is unclear

but could be argued to contribute to the relatively reduced improvements in basal EGP in the present study, if a true finding.

In that study, Rd improved in the South Asian population only, through non-oxidative glucose disposal and increased insulin-induced activation of the skeletal muscle mTOR pathway.[27] Whole-body insulin sensitivity and MCR glucose also improved significantly in the present study. Interestingly, a variable effect of VLCD interventions on whole-body glucose disposal has been described in the literature, with improvements seen in some,[24, 28-31] but not other studies.[22-23, 25] Given these findings, it is feasible that differences in metabolic adaptations to VLCD by ethnicity may exist and warrants larger sample investigation.

HOMA2-β significantly reduced with 5% and 10% weight loss in our study, and there was a trend towards improvement in IGI and DI. These changes suggest improvements in glucose-mediated insulin secretion in the setting of reduced whole-body insulin resistance. Whilst a lower HOMA2-β may be representative of poorer β-cell function, in this context, the reduction would be expected due to the significant reduction in fasting insulin and corresponding absence of alteration in fasting glucose. This finding is consistent with other literature on VLCDs in prediabetes.[32]

Body composition

After 10% weight loss, total body weight reduced by 10.5% and BMI by 10.5%. The degree and timing of weight change is comparable to meta-analysis data of VLCD use in T2DM, suggesting no appreciable differences in the effect of VLCD on weight loss in the AoNZ context.[33] Whilst degree of weight loss and reduction in BMI in the 'all participants' group was lower (5.7% and 6.3% respectively), 5% weight loss remains clinically meaningful and improves cardiometabolic and glycaemic outcomes.[34] The clinically significant reductions in HbA1c, fasting triglycerides and systolic and diastolic BP in this group are consistent with this observation. Achievement of this degree of weight loss with reduced VLCD adherence is significant and suggests a role for VLCDs for weight loss and management of metabolic disease in the real-world setting in AoNZ.

The increased relative lean mass is consistent with the improvements in M value seen. Improvement in peripheral insulin sensitivity despite reductions in total lean mass have been demonstrated post VLCD and may relate to significant reductions in intramyocellular lipid.[30]

Tolerability and cultural acceptability

Overall tolerability of the VLCD was high. Whilst 2/15 participants withdrew from the study, intolerance of the VLCD was not cited as a reason. This is consistent with low attrition rates with VLCD in research and real-world settings.[9,35] The spectrum of adverse effects reported by participants was similar to other published studies.[12, 35] Adverse effects were more common in the 10% WL group, likely secondary to greater adherence. Constipation was the most common side-effect and improved for most with increased fibre intake or laxative use. Prescription of greater fibre at diet commencement was listed by some participants as the most important measure to improve tolerability.

Four participants did not achieve weight loss targets; this group had lower daily Optifast intake and ingested greater amounts of non-prescribed foods per week. Data from a European population suggest that physical and social environments are leading factors affecting VLCD adherence.[36] In in the present study, frequent travelling for work; long hours of shift work and employment as a heavy-vehicle driver were deemed significant barriers to adherence. A one-size fits all meal replacement protocol is not suitable for all; greater flexibility and provision of other meal replacement options may improve VLCD adherence.

Three out of four Pacific participants withdrew or experienced difficulties with dietary adherence, highlighting the need to better understand factors which would improve VLCD acceptability for this population. Challenges with dietary adherence in the setting of cultural obligations was a clear theme for NZ Māori and Pacific participants. Few studies have examined tolerability and cultural acceptability of VLCDs in non-European populations. Cultural expectations dictating acceptance of food was a barrier to VLCD intervention success in a Barbadian population.[11] For many Pacific communities, the provision of food is of significant sociocultural importance. Dietary interventions without culturally appropriate foods may be less favourable for some Pacific participants.[7,37]

The NZ Māori participant “avoided” attending his marae to improve VLCD adherence. In Te Ao Māori [the Māori worldview], the marae is considered to be tūrangawaewae [a place to stand and belong]. Kaupapa Māori [by Māori, for Māori] research suggests that individualised dietary interventions are not culturally aligned with Te Ao Māori, and do not take into account holistic determinants of health.[38] Individualised interventions, particularly those leading to avoidance of the marae, may increase risk of acculturation and assimilation. Interventions aligning with Te Ao Māori are important;8,38 a greater understanding of the cultural context of VLCDs in AoNZ is required.

The present study is the first to describe the feasibility of a VLCD in AoNZ and has a number of strengths. The use of reference-standard HIC techniques allowed for accurate assessment of whole-body and hepatic insulin sensitivity. To our knowledge, this is the first study assessing the impact of a VLCD of greater than 8 days duration on these parameters in a South Asian or AoNZ cohort. There are however various limitations. Due to the in-depth physiological assessments undertaken, sample size was necessarily small, increasing risk of Type II error. There was a risk of Type I error through multiple testing. A greater sample size would allow a more accurate assessment of the physiological changes in response to the VLCD and an exploration of ethnic differences in response. This feasibility study provides confidence in the ability to undertake larger-scale research in this area.

Whilst the reduction in HbA1c seen in this cohort was clinically significant, longer follow-up is needed to assess the significance of this finding on rates of progression to and complications from T2DM.

Finally, whilst cultural acceptability of the VLCD in this present study was high, sample size makes extrapolation of these findings difficult and may be confounded by volunteer bias. A greater NZ Māori and Pacific voice is required to further understand the role of VLCDs in diabetes management and prevention in AoNZ. A kaupapa Māori approach to this question is significantly important. Additionally, while over one third of EOIs were from NZ Māori and Pacific individuals, further work to explore barriers to interest in VLCD interventions would be beneficial.

Conclusions

This study has demonstrated that a VLCD intervention leads to favourable improvements in body composition, glycaemic control, and other metabolic parameters after 5% and 10% weight loss in a multi-ethnic cohort of New Zealanders with prediabetes. Weight loss and improvements in HbA1c remain in the absence of weight loss target achievement. The intervention was tolerable and culturally acceptable to participants, however challenges with dietary adherence and impact of the intervention on cultural obligations were observed. Overall, findings suggest the feasibility of VLCD interventions in AoNZ, in both the research setting and in the clinical management of prediabetes and T2DM.

The VLCD diet is now an established treatment option for the management of obesity and T2DM internationally. Results from the present study support its use in AoNZ, however further work must be undertaken to explore the role of this intervention for NZ Māori, Pacific

and South Asian peoples and to further investigate possible ethnic differences in physiological response to the intervention.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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Table 1. Baseline characteristics

	10%WL group (n=9)	All participants (n=15)
Characteristic	Mean (SD)	Mean (SD)
Age (years)	43.9 (10.5)	45.6 (8.9)
Height (cm)	176.5 (6.5)	177.1 (6.6)
Weight (kg)	115.7 (20.8)	115.0 (20.0)
BMI (kg/m^2)	37.2 (6.1)	36.7 (5.9)
HbA1c (mmol/mol)	44.3 (5.2)	46.1 (5.1)
	n/9 (%)	n/15 (%)
Ethnicity		
NZ European	3 (33%)	5 (33%)
NZ Māori	1 (11%)	1 (7%)
Pacific	1 (11%)	4 (27%)
South Asian	4 (44%)	5 (33%)
Diagnosis		
Prediabetes	8 (88.9%)	12 (80%)
Type 2 DM	1 (11.1%); HbA1c 51mmol/mol	3 (20%); HbA1c range 51 to 60mmol/mol

10%WL, 10% weight loss; DM, diabetes mellitus

Table 2. Time to weight loss target visits for study participants

	10%WL group	All participants
Time (days)	Mean (SD)	Mean (SD)
Time to 5% visit	29.8 (14.7)	33.5 (18.5)
Time to 10% visit	83.6 (23.6)	108.6 (78.0)

Table 3. Change in metabolic outcomes at 5% and 10% weight loss visits

	10%WL group				All participants		
	Baseline	5% weight loss visit	Mean change from baseline		Baseline	5% weight loss visit	Change from baseline
Outcome variable	Mean (SD)		Estimate (95% CI)	p value	Mean (SD)		Mean change (SD)
Fasting glucose (mmol/L)	5.7 (1.3)	5.7 (1.2)	-0.12 (-1.4 to 1.1)	0.82	6.4 (1.9)	5.9 (1.2)	-0.4 (1.6)
Fasting insulin (pmol/L)†	124.0 (37.4)	76.7 (27.3)	-47.3 (-91.8 to -2.8)	0.04	140.1 (69.3)	72.9 (27.6)	-48.0 (42.8)
OGTT derived parameters							
Matsuda Index	1.7 (0.7)	3.2 (1.4)	1.5 (0.3 to 2.6)	0.02	1.7 (0.7)	3.4 (1.3)	1.6 (0.9)
Insulinogenic Index (IGI)	2.0 (1.9)	15. (1.3)	-0.5 (-1.8 to 0.8)	0.36	1.5 (1.5)	1.4 (1.2)	-0.5 (1.3)
Disposition Index (DI)	3.5 (2.9)	8.1 (12.2)	0.7 (-1.5 to 26.7)	0.56	2.4 (2.5)	6.8 (10.9)	4.0 (8.7)
HOMA2-IR	2.4 (1.3)	1.4 (0.5)	-0.9 (-2.1 to -0.4)	0.02	2.7 (1.2)	1.4 (0.5)	-1.1 (0.8)
Log HOMA2-IR	0.4 (0.1)	0.1 (0.2)	-0.3 (-0.5 to 0.07)	0.02	0.4 (0.2)	0.1 (0.1)	-0.3 (0.2)
HOMA2-%B	154.2 (93.2)	107.4 (55.6)	-13.1 (-65.9 to 39.8)	0.57	139.4 (93.1)	103.9 (56.5)	-16.5 (50.0)
	Baseline	10% weight loss visit	Mean change from baseline		Baseline	10% weight loss visit	Change from baseline
HbA1c (mmol/mol)	44.3 (5.2)	39.6 (7.0)	-4.8 (-7.1 to -2.4)	0.002	46.1 (5.2)	42.1 (7.0)	-3.4 (3.5)
Fasting glucose (mmol/L)	5.7 (1.3)	5.6 (0.7)	-0.1 (-0.8 to 0.6)	0.76	6.4 (1.9)	6.3 (1.9)	0.1 (0.9)
Fasting insulin (pmol/L)†	124.0 (37.4)	77.2 (32.3)	-46.8 (-86.4 to -7.2)	0.03	140.1 (69.3)	132.1 (157.0)	-12.4 (87.2)
OGTT derived parameters							
Matsuda Index	1.8 (0.7)	3.2 (1.8)	1.4 (0.3 to 2.6)	0.02	1.7 (0.7)	2.7 (1.8)	1.0 (1.3)
Insulinogenic Index (IGI)	2.0 (1.9)	3.8 (4.2)	1.7 (-2.1 to 5.6)	0.32	1.5 (1.5)	3.2 (3.7)	1.4 (3.7)
Disposition Index (DI)	3.5 (2.9)	15.1 (23.3)	1.1 (-1.8 to 33.4)	0.55	2.4 (2.5)	11.4 (20.8)	8.5 (20.1)
HOMA2-IR	2.4 (1.3)	1.5 (2.8)	-0.9 (-1.7 to -0.1)	0.03	2.7 (1.2)	2.5 (2.7)	-0.7 (0.9)
HOMA2-%B	154.2 (93.2)	89.9 (56.5)	-29.8 (-57.3 to -2.2)	0.04	139.4 (93.1)	103.9 (56.5)	-21.8 (30.7)
Clamp derived parameters							
M value (mg kg_{FFM}^{-1} min^{-1})	4.8 (1.5)	6.3 (1.9)	1.5 (0.7 to 2.2)	0.002	4.8 (1.4)	5.8 (1.8)	1.3 (0.9)
MCR (mL kg_{FFM}^{-1} min^{-1})	4.3 (1.6)	5.8 (1.8)	1.5 (0.3 to 2.7)	0.02	4.1 (1.7)	5.3 (2.0)	1.4 (1.4)
Other metabolic parameters							
Systolic BP (mmHg)	136.6 (13.0)	120.4 (8.0)	-12.4 (-19.6 to -5.3)	0.01	135.7 (13.0)	120.4 (8.0)	-10.9 (7.9)
Diastolic BP (mmHg)	88.3 (8.4)	79.0 (3.0)	-6.6 (-13.1 to -0.03)	0.05	86.4 (8.4)	78.9 (3.0)	-5.3 (7.0)
Total cholesterol (mmol/L)	4.4 (1.1)	4.2 (0.3)	-0.1 (-0.4 to 0.1)	0.4	4.8 (1.1)	4.4 (1.0)	-0.1 (0.3)
LDL cholesterol (mmol/L)	2.5 (1.0)	2.6 (0.8)	0.1 (-0.2 to 0.4)	0.40	2.9 (1.0)	2.7 (0.8)	0.1 (0.3)
HDL cholesterol (mmol/L)	1.2 (0.3)	1.2 (0.2)	0.02 (-0.1 to 0.2)	0.71	1.1 (0.3)	1.2 (0.2)	0.01 (0.2)
Fasting TG (mmol/L)†	1.7 (1.1)	1.1 (0.6)	-0.4 (-1.1 to -0.2)	0.01	1.8 (1.1)	1.3 (0.6)	-0.5 (0.6)
Adiponectin (ng/mL)	4009.2 (2454.6)	4580.0 (2001.0)	374.3 (-763.0 to 1511.6)	0.46	3295.0 (2057.0)	3826.2 (2037.9)	127.8 (1174.6)
Leptin (pg/mL)	25154.8 (17017.1)	11279.2 (5454.6)	-15725.9 (-27359.0 to 4092.8)	0.02	21583.6 (15511.6)	13752.7 (10701.8)	-9643.8 (15197.3)
REE Abs (kcal/24hours)	2029 (416.4)	1944 (317.5)	-123.2 (-274.8 to 28.4)	0.10	2088.0 (416.4)	2000.0 (317.5)	-106.7 (159.4)

BP, blood pressure; TG, triglycerides; REE Abs, absolute resting energy expenditure

†Denotes that logarithm transformation also performed with nil change in statistical significance

Table 4. Change in hepatic glucose metabolism in subset of 10%WL participants

Participant	1		2		3		4		5†	
Visit	0	10%	0	10%	0	10%	0	10%	0	10%
$EndoRa_{BL}$ (μmol kg_{FFM}^{-1} min^{-1})	22.5	19.1	22.9	25.1	19.5	18.4	19.0	17.8	17.3	14.6
$EndoRa_{Clamp}$ (μmol kg_{FFM}^{-1} min^{-1})	10.7	7.0	7.3	10.0	8.9	8.3	8.2	5.7	18.9	13.4
% sup EGP	64.4	63.4	68.1	60.3	54.3	54.7	56.8	67.8	-8.9	8.3

Participant	Baseline	10% weight loss	Change from baseline	
Visit	Mean (SD)	Mean (SD)	Point estimate (95% CI)	p value
$EndoRa_{BL}$ (μmol kg_{FFM}^{-1} min^{-1})	20.2 (2.1)	19.0 (3.4)	-1.3 (-4.0, 1.4)	0.26
$EndoRa_{Clamp}$ (μmol kg_{FFM}^{-1} min^{-1})	10.8 (4.2)	8.9 (2.6)	-1.9 (-5.8, 2.0)	0.24
% sup EGP	46.9 (28.3)	50.9 (21.7)	3.9 (-8.4, 16.3)	0.43

BL, baseline; % sup EGP, percentage suppression endogenous glucose production
†Nil change in statistical outcomes after removal of participant 5 from the analysis

Table 5. Change in anthropometric and body composition parameters at 5% and 10% weight loss visits

Parameter	10%WL group				All participants		
	Baseline	5% weight loss visit	Mean change from baseline		Baseline	5% weight loss visit	Change from baseline
	Mean (SD)		Estimate (95% CI)	p value	Mean (SD)		Mean change (95% CI)
Weight (kg)	115.7 (20.8)	108.1 (18.4)	-7.5 (-9.2 to -5.8)	<0.001	115.0 (20.8)	105.3 (17.6)	-6.8 (2.3)
BMI (kg/m^2)	37.2 (6.1)	34.8 (6.1)	-2.3 (-3.4 to -1.9)	0.004	36.7 (6.1)	33.4 (5.8)	-2.9 (1.8)
	Baseline	10% weight loss visit	Mean change from baseline		Baseline	10% weight loss visit	Change from baseline
Weight (kg)	115.7 (20.8)	103.6 (22.5)	-12.0 (-13.1 to -11.0)	<0.001	115.0 (20.8)	108.5 (22.5)	-9.0 (5.7)
BMI (kg/m^2)	37.2 (6.1)	33.3 (6.2)	-3.9 (-4.3 to -3.5)	<0.001	36.7 (6.1)	34.3 (6.2)	-2.9 (1.9)
WC (cm)	119.2 (12.8)	110.7 (12.8)	-8.6 (-13.8 to -3.3)	0.005	118.6 (12.8)	114.1 (12.8)	-5.7 (7.6)
HC (cm)	121.1 (11.8)	114.6 (12.4)	-6.5 (-10.4 to -2.6)	0.005	118.7 (11.8)	116.4 (12.4)	-4.8 (5.5)
WHR	0.99 (0.06)	0.97 (0.05)	-0.003 (-0.1 to -0.0)	0.91	1.0 (0.06)	1.0 (0.1)	-0.01 (0.06)
Fat Mass %	38.3 (5.1)	35.5 (4.1)	-2.9 (-3.9 to -1.8)	<0.001	35.9 (5.1)	34.8 (4.1)	-1.9 (2.0)
Fat Mass (kg)	44.6 (11.2)	37.3 (10.7)	-7.3 (-8.8 to -5.8)	<0.001	41.8 (11.2)	38.3 (4.1)	-5.0 (4.3)
Lean Mass %	59.3 (4.8)	61.8 (3.8)	2.5 (1.5 to 3.5)	<0.001	61.6 (4.8)	62.5 (3.9)	1.6 (1.9)
Lean mass (kg)	68.6 (11.7)	64.5 (13.2)	-4.1 (-5.7 to -2.4)	<0.001	70.6 (11.7)	68.2 (13.1)	-3.3 (2.3)
Visceral Fat (g)	806.1 (294.0)	656.2 (180.7)	-149.9 (-259.3 to -40.5)	0.01	744.3 (294.0)	699.8 (180.7)	-127.9 (135.2)

WC, waist circumference; HC, hip circumference; WHR, waist:hip ratio; 10%WL, 10% weight loss group.

Table 6. Baseline characteristics

	10%WL group			All participants		
	Total	First 4 weeks	Final 4 weeks	Total	First 4 weeks	Final 4 weeks
Sachets/week ingested	21.6 (4.2)	23.3 (4.2)	21.7 (5.7)	19.1 (6.4)	21.3 (6.1)	19.1 (7.3)
Days with non-prescribed food/week	2.6 (1.2)	1.1 (1.0)	3.8 (1.8)	3.1 (1.3)	1.9 (1.5)	3.8 (1.8)
Side-effects (proportion)	0.45 (0.3)	0.5 (0.4)	0.3 (0.3)	0.4 (0.3)	0.5 (0.4)	0.3 (0.3)

10%WL, 10% weight loss; DM, diabetes mellitus

Table 7. Side-effects experienced during the VLCD intervention

Symptoms	n/15 (%)
Constipation	8 (53)
Headache	4 (27)
Fatigue	4 (27%)
Irritability	2 (13%)
Thirst	2 (13%)
Abdominal discomfort	2 (13%)
Reduction in appetite	1 (7%)
Hunger	1 (7%)
Loose bowels	1 (7%)
Poor sleep	1 (7%)
Reduced alcohol tolerance[†]	1 (7%)

[†]Alcohol is a non-prescribed food item

Timepoint	Pre	Baseline	5% weight loss	10% weight loss
Pre-Allocation				
Eligibility screen	✓			
Informed consent	✓			
Enrolment	✓			
Investigations				
OGTT[†]		✓	✓	✓
Hyperinsulinaemic isoglycaemic clamp		✓		✓
Hood calorimetry		✓		✓
DXA		✓		✓
Interventions				
VLCD		◆—	—◆	
VLCD monitoring visit			✓	✓
Phone contact with team		◆—	—◆	
Participant monitoring				
IPAQ/Food diary		✓		
Urinary ketones			✓	✓
Qualitative assessments				
Satisfaction questionnaires		✓		✓

Figure 1. PROGRESS NZ study schedule. [†]OGTT, oral glucose tolerance test; DXA, dual-energy x-ray absorptiometry; VLCD, very low calorie diet; IPAQ, International Physical Activity Questionnaire

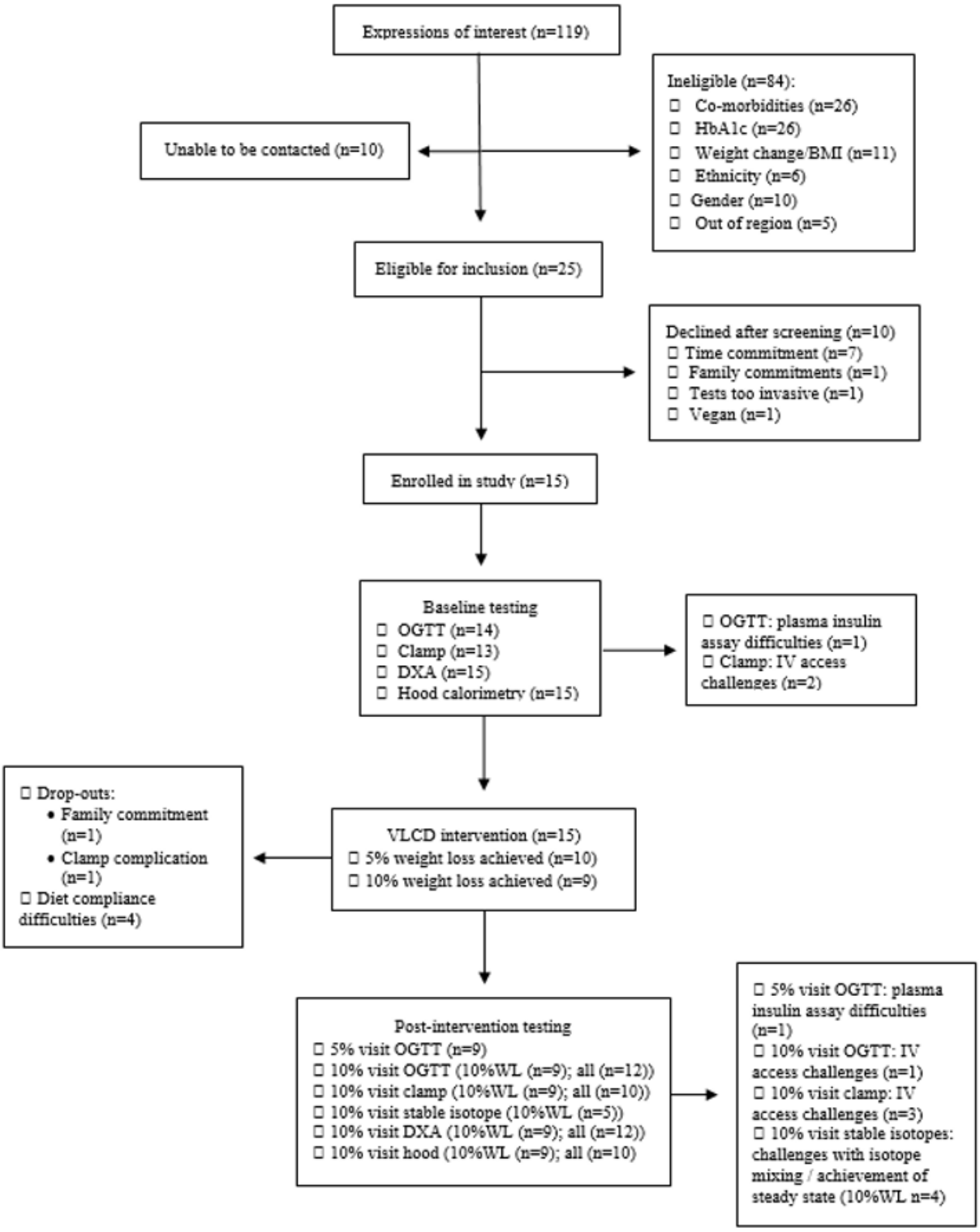

Figure 2. Study flowchart. OGTT, oral glucose tolerance test; 10%WL, 10% weight loss group

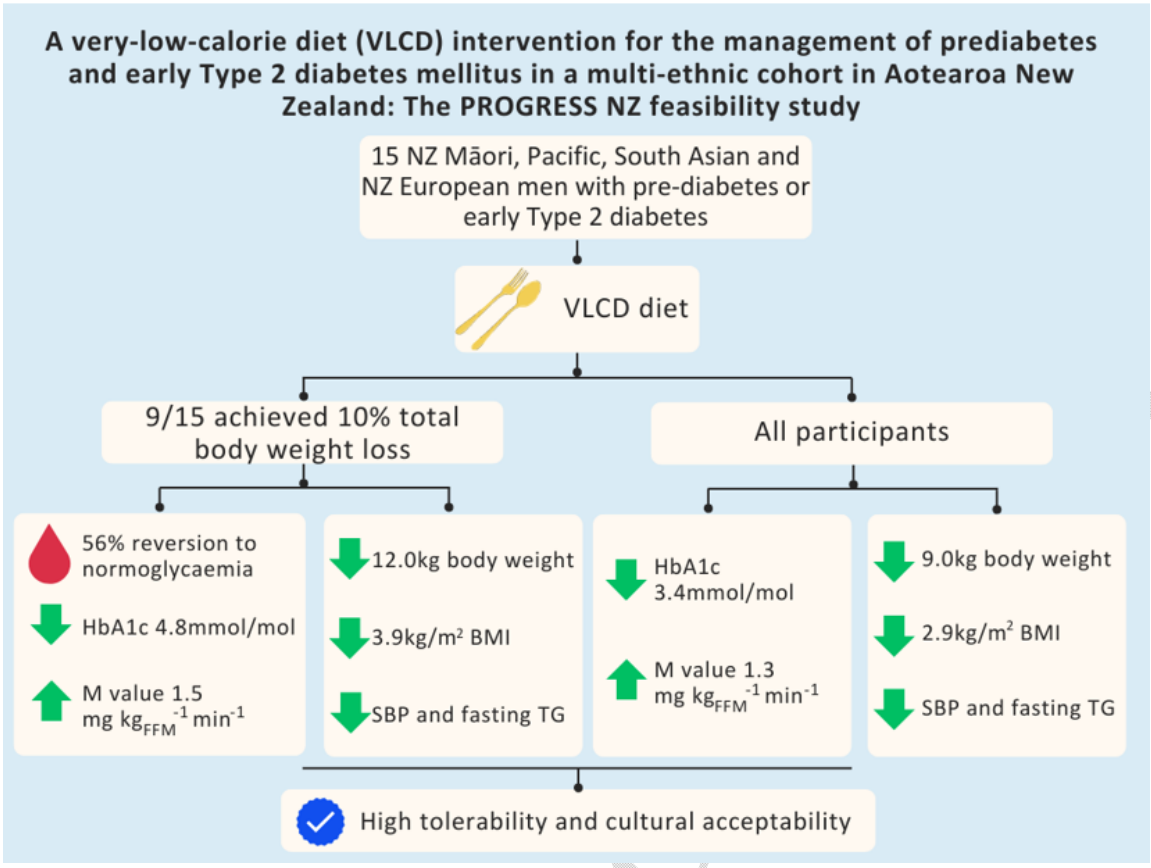

Figure 3. Graphical abstract for the PROGRESS NZ feasibility study