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Feasibility of a very low calorie diet to achieve a sustainable 10% weight loss in patients with non-alcoholic fatty liver disease

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Study Highlights:

What is known:

- A weight loss goal of ≥10% has been recommended as the primary treatment for NAFLD
- Only a minority of patients achieve this level of weight reduction with standard dietary approaches

What is new here:

- A very low calorie diet (VLCD) is a feasible and acceptable intervention to induce a sustainable 10% weight loss in patients with NAFLD
- Weight losses achieved in this study exceed those reported for standard clinical care
- Sustained improvements were observed in liver health, metabolic control, cardiovascular risk and QoL in those completing the intervention at 9-months

Translational impact:

A VLCD intervention offers a holistic treatment option that could be incorporated as part of clinical care for some patients with NAFLD

Abstract

Objectives: Non-alcoholic fatty liver disease (NAFLD) is the most common liver condition worldwide. A weight loss goal of ≥10% is the recommended treatment for NAFLD, however only a minority of patients achieve this level of weight reduction with standard dietary approaches. This study aimed to determine whether a very low calorie diet (VLCD) is an acceptable and feasible therapy to achieve and maintain a ≥10% weight loss in patients with clinically significant NAFLD.

Methods: Patients with clinically significant NAFLD were recruited to a VLCD (~800 kcal/day) intervention using meal replacement products. Anthropometrics, blood tests (liver and metabolic), liver stiffness and cardiovascular disease risk were measured at baseline, post-VLCD, and at 9-months follow-up.

Results: 45 patients were approached, 30 were enrolled, 27 (90%) completed the VLCD intervention and 20 (67%) were retained at 9-months follow-up. The VLCD was acceptable to patients and feasible to deliver. Intention to treat analysis found that 34% of patients achieved and sustained ≥10% weight loss, 51% achieved ≥7% weight loss and 68% achieved ≥5% weight loss at 9-months follow-up.

For those completing the VLCD, liver health (liver enzymes and liver stiffness), cardiovascular disease risk (blood pressure and QRISK2), metabolic health (fasting glucose, HbA1c and insulin) and body composition significantly improved post-VLCD and was maintained at 9-months.

Conclusions: VLCD offers a feasible treatment option for some patients with NAFLD to enable a sustainable ≥10%, weight loss, which can improve liver health, cardiovascular risk and quality of life in those completing the intervention.

Keywords: non-alcoholic fatty liver disease (NAFLD); very low calorie diet (VLCD); lifestyle; weight loss; clinical management; feasibility

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver condition worldwide, affecting an estimated 20-33% of the population in Western countries (1). This condition is directly linked to chronic excess calorie consumption, lack of physical activity/exercise and overweight/obesity. NAFLD is a spectrum of liver disease ranging from isolated fatty liver through to non-alcoholic steatohepatitis (NASH), which can progress to cirrhosis. Dual biopsy studies indicate that approximately 40% of patients with NAFLD develop progressive liver fibrosis (2). Ultimately, 5-11% develop advanced liver disease and have the potential to develop cirrhotic complications (2, 3). As a result, NASH is a common indication for liver transplantation (4, 5). Stage of liver fibrosis is a strong predictor of both liver-related and all-cause mortality in patients with NAFLD (6, 7). As such, a therapy that could halt or reverse liver fibrosis may reduce risk of liver-related complications.

In the absence of approved pharmaceutical agents, lifestyle modification, involving weight loss, is the primary recommended therapy for NAFLD (8-10), and a weight loss goal of 10% is recommended for patients with advanced NAFLD (11-13). A 2015 study found that 90% of participants losing >10% body weight had resolution of steatohepatitis, and 81% showed improvement in fibrosis (11). However, only 10% of those participants maintained 10% weight loss at one year. A randomised controlled trial assessing the effect of weight loss on NASH (14) reported a relationship between percent weight loss and improvement in NAFLD activity score (NAS). Participants who achieved weight loss of >7% had significant histological improvements in steatosis, lobular inflammation, ballooning injury and NAS when compared to those losing <7%. No change in fibrosis scores were reported, and mean weight loss in the intervention arm was 9.3%. These studies highlight the need for acceptable alternative interventions to elicit sustained weight loss of greater magnitude in a larger proportion of individuals.

Very low calorie diets (VLCDs) have demonstrated to be a viable treatment strategy for people with type 2 diabetes mellitus (T2DM) (15). Research has shown that VLCDs are effective for achieving substantial weight loss, with high levels of adherence and low levels of attrition in overweight and obese people with T2DM (16). A large randomised controlled trial of VLCD (DiRECT) conducted in primary care involving patients with T2DM found that 24% of those in the intervention group lost ≥15kg, and mean body weight fell by 10kg at one year follow-up (17). As well as this study reporting sustained weight loss, 46% of participants had normalisation of blood glucose control. Another study showed that 45% of obese patients undertaking a 12-week VLCD maintained ≥10% weight loss at one year follow-up (18). Research suggests that VLCD may also have a positive impact on fatty liver. A small

study in patients with T2DM (19) found that individuals treated with VLCD had a reduction in liver fat (measured by MR spectroscopy) from 13% to 3%. Despite these findings, the VLCD approach has not been formally assessed as a treatment strategy for NAFLD. The totality of these changes could be beneficial to patients with NAFLD in reversing liver disease or halting disease progression, and reducing other obesity-related risk factors.

The primary aim of this study was to determine whether a minimum 8-week VLCD is a feasible and acceptable therapy to achieve a target weight loss of 10% in patients with clinically significant NAFLD, and whether weight loss could be maintained for at least 6-months following completion of the VLCD. Secondary outcome data were collected to explore the potential effects of the VLCD upon factors that influence the development and progression of NAFLD. However, these outcomes were exploratory.

Patients and Methods

Recruitment and patients: Forty five patients with a diagnosis of clinically significant NAFLD and a BMI > 27kg/m^2 were approached to take part in the study. Thirty patients agreed and were subsequently recruited from hepatology clinics within the Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) from January to July 2019. To facilitate recruitment, clinically significant NAFLD was defined using imaging evidence of steatosis plus an indeterminate or high NAFLD Fibrosis Score (NFS) (≥ -1.455) or Fibrosis-4 (FIB-4) (≥1.3 if age <65; ≥ 2.0 if age ≥65) (20-22), or histological evidence of NASH with fibrosis. By including patients with “indeterminate/high risk” NAFLD without a liver biopsy, the pool of eligible patients was substantially increased and this also meant that the results of the study were applicable to a wider NAFLD population. Patients with compensated NASH cirrhosis (Child-Pugh score <7) were also eligible to participate. Other inclusion criteria specified age ≥18years, weight stability (+/-3%) since biopsy/non-invasive assessment of liver health and capacity to provide informed consent.

Patients were excluded if they had evidence of co-existing liver disease (e.g. autoimmune liver disease, viral hepatitis, alpha-1 anti-trypsin deficiency, haemochomatosis or Wilson’s disease), decompensated NASH cirrhosis (Child Pugh score ≥ 7), current treatment with anti-obesity drugs, a diagnosed/previous eating disorder or purging, excessive alcohol consumption (>21 units/week for males; >14 units/week for females), insulin use to manage T2DM, known cancer, myocardial infarction within six months and pregnant/considering pregnancy. Subject characteristics can be found in **Table 1**.

The study protocol was approved by North East-Newcastle & North Tyneside 1 Research Ethics Committee (REC reference: 18/NE/0179) (ISRCTN Register: ISRCTN85177264). All participants provided written informed consent. Following withdrawal from the study, patients

were no longer followed up by the research team and usual clinical care continued. Data was collected and analysed up until their most recent visit.

Figure 1 shows a summary of the study schedule and highlights the investigations completed at each visit.

Primary outcomes: Feasibility and acceptability of the VLCD, including feasibility of recruitment, retention, VLCD delivery, and percentage of patients achieving ≥10% weight loss and sustaining it for at least 6-months following completing the VLCD intervention.

Secondary outcomes: Absolute change in body weight; change in clinical blood markers; change in cardiac (QRISK2/blood pressure/lipids) and T2DM risk (HbA1c/HOMA-IR/glucose/medication changes); and quality of life (all measured post-VLCD and at 9-months).

Anthropometry: Body weight (kg) and height (cm) were measured using an electronic stadiometer (SECA 799, SECA UK). In those lost to follow-up, weight was measured at their next routine clinic visit as per standard care, the majority within 8-weeks of their planned final study visit. Waist circumference was measured at the mid-point between the lower costal margin and the level of the anterior superior iliac crests. Hip circumference was measured at the level of the greater trochanter. Body composition was measured using 8-point Bioelectrical Impedance Analysis (SECA BIA mBCA 525 machine, SECA, UK).

Blood samples: Fasting samples were analysed in a Clinical Pathology Accredited laboratory (Newcastle Upon Tyne Hospital NHS Foundation Trust, Department of Clinical Biochemistry) for: Liver enzymes (including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyltransferase (GGT)), fasting glucose, HbA1c, insulin, lipid profile and full blood count (FBC).

Liver stiffness: Liver stiffness measurement (LSM) was obtained using FibroScan Mini 430 (Echosens, Paris). All patients were fasted for at least 8h before the procedure. The LSM score was represented by the median of 10 measurements and was considered reliable only if at least 10 successful acquisitions were obtained and the IQR-to-median ratio of the 10 acquisitions was ≤0.3 or if the LSM was <7.1kPa.

Non-invasive risk scores: The NFS (20) and FIB-4 Score (23) - validated non-invasive systems to diagnose or exclude advanced liver fibrosis, were calculated from blood tests at clinic visits. The QRISK2 (24) was calculated to estimate the risk of an individual having a cardiovascular event within the next 10 years. The homeostasis model assessment of insulin resistance (HOMA-IR) was used to determine insulin resistance (25). All were calculated for each patient at baseline, post-VLCD and at 9-months follow-up.

Quality of life: Patients completed the Obesity and Weight-Loss Quality-of-Life (OWLQOL) Instrument (26) which gives a Quality of Life (QOL) score (17 item) and a Weight-Related Symptom Measure (WRSM) (20 item). Lower scores in the QOL section indicate a poorer QOL; higher scores in the WRSM section indicate greater symptom burden.

VLCD Intervention: Patients were prescribed an 8-week VLCD (~800 kcal/day) intervention. In the event that consistent compliance with the diet was not possible throughout the 8-week period due to external factors (e.g. hospital admissions or travel), the intervention was extended for an additional four weeks, to a maximum VLCD intervention of 12 weeks. Following completion, patients moved on to the food-reintroduction phase of the intervention.

The VLCD intervention was supervised by a member of the Research Team and patients were provided with meal replacement products (Optifast, Nestlè Health Science. Nutritional content: fat 19.4%kcal; carbohydrate 43.4%kcal; fibre 3.5%kcal; protein 33.7%kcal) free of charge. In addition, patients were encouraged to eat three portions (240g) of non-starchy vegetables and drink at least two litres of water or calorie-free beverages each day. One-to-one support was provided weekly throughout the VLCD phase by a tailored combination of phone calls, emails and face-to-face appointments to maximise adherence to the protocol and to minimise drop out. Patients were provided with scales to weigh themselves at home if needed*.* Dietary compliance was monitored by change in body weight. Patients were asked to maintain their usual physical activities during the VLCD but not to increase their activity levels during this phase.

Food reintroduction: Following completion of the VLCD phase, patients were supported by two members of the research team (JS and KH - both experienced in delivering lifestyle behaviour change interventions) to follow a stepped return to normal eating over a 4-week time period. This involved replacing one meal replacement product with normal food in the first two weeks, with education on portion size using the “Carb and Calorie Counter” manual (27). Two normal meals were introduced during weeks 3 and 4. If desired, this phase was extended to 6-weeks to help manage individual needs. Specific individualised dietary advice was provided using a food exchange model. The goal was to limit energy intake to individual requirements to maintain weight and patients received support to overcome behavioural barriers (e.g., resisting temptation). Patients were advised to monitor their weight weekly at home and were encouraged to monitor their caloric intake - each patient was provided with two resource books which contained low calorie meal plans, recipes and snack ideas (28), and information relating to the portion sizes and nutritional value (calories, protein, fat, carbohydrate and fibre) of common foods (27). Patients were encouraged to increase their physical activity levels during food introduction, and pedometers were provided for self-

monitoring of daily step counts. If appropriate, patients were referred to local “Exercise on Referral Schemes” for more structured exercise programmes (seven of our cohort were referred).

Weight maintenance: Each person was seen monthly/bimonthly post VLCD-intervention to measure blood pressure, weight, blood glucose, lipids and liver enzymes. Participants were advised to follow a food-based diet and were provided with an individually tailored energy prescription, in order to prevent weight regain and support weight stabilisation and/or further weight loss. Those who were physically capable were advised to increase their daily physical activity or exercise.

Changes to medication: Sulphonylurea oral hypoglycaemic agents (Gliclazide, Glimepiride, Tolbutamide) were withdrawn on commencing the VLCD, as per the study protocol. Any other diabetic medication was continued as normal throughout the study unless specifically instructed by a member of the research team and regular glucose monitoring was undertaken. Blood pressure was monitored regularly as part of the study protocol, and adjustments made to blood pressure lowering medications made as required. All other medications were continued as usual. Any changes to medication were made by a qualified member of the research team and the patient’s GP informed.

Data analysis

All primary and secondary data analyses were performed using IBM SPSS version 24 (IBM, NY, US). Continuous data were tested for normality using the Shapiro-Wilk test and data are presented as means ± SD, unless otherwise stated (the majority of the data was normally distributed). Within-group changes were assessed by repeat measure one-way ANOVA, or by Kruskal-Wallis analysis where data was non-parametrically distributed. P-values <0.05 were considered statistically significant. Correlations were measured using a Pearson Correlation Coefficient. Overall p-value in Table 1 represents results derived from one-way ANOVA, with further significance explored using a Bonferonni corrected post-hoc analysis. Data for the primary endpoint and overall weight loss outcomes were analysed per ‘intention to treat’ (ITT). A ‘per protocol’ analysis was conducted to assess the changes in clinical parameters between the time points because data was not available for those who withdrew from the study, or who were lost to follow up.

Results

Primary outcomes: Feasibility, acceptability and percentage of participants achieving 10% weight loss at follow-up – This study was fully recruited at a single site within six months. Of

the 45 patients approached to take part in this study, 30 (67%) consented to enrol. Overall, 27 (90%) patients completed the VLCD phase of the intervention (16 patients completed 8-weeks of VLCD; 11 completed 8-weeks plus the optional 4-week extension period). Of these, 20 (67%) remained in the study to the end of the 9-month follow-up period - see **Figure 2** for patient flow through the study and description of withdrawals/dropouts.

ITT analysis of weight change at 9-months: Overall 34% (n=10) of patients achieved the primary outcome of a sustained ≥10% weight loss at 9-months follow up, 51% achieved ≥7% weight loss and 68% achieved ≥5% weight loss. Mean weight loss was 10.3 ± 10.3kg (range: -42.2 to +6.8kg) or 8.9 ± 8.1% (range: -29.5 to +5.2%). At 9-months, those who completed 12-weeks of the VLCD had maintained significantly more weight loss than those who completed 8-weeks of the VLCD (13.4 ± 7.8% vs 4.4 ± 5.4%, p=0.002).

ITT analysis of weight change post-VLCD phase: At the end of the VLCD phase, 53% (n=16) of patients achieved ≥10% weight loss, 63% achieved ≥7% weight loss and 77% achieved ≥5% weight loss. Mean weight loss was 11.3 ± 7.7kg (range: -38.7 to +1.7kg) or 9.7 ± 5.8% (range: -26.4 to +1.3%). Post VLCD, those who completed 12-weeks of the VLCD had lost significantly more weight than those who completed 8-weeks (13.6 ± 5.1% vs 7.2 ± 4.6%, p=0.002).

No treatment related serious adverse events were reported during the study. The most common side effects reported during the VLCD phase were constipation, dizziness, headaches and increased sensitivity to cold, reported by 37%, 19%, 11% and 7% of patients respectively. No side effects were reported during food reintroduction and follow up.

*Baseline characteristics (see **Table 1**):* 60% of patients recruited were male and mean age was 56 ± 12 years. The mean weight and BMI at baseline were 119 ± 25kg and 42 ± 8kg/m^2 respectively. At baseline, 14 (47%) patients had a BMI between 30-40kg/m^2, 13 (43%) had a BMI between 40-50kg/m^2 and 3 (10%) had a BMI >50kg/m^2. Overall, 16 (53%) patients had T2DM and 13 (43%) patients had the full metabolic syndrome, at baseline (29, 30).

All patients had either an intermediate/high NFS or intermediate/high FIB-4; 16/30 also had NASH with fibrosis on biopsy (2 with F1, 6 with F2, 5 with F3 and 3 with F4), as reported using the Kleiner (31) scoring system. The baseline LSM was 13.0kPa (± 6.0kPa; n=27) and 17 had an LSM >8kPa. Baseline NFS and FIB4 were -0.05 (± 2.1) and 1.5 (± 1.0) respectively.

Per-protocol analysis of weight and body composition outcomes: All patients completing the VLCD (n=27) lost weight and maintained weight loss at 9-months follow-up. 59% (n=16) of those who completed the VLCD phase achieved ≥10% weight loss post-VLCD. Mean weight

loss immediately after the VLCD, in those completing the intervention was 12.6 ± 7.7kg (range: -38.7 to -3.2kg) or 10.8 ± 5.8% (range: -26.4 to -3.3%), as shown in **Figure 3**. Weight loss at 12-weeks for all patients completing the VLCD (regardless of length of VLCD) was 12.9 ± 8.3kg and 11.4 ± 6.1%. Overall, 80%, 75% and 50% of patients achieved ≥5%, ≥7% and ≥10% weight loss respectively at 9-month follow-up, and the mean overall weight loss was 13kg (range: -42.6 to -0.3kg) (12% of total body weight).

Between the end of the VLCD and 9-month follow-up, 45% of patients lost further weight (mean further weight loss of 3.3kg (range: -11.0 to -0.8kg)) and 55% regained weight, with a mean overall weight regain of 3.2kg (range: 1.3 to 4.8kg) from their post-VLCD weight, equivalent to 3.4% (range: 0.9 to 5.7%). Following weight regain, no patients exceeded their baseline weight at 9-months. Mean BMI decreased from 42kg/m^2 (range: 30.3 to 62.3kg/m^2) at baseline to 37kg/m^2 (range: 26.3 to 58.8kg/m^2) post-VLCD and 35kg/m^2 (range: 27.5 to 57.8kg/m^2) at 9-month follow-up. Moreover, mean total body fat mirrored these findings falling from 45% to 40% post-VLCD and 41% at 9-months. Skeletal muscle mass did not change significantly between baseline and post-VLCD (29 ± 5kg vs. 27 ± 5kg, p=0.219), or between post-VLCD and 9-month follow-up (27 ± 5kg vs. 26 ± 6kg, p=0.617). However, there was a significant decrease observed between baseline and 9-months (29 ± 5kg vs. 26 ± 6kg, p=0.009).

Secondary outcomes:

Liver health: **Figure 4** presents the changes in ALT, AST and GGT throughout the VLCD intervention and through the maintenance period to 9-month follow-up. Overall, liver enzymes significantly improved from baseline to post-VLCD, and these improvements were maintained at 9-months. Interestingly, there was a significant rise in liver enzymes one week into the VLCD that had returned to baseline by week four. There were no significant relationships between total weight loss (%) and change in AST (r=0.365, p=0.061), ALT (r=0.215, p=0.281) or GGT (r=0.181, p=0.377) over the study period in the whole cohort or in the subset of patients with elevated liver enzymes at baseline (data not shown). There were no significant changes in bilirubin or platelets throughout the study period.

LSM (**Figure 4**) also improved significantly between baseline and post VLCD (13.0 ± 6.7kPa to 7.9 ± 2.9kPa; n=22) and this was maintained at 9-month follow-up (7.0 ± 2.0kPa; n=18). P=0.001

Metabolic control: Metabolic control (Glucose, HbA1c and insulin; **Figure 5** and **Table 1**) improved from baseline to post-VLCD and these improvements were maintained at 9-months. Overall, 47% of patients were prescribed oral antidiabetic medications at baseline and this reduced to 30% at 9-month follow-up. Three patients (10%) had their diabetes

medications withdrawn altogether and five other patients (16%) had their dosage reduced. At 9-months, 9/12 patients with diabetes had achieved good control of their diabetes (HbA1c <48mmol/mol) (32). Insulin sensitivity also improved with a reduction in HOMA-IR from 2.7 at baseline to 1.7 post-VLCD, although this returned to baseline at 2.6 at 9-month follow-up.

Cardiovascular disease (CVD) risk: Cardiovascular changes seen during the study period are shown in **Figure 5** and **Table 1**. Overall, there was a significant reduction in blood pressure from 144/86mmHg to 133/81mmHg post-VLCD, which elevated slightly at 9-month follow-up, but did not exceed baseline with a mean blood pressure of 138/83mmHg. QRISK2, a measure of 10-year risk of cardiovascular events, reduced significantly from 15.5% to 11.8% post-VLCD suggesting a global improvement in CVD risk. This also increased slightly at 9-month follow-up but did not exceed baseline with a final QRISK2 score of 13.3%. QRISK2 fell from >10%, a treatment threshold determined by NICE for primary prevention of CVD, to <10% for 5 (19%) patients post-VLCD and 12 (60%) of those who completed the 9-month follow-up phase (33, 34).

Quality of life (QoL): Patients reported a significantly increased quality of life at 9-month follow-up with a decrease in weight-related symptoms. QoL score improved from 44 at baseline to 55 post-VLCD, and further improved to 57 at 9-months follow-up (**Figure 6**). Weight-related symptoms score improved from 46 at baseline to 31 post-VLCD and 28 at 9-months follow-up. In addition, 30% of patients reduced the number of medications they were taking during the study.

Discussion

Weight loss achieved through lifestyle behaviour change is currently the recommended first-line treatment for NAFLD. Previous studies have shown that, if successful, these changes can improve liver histology and reduce risk of disease progression (11, 35). However, few patients (10%) achieve the recommended target of sustained weight loss of >10% using standard lifestyle interventions (11). Therefore, alternative approaches are needed. This current study shows that a VLCD intervention is an acceptable and feasible method to enable significant sustainable weight loss in obese individuals with NAFLD. Overall, 90% of those enrolled completed the VLCD phase of the intervention and 59% of completers achieved ≥10% weight loss post-VLCD. Importantly, a large proportion of the whole cohort (34%) maintained ≥10% weight loss for at least 6-months after completing the VLCD intervention. Absolute weight losses were impressive, with a mean loss of 10.3kg at 9-month follow-up consistent with previous studies of VLCD (17, 36). This compares favourably to a study of standard clinical care (11). Overall these results suggest that VLCD is a viable

treatment option for some patients with NAFLD to enable significant weight loss. Despite the potentially perceived drastic nature of the intervention, recruitment to the study was straightforward. 30 patients were recruited at a single site within six months, and 67% of patients offered the opportunity to take part in the study were enrolled.

Previous studies of VLCD have largely been conducted in individuals with obesity and T2DM and these have consistently shown that a VLCD can facilitate weight loss, and this was associated with reversal of diabetes in 46% of participants (17). While it is acknowledged that many of the diabetic patients taking part in DiRECT would have had diagnosed or undiagnosed NAFLD, they were enrolled on the basis of treating their T2DM. Our research suggests that the motivations for uptake of the VLCD by NAFLD patients are different than those of patients with T2DM (i.e. those embarking on a VLCD for T2DM). This is largely because NAFLD is less well understood by patients and does not raise the same level of concern (37-39). To date, the use, acceptability and feasibility of the VLCD with NAFLD patients has not been explored. Therefore, it was important to establish these important outcomes before trialling the intervention to assess the impact on clinical outcomes. In the current study, patients with fibrotic NAFLD were included because these individuals are at risk of progression to cirrhosis. Significant improvements in liver enzymes (ALT, AST and GGT) were seen at the end of the VLCD phase and this was maintained at 9-months follow-up. Previous studies assessing vitamin E and obeticholic acid showed that falls in ALT were associated with improvements in hepatic inflammation, so it is likely that improvements in liver enzymes associated with the VLCD indicate improved liver health of these individuals. In addition, liver stiffness significantly improved at 9-month follow-up providing further evidence of improved liver health.

Although NAFLD is a disease of the liver, CVD is the most common cause of death in patients with NAFLD, accounting for approximately 40% of deaths (40). In the current study, there were improvements in the patients' cardiometabolic status following the VLCD, with significant reductions in blood pressure, cholesterol levels and 10-year CVD risk, and improved blood glucose control. These findings were consistent with previous studies of the VLCD (11, 41). In contrast, other drugs that have shown benefit in NASH, such as vitamin E and obeticholic acid, have not shown to have a positive effect on cardiometabolic status. Moreover, use of obeticholic acid in patients with NASH was associated with a rise in LDL cholesterol and total cholesterol levels and a fall in HDL cholesterol within the first month of treatment (42).

Interestingly, one week into the VLCD there was a significant rise in serum ALT and AST in participants which returned to baseline by week 4, and transaminases fell thereafter. The

cause of this acute rise in transaminases was not determined. One potential mechanistic explanation may be that rapid weight loss increases lipolysis in adipose tissue resulting in high levels of circulating free fatty acids that are taken up by the liver. These free fatty acids may cause lipotoxicity in hepatocytes leading to apoptosis and cell death and a consequent rise in liver enzymes. This pathophysiology of this phenomenon requires further investigation.

At baseline, the mean BMI of our cohort was 42kg/m^2 (morbidly obese) and this reduced to 35kg/m^2 9-months after the intervention meaning the majority of the cohort were still obese. Despite this, there were significant improvements in liver and cardiometabolic health in the cohort even though patients did not achieve a "normal" BMI. This is an extremely important message to relay to patients who may feel that reaching a "normal" BMI is unachievable. A weight loss target of >10%, with appropriate support, may be a more realistic goal that can have significant health benefits. Previously there have been concerns that VLCD interventions may induce or increase sarcopenia amongst cohorts of overweight and obese patients (43). In our study there was no significant change in skeletal muscle mass after the VLCD. Although this had decreased slightly at 9-month follow up. This highlights the importance of monitoring muscle mass closely during and after a VLCD intervention and encouraging patients to increase their physical activity/exercise levels during the food reintroduction and weight maintenance phases and to maintain this in the long term to avoid sarcopenia.

As well as improving liver and cardiometabolic health, it would be advantageous for a treatment for NAFLD to improve QoL as previous studies have shown that patients with NAFLD report significantly impaired QoL. A recent study indicated a negative correlation between QoL and obesity, T2DM and dyslipidaemia in a NAFLD population (44). Therefore, a treatment option that significantly reduced patients' weight to improve obesity and associated comorbidities would be worthwhile in order to improve QoL. Data have also shown that NAFLD populations are more likely to report burdens related to bodily pain, anxiety, shortness of breath and an overall impairment in daily physical function (45). Importantly, in the current study we found that there were significant improvements in QoL and there was a decrease in weight-related symptoms. Improvements in QoL following an intervention are very important, over and above improving liver and cardiometabolic health, because they may promote greater adherence to a treatment in the longer term as patients notice a benefit in their day-to-day life (46, 47). It is worth highlighting that our sample included a large proportion of patients who had previously received advice to lose weight without success. Therefore there is a case to be made for presenting patients with VLCD as a treatment option – i.e. it may not necessarily be those who are most motivated who

engage with this approach, it may be a case of preference and the desire for rapid weight loss outcomes.

A feature of the current study is that patients were not required to have a liver biopsy for inclusion in the study, which increases the widespread applicability of the findings. Patients with a clinical diagnosis of NAFLD with an indeterminate NFS or FIB-4 score were eligible. These criteria were chosen because previous studies have shown that both the NFS and FIB-4 predict long-term outcomes, and patients with NAFLD and indeterminate or high scores have increased risk of liver-related and all-cause mortality. Therefore, these inclusion criteria are likely to have identified individuals in need of treatment for their NAFLD. Moreover, in contrast to many of the currently recruiting trials of pharmaceutical agents, our eligibility criteria were very inclusive and allowed patients with comorbidities, such as poorly controlled diabetes and/or morbid obesity to take part. This means that the results of this study may more generalisable to “real” NAFLD populations where patients frequently have multiple comorbidities, when compared to some studies of pharmaceutical agents.

Study limitations:

We have presented the findings of a feasibility study designed to assess acceptability and feasibility of the VLCD intervention for achieving >10% weight loss and associated study procedures. Therefore the results of the secondary outcomes should be considered exploratory, i.e. the study was uncontrolled and not powered to detect changes in secondary outcomes. While it is acknowledged that a pilot randomised controlled trial design would have allowed us to explore estimates of variability, it was important to assess acceptability and feasibility prior to committing resource to a study involving a larger sample of participants. Now that we have established the intervention is acceptable and feasible, we can proceed with a pilot RCT to rehearse a future main trial. Secondly, non-invasive tests rather than liver biopsy were used for inclusion of participants and monitoring of liver outcomes in the study, and as such we were only able to report a global assessment of liver health using liver enzymes and liver stiffness measurement and we were unable to report whether the improvements were in steatosis, hepatic inflammation or fibrosis. We acknowledge that the NFS and FIB-4 are better tools for excluding fibrosis (as opposed to ruling in fibrosis) but were used as a pragmatic way to recruit patients with clinically significant NAFLD, alongside imaging, in the absence of liver biopsy. The outcomes selected mirror those recorded during routine clinical practice, thus we did not include a precise measure of liver fat. We acknowledge the issues concerning the reliability of Fibroscan to measure liver stiffness in obese patients (48), however, this approach represents current clinical practice. Thirdly, a significant proportion of patients (33%) were lost to follow up at 9-months follow-up and data on their outcomes was limited (although we did have follow-up

data for weight). We were therefore unable to accurately describe all “intention to treat” outcomes for the whole population. Furthermore, if all outcomes for patients were included, overall cardiometabolic and liver outcomes may have been less pronounced. Fourthly, patients on insulin for diabetes were excluded, which represents a significant proportion of the NAFLD population. The decision to exclude patients on insulin was taken to ensure safety because rapid weight loss can cause hypoglycaemia. Fifthly, one of the primary objectives of this study was to assess the proportion of patients willing to undertake the VLCD as a treatment for NAFLD, however, is likely to be a selection bias with clinicians potentially approaching more motivated patients. This could have contributed to the successful outcomes. Finally, the length of VLCD phase was not standardised and participants could extend the intervention from 8 to 12 weeks if there were mitigating circumstances, and this allowed some participants to optimise their weight loss outcomes. Given that intervention effects started to wear off towards the end of the follow-up period, it is likely that 6-months post-intervention follow-up is insufficient to assess weight loss maintenance. Further work is needed to assess outcomes in a larger cohort in a “real world” setting using VLCD interventions of varying length.

Conclusions:

Overall this study showed that delivery of a VLCD is feasible, acceptable and a potential treatment option for some individuals with NAFLD, with a significant proportion of those who complete the intervention achieving >10% weight loss and maintaining it at 9-month follow-up. Importantly, the weight losses achieved in this study exceed those reported for standard clinical care. Improvements were also observed in liver health, metabolic control, cardiovascular risk and QoL in those completing the intervention at 9-months follow-up. A VLCD intervention offers a holistic treatment option that could be incorporated as part of clinical care for some patients with NAFLD.

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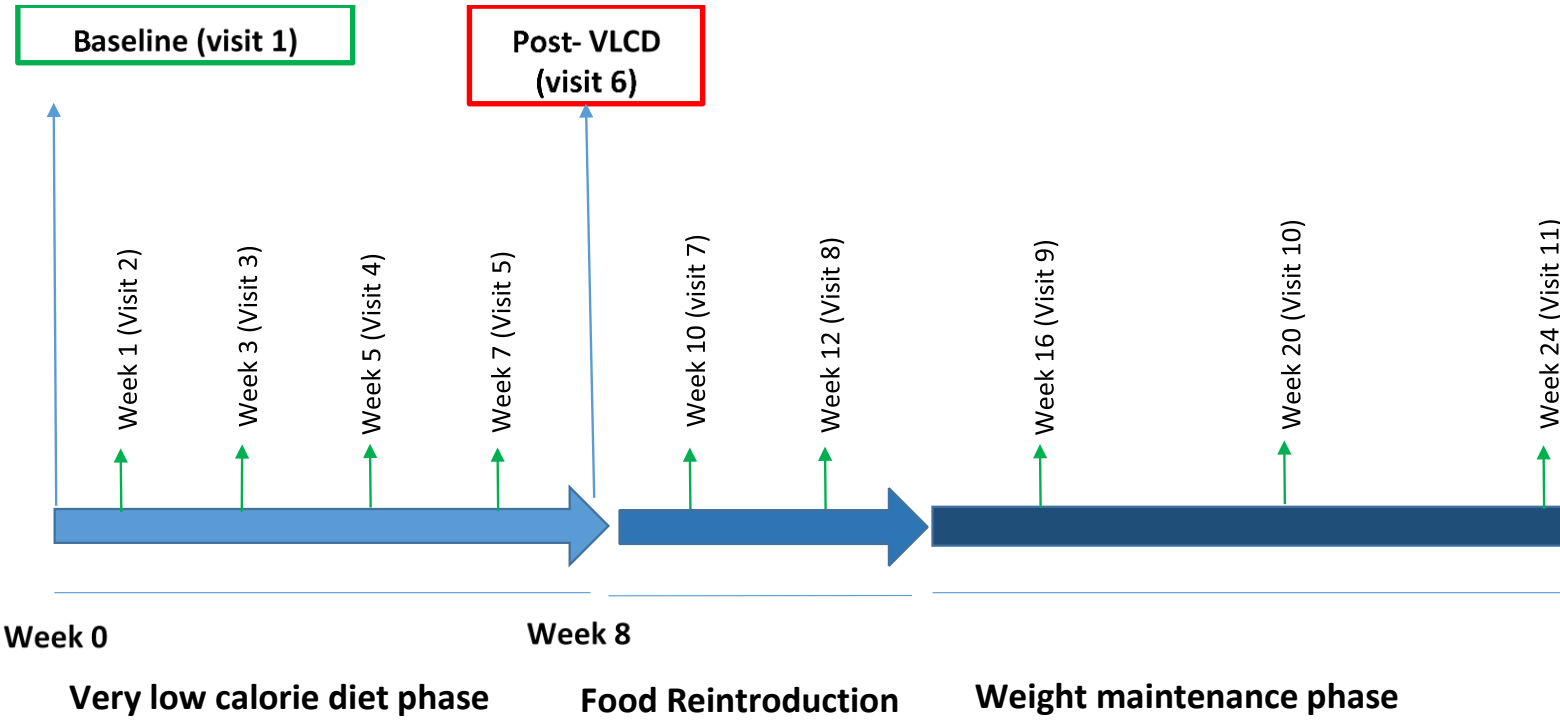
Table 1. Subject characteristics. Per protocol analysis unless specified.

Subject Characteristics	**Baseline (n=30)**	**Post-VLCD (n=27)**	**9-month (n=20)**	**Overall P value**
Age (years)	56 ± 12	55 ± 11	57 ± 11	
Sex (n) male/female	18/12	17/10	10/10	
Time since NAFLD Diagnosis (months): Mean Median (range)	 28.4 ± 31.7 13.5 (1-113)			
Anthropometry				
Weight (kg)	119 ± 25	104 ± 21	100 ± 18	0.000**
Height (m)	1.7 ± 0.9			
BMI (kg/m^2)	42 ± 8	37 ± 8	35 ± 8	0.004
Waist circumference (cm)	126 ± 16	112 ± 17	104 ± 13	0.000**
Hip circumference (cm)$^{\#}$	126 ± 15	117 ± 16	114 ± 15	0.002*
Fat mass (%)	45 ± 7	40 ± 9	41 ± 10	0.039*
Skeletal muscle mass (kg):	29 ± 5	27 ± 5	26 ± 6	0.009*
Blood pressure: systolic (mmHg)$^{\#}$ diastolic (mmHg)	144 ± 15 86 ± 11	133 ± 14 81 ± 9	138 ± 15 81 ± 7	0.009* 0.207
Mean weight loss (%); PP:		11 ± 6	12 ± 8	0.667
Mean weight loss (%); ITT (n=30):		10 ± 6	9 ± 8	0.061
Blood samples				
Total cholesterol (mmol/L)	4.3 ± 0.9	4.3 ± 1.1	4.3 ± 1.2	0.491
Triglycerides (mmol/L)	2.1 ± 1.8	2.0 ± 1.4	2.0 ± 1.8	0.049*
HDL (mmol/L)	1.2 ± 0.3	1.6 ± 1.9	1.3 ± 0.4	0.251
LDL (mmol/L)	2.2 ± 0.8	2.2 ± 0.9	2.2 ± 1.1	0.145
AST (IU/L)	35 ± 18	25 ± 9	24 ± 14	0.000**
ALT (IU/L)	47 ± 30	31 ± 16	23 ± 10	0.000**
GGT (IU/L)	82 ± 74	52 ± 72	35 ± 20	0.000**
Fasting glucose (mmol/L)	7.5 ± 2.3	6.1 ± 1.1	6.2 ± 1.4	0.046*
HbA1c (mmol/mol)	50 ± 13	42 ± 9	42 ± 9	0.000*
Insulin (pmol/L)	156 ± 101	101 ± 94	136 ± 76	0.008*
Fibroscan				
Stiffness (kPa)	13.0 ± 6.6	8.0 ± 2.9	6.9 ± 2.0	0.000*
IQR (kPa)	3.5 ± 3.0	2.5 ± 2.8	1.8 ± 1.0	0.107
Non-invasive scores				
FIB-4	1.5 ± 1.0	1.2 ± 0.7	1.2 ± 0.5	0.082

NAFLD Fibrosis Score	-0.5 ± 1.9	-0.8 ± 1.9	-0.9 ± 1.4	0.163
QRISK2	15.5 ± 14.2	11.9 ± 9.8	13.3 ± 12	0.027*
HOMA-IR	2.6 ± 1.7	1.7 ± 1.4	2.6 ± 1.4	0.018*
Weight-related Quality of Life (OWLQOL)				
Quality of Life	44 ± 26	55 ± 20	56 ± 25	0.005*
Weight-related symptom measure	46 ± 31	31 ± 23	28 ± 22	0.005*

Figure 1: Schedule of study visits



Baseline visit: informed consent, weight, height, waist/hip circumference, blood pressure, fasting bloods, PA measurement, body composition, Fibroscan, non-invasive scores (NFS, FIB-4, QRISK2), OWLQOL questionnaire

Post-VLCD/post-weight maintenance visits: weight, waist/hip circumference, blood pressure, fasting bloods, PA measurement, body composition, Fibroscan, non-invasive scores (NFS, FIB-4, QRISK2), OWLQOL questionnaire

Interim visits: weight, waist/hip circumference, fasting bloods, blood pressure

Figure 2: Patient flow throughout the study

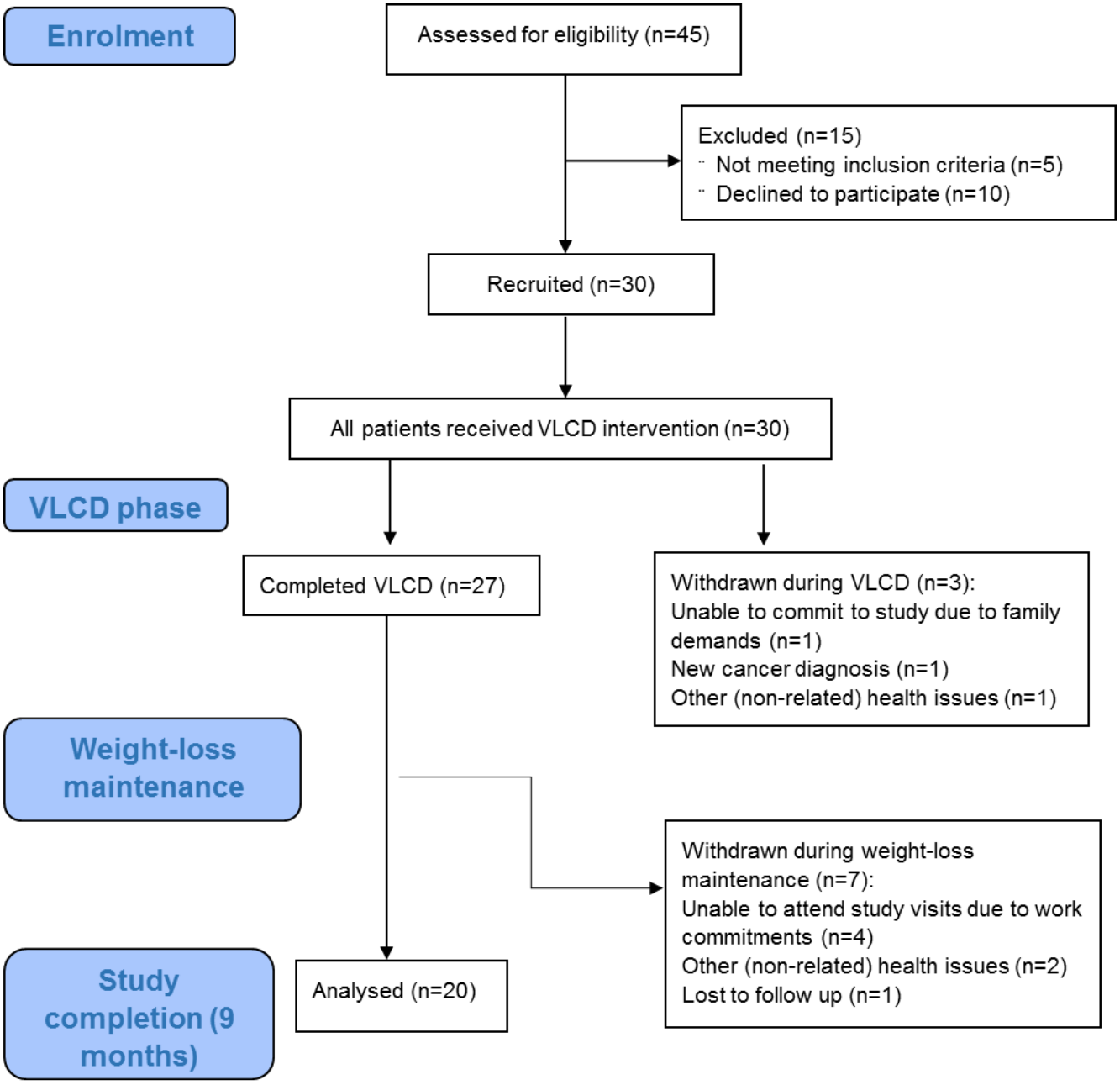


Figure 3. 'Per protocol' percentage weight loss for the duration of the study. 16 patients completed the VLCD phase at week 8 (visit 6), while 11 patients extended the VLCD phase to week 12 (visit 8). 20 patients completed the 9-month visit (visit 13).

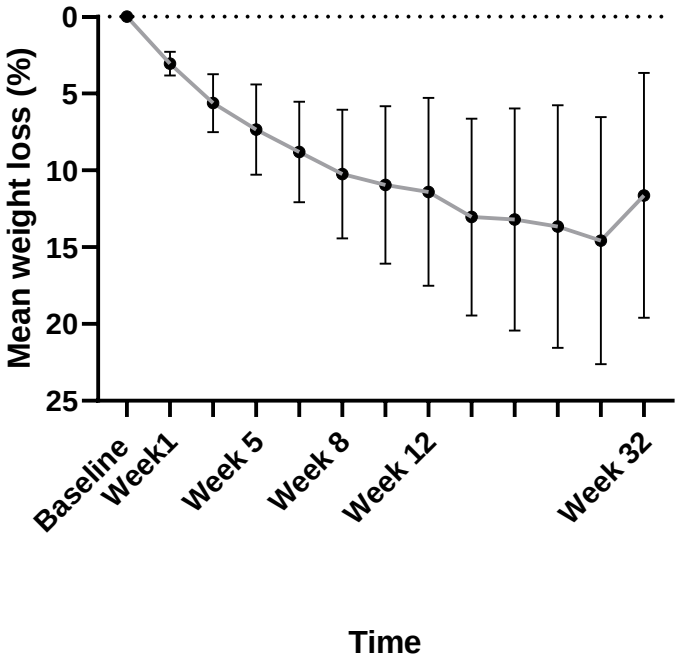
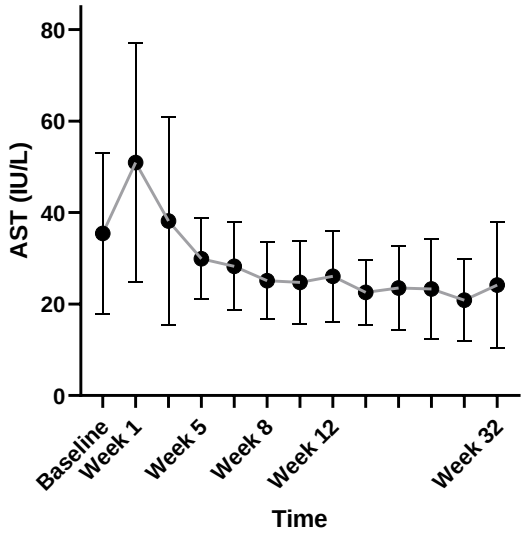
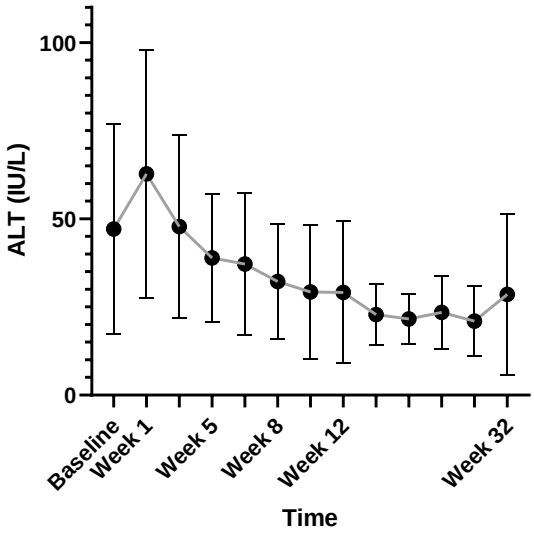
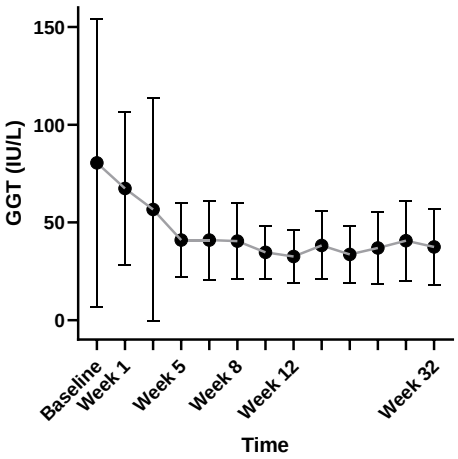


Figure 4. Liver health: AST, ALT and GGT for the duration of the study (n=30 at baseline, n=28 at visit 3, n=27 at visit 5, n=20 at visit 13). Liver stiffness (kPa) at baseline, post-VLCD and 9-months. Per protocol analysis.







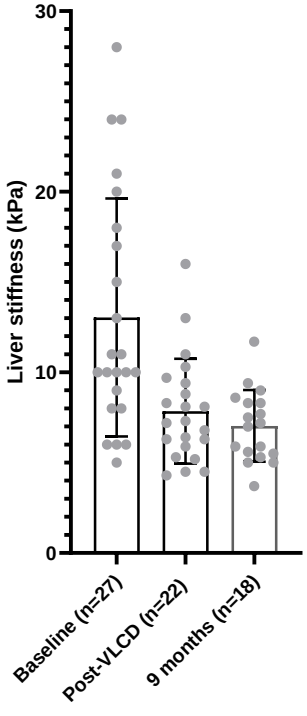


Figure 5. Cardiometabolic risk factor changes throughout study period. Per protocol analysis

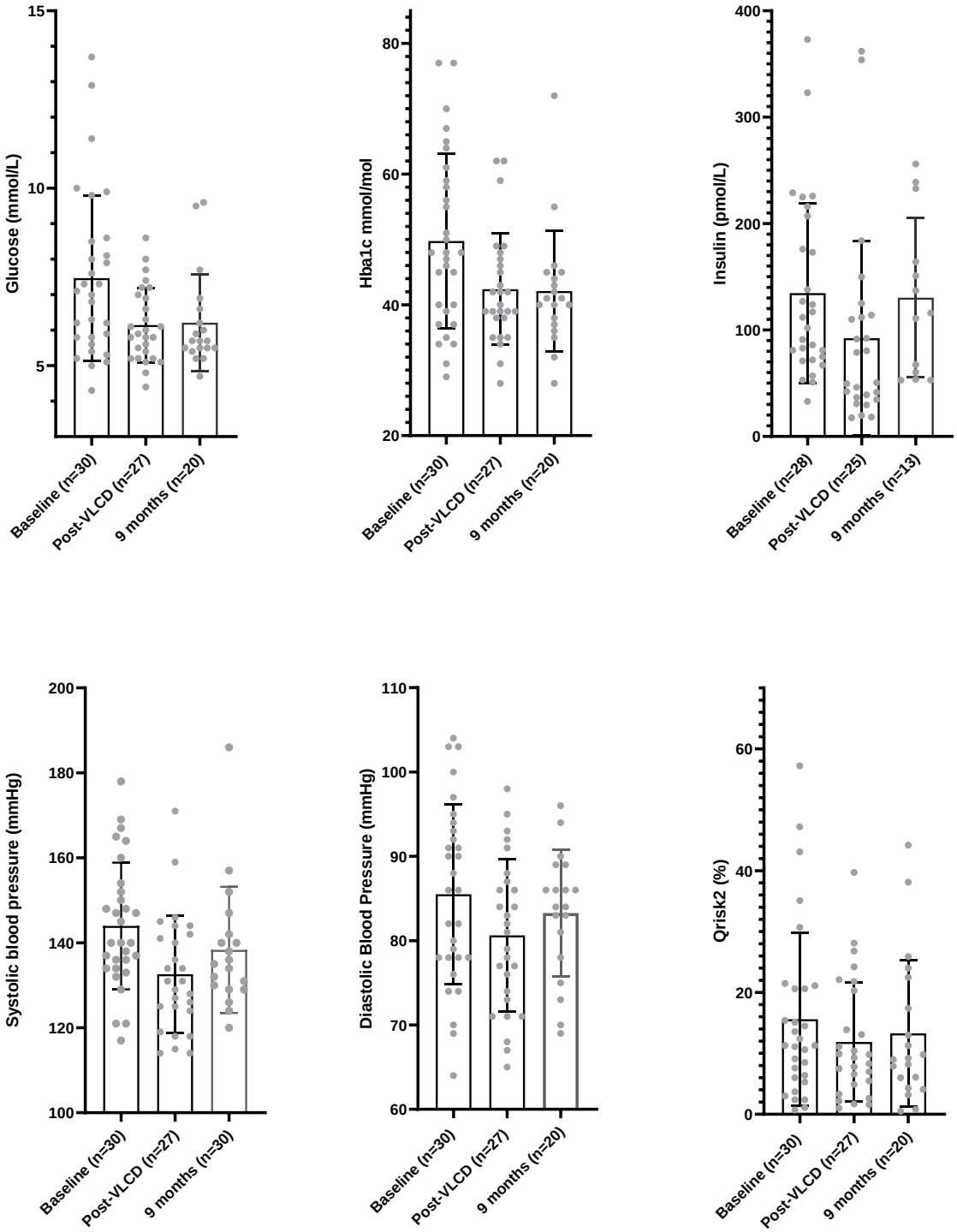


Figure 6. Quality of Life and Weight Related Symptoms at key time points in the study. (An increase in QoL scores indicates better QoL and a decrease in weight-related symptoms indicates an improvement). Per protocol analysis