Feasibility of a Very Low Calorie Diet to Achieve a Sustainable 10% Weight Loss in Patients With Nonalcoholic Fatty Liver Disease

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INTRODUCTION: **Nonalcoholic 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/d) 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-month follow-up.**

RESULTS: **A total of 45 patients were approached of which 30 were enrolled 27 (90%) completed the VLCD intervention, and 20 (67%) were retained at 9-month 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-month 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.**

DISCUSSION: **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.**

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INTRODUCTION

Nonalcoholic 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 might 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 1 year. A randomized controlled trial assessing the effect of weight loss on NASH (14)

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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 with 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 randomized controlled trial of VLCD (DiRECT) conducted in primary care involving patients with T2DM found that 24% of those in the intervention group lost ≥15 kg and mean body weight fell by 10 kg at 1-year follow-up (17). In addition to this study reporting sustained weight loss, 46% of participants had normalization of blood glucose control. Another study showed that 45% of obese patients undertaking a 12-week VLCD maintained ≥10% weight loss at 1-year follow-up (18). Research suggests that VLCD might 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 magnetic resonance 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 after completion of the VLCD. Secondary outcome data were collected to explore the potential effects of the VLCD on 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 body mass index (BMI) >27 kg/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 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 years; ≥2.0 if age ≥65 years) (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 ≥18 years, weight stability (±3%) since biopsy/noninvasive assessment of liver health, and capacity to provide informed consent.

Patients were excluded if they had evidence of coexisting liver disease (e.g., autoimmune liver disease, viral hepatitis, alpha-1 antitrypsin deficiency, hemochomatosis, or Wilson disease), decompensated NASH cirrhosis (Child Pugh score ≥7), current treatment with antiobesity drugs, a diagnosed/previous eating disorder or purging, excessive alcohol consumption (>21 units/wk for men; >14 units/wk for women), insulin use to manage T2DM, known cancer, myocardial infarction within 6 months, and pregnant/considering pregnancy. Subject characteristics are summarized in Table 1.

The study protocol was approved by North East-Newcastle and North Tyneside 1 Research Ethics Committee (REC reference: 18/NE/0179) (ISRCTN Register: ISRCTN85177264). All participants provided written informed consent. After withdrawal from the study, patients were no longer followed up by the research team, and usual clinical care continued. Data were collected and analyzed 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 after completing the VLCD intervention were the primary outcomes.

Secondary outcomes

Secondary outcomes of this study were as follows: absolute change in body weight; change in clinical blood markers; change in cardiac (QRISK2/blood pressure/lipids) and T2DM risk (HbA1c/homeostasis model assessment of insulin resistance [HOMA-IR]/glucose/medication changes); and quality of life (QoL; all measured post-VLCD and at 9 months).

Anthropometry

Body weight (in kilograms) and height (in centimeters) were measured using an electronic stadiometer (SECA 799; SECA, United Kingdom). 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 midpoint 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).

Blood samples

Fasting samples were analyzed 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 γ-glutamyl transferase [GGT]), fasting glucose, HbA1c, insulin, lipid profile, and full blood count.

Liver stiffness

Liver stiffness measurement (LSM) was obtained using FibroScan Mini 430 (Echosens, Paris). All patients were fasted for at least 8 hours before the procedure. The LSM score was represented by the median of 10 measurements and was considered reliable only

Table 1. Subject characteristics

Subject characteristics	Baseline (n = 30)	Post-VLCD (n = 27)	9 mo (n = 20)	Overall *P*	Baseline vs post-VLCD, *P*	Baseline vs 9 mo, *P*
Age (yr)	56 ± 12	55 ± 11	57 ± 11			
Sex (n) male/female	18/12	17/10	10/10			
Time since NAFLD diagnosis (mo)						
Mean	28.4 ± 31.7					
Median (range)	13.5 (1–113)					
Anthropometry						
Weight (kg)	119 ± 25	104 ± 21	100 ± 18	0.000[a]	0.000[a]	0.000[a]
Height (m)	1.7 ± 0.9					
BMI (kg/m^2)	42 ± 8	37 ± 8	35 ± 8	0.004[b]	0.000[a]	0.000[a]
Waist circumference (cm)	126 ± 16	112 ± 17	104 ± 13	0.000[a]	0.000[a]	0.000[a]
Hip circumference (cm)	126 ± 15	117 ± 16	114 ± 15	0.002[b]	0.023[c]	0.003[b]
Fat mass (%)	45 ± 7	40 ± 9	41 ± 10	0.039[c]	0.009[b]	0.004[b]
Skeletal muscle mass (kg)	29 ± 5	27 ± 5	26 ± 6	0.009[b]	0.219	0.009[b]
Blood pressure						
Systolic (mm Hg)	144 ± 15	133 ± 14	138 ± 15	0.009[b]	0.006[b]	0.360
Diastolic (mm Hg)	86 ± 11	81 ± 9	81 ± 7	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[c]	0.079	0.113
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[a]	0.009[b]	0.002[b]
ALT (IU/L)	47 ± 30	31 ± 16	23 ± 10	0.000[a]	0.012[c]	0.002[b]
GGT (IU/L)	82 ± 74	52 ± 72	35 ± 20	0.000[a]	0.000[a]	0.000[a]
Fasting glucose (mmol/L)	7.5 ± 2.3	6.1 ± 1.1	6.2 ± 1.4	0.046[c]	0.028[c]	0.047[c]
HbA1c (mmol/mol)	50 ± 13	42 ± 9	42 ± 9	0.000[c]	0.000[a]	0.002[b]
Insulin (pmol/L)	156 ± 101	101 ± 94	136 ± 76	0.008[b]	0.034[c]	1.000
FibroScan						
Stiffness (kPa)	13.0 ± 6.6	8.0 ± 2.9	6.9 ± 2.0	0.000[c]	0.009[b]	0.004[b]

Table 1. (*continued*)

Subject characteristics	Baseline (n = 30)	Post-VLCD (n = 27)	9 mo (n = 20)	Overall *P*	Baseline vs post-VLCD, *P*	Baseline vs 9 mo, *P*
IQR (kPa)	3.5 ± 3.0	2.5 ± 2.8	1.8 ± 1.0	0.107		
Noninvasive 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[c]	0.074	0.085
HOMA-IR	2.6 ± 1.7	1.7 ± 1.4	2.6 ± 1.4	0.018[c]	0.034[c]	0.273
Weight-related quality of life						
Quality of life	44 ± 26	55 ± 20	56 ± 25	0.005[c]	0.000[a]	0.049[c]
Weight-related symptom measure	46 ± 31	31 ± 23	28 ± 22	0.005[c]	0.024[c]	0.021[c]

Per-protocol (PP) analysis unless specified.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, γ-glutamyl transferase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; IQR, interquartile range; ITT, intention to treat; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; VLCD, very low calorie diet.
[a]Significant to $P < 0.001$.
[b]Significant to $P < 0.01$.
[c]Significant to $P < 0.05$.

if at least 10 successful acquisitions were obtained and the interquartile range-to-median ratio of the 10 acquisitions was ≤0.3 or if the LSM was <7.1 kPa.

Non-invasive risk scores

The NFS (20) and FIB-4 score (23)—validated noninvasive 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 HOMA-IR was used to determine insulin resistance (25). All were calculated for each patient at baseline, post-VLCD, and at 9-month follow-up.

Quality of life

Patients completed the Obesity and Weight-Loss Quality of Life instrument (26) that gives a QoL score (17 item) and a Weight-Related Symptom Measure (20 item). Lower scores in the QoL section indicate a poorer QoL; higher scores in the Weight-Related Symptom Measure section indicate greater symptom burden.

VLCD intervention

Patients were prescribed an 8-week VLCD (~800 kcal/d) 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 4 weeks, to a maximum VLCD intervention of 12 weeks. After 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; fiber 3.5% kcal; and protein 33.7% kcal) free of charge. In addition, patients were encouraged to eat 3 portions (240 g) of nonstarchy vegetables and drink at least 2 L 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 maximize adherence to the protocol and to minimize 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

After completion of the VLCD phase, patients were supported by 2 members of the research team (J.S. and K.H.—both experienced in delivering lifestyle behavior change interventions) to follow a stepped return to normal eating over a 4-week time period. This involved replacing 1 meal replacement product with normal food in the first 2 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 individualized 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 behavioral barriers (e.g., resisting temptation). Patients were advised to monitor their weight

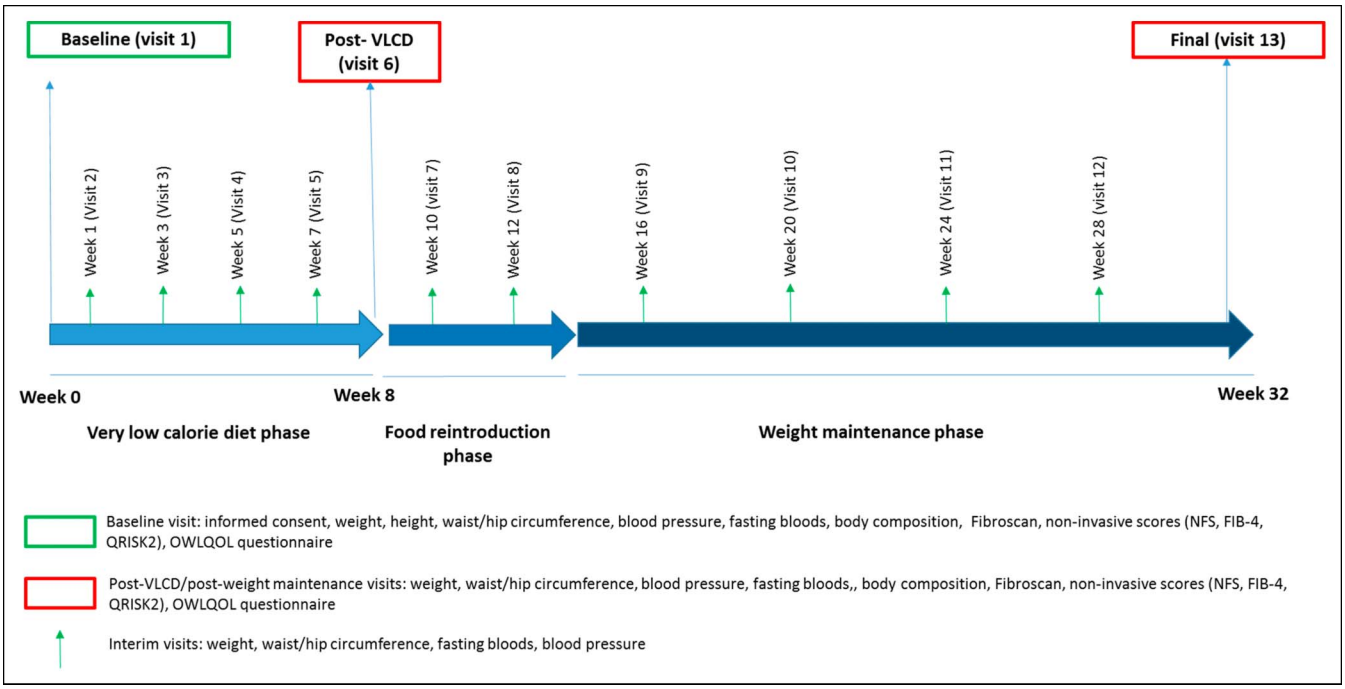

Figure 1. Schedule of study visits. VLCD, very low calorie diet.

weekly at home and were encouraged to monitor their caloric intake—each patient was provided with 2 resource books that 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 fiber) 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 programs (7 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 to prevent weight regain and support weight stabilization and/or further weight loss. Those who were physically capable were advised to increase their daily physical activity or exercise.

Changes to medication

Sulfonylurea oral hypoglycemic agents (gliclazide, glimepiride, and 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 to blood pressure–lowering medications were 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 general practitioner informed.

Data analysis

All primary and secondary data analyses were performed using IBM SPSS (version 24; IBM, New York, NY). Continuous data were tested for normality using the Shapiro-Wilks test, and data are presented as means ± SD, unless otherwise stated (most data were normally distributed). Within-group changes were assessed by repeated-measures 1-way analysis of variance or by Kruskal-Wallis analysis where data were nonparametrically 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 1-way analysis of variance, with further significance explored using a Bonferroni-corrected post hoc analysis. Data for the primary endpoint and overall weight loss outcomes were analyzed per "intention-to-treat" (ITT) analysis. A "per-protocol" analysis was conducted to assess the changes in clinical parameters between the time points because data were 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 6 months. Of the 45 patients approached to take part in this study, 30 (67%) consented to enroll. 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%

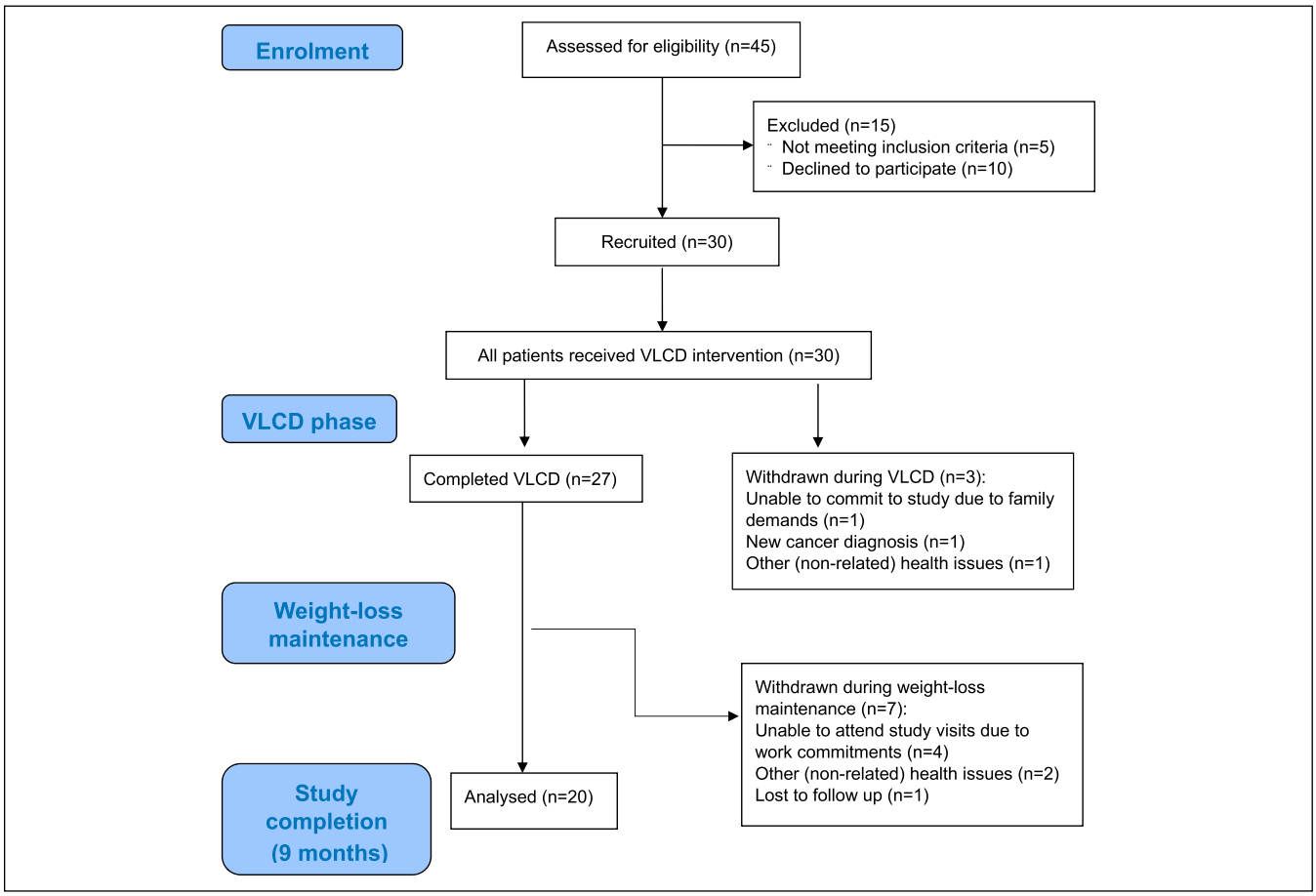

Figure 2. Patient flow throughout the study. VLCD, very low calorie diet.

weight loss at 9-month follow-up, 51% achieved ≥7% weight loss, and 68% achieved ≥5% weight loss. Mean weight loss was 10.3 ± 10.3 kg (range: −42.2 to +6.8 kg) 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 ± 7.7 kg (range: −38.7 to +1.7 kg) or 9.7% ± 5.8% (range: −26.4% to +1.3%). Post-VLCD implementation, 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. Sixty percent of patients recruited were men, and mean age was 56 ± 12 years (see Table 1). The mean weight and BMI at baseline were 119 ± 25 kg and 42 ± 8 kg/m^2, respectively. At baseline, 14 (47%) patients had a BMI between 30 and 40 kg/m^2, 13 (43%) had a BMI between 40 and 50 kg/m^2, and 3 (10%) had a BMI >50 kg/m^2. Overall, 16 (53%) patients had T2DM and 13 (43%) patients had full metabolic syndrome at baseline (29,30).

All patients had either an intermediate/high NFS or intermediate/high FIB-4; 16 of 30 patients also had NASH with fibrosis on biopsy (2 with F1, 6 with F2, 5 with F3, and 3 with F4), as reported using the scoring system by Kleiner et al. (31). The baseline LSM was 13.0 kPa (±6.0 kPa; n = 27) and 17 had an LSM >8 kPa. 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-month follow-up. Fifty-nine percent (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 ± 7.7 kg (range: −38.7 to −3.2 kg) 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 ± 8.3 kg 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 13 kg (range: −42.6 to −0.3 kg) (12% of total body weight).

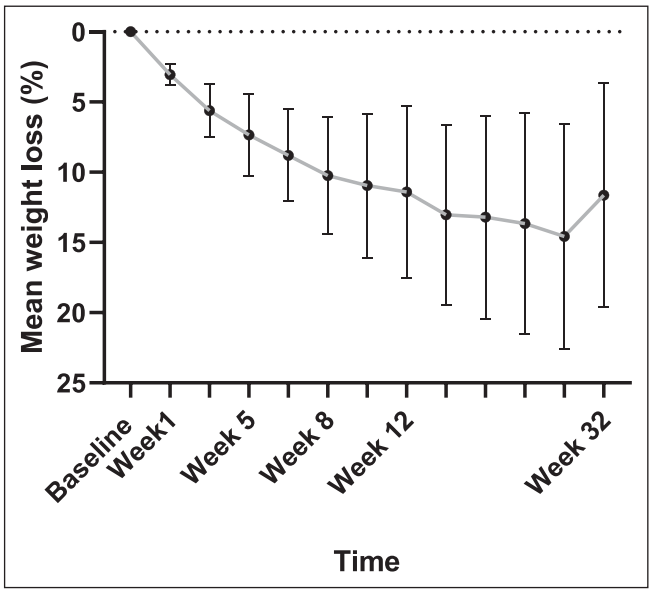

Figure 3. Per-protocol percentage weight loss for the duration of the study: 16 patients completed the VLCD phase at week 8 (visit 6), whereas 11 patients extended the VLCD phase to week 12 (visit 8). Twenty patients completed the 9-month visit (visit 13). VLCD, very low calorie diet.

Between the end of the VLCD and 9-month follow-up, 45% of patients lost further weight (mean further weight loss of 3.3 kg [range: −11.0 to −0.8 kg]) and 55% regained weight, with a mean overall weight regain of 3.2 kg (range: 1.3–4.8 kg) from their post-VLCD weight, equivalent to 3.4% (range: 0.9%–5.7%). After weight regain, no patients exceeded their baseline weight at 9 months. Mean BMI decreased from 42 kg/m^2 (range: 30.3–62.3 kg/m^2) at baseline to 37 kg/m^2 (range: 26.3–58.8 kg/m^2) post-VLCD and 35 kg/m^2 (range: 27.5–57.8 kg/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 ± 5 kg vs 27 ± 5 kg, $P = 0.219$) or between post-VLCD and 9-month follow-up (27 ± 5 kg vs 26 ± 6 kg, $P = 0.617$). However, there was a significant decrease observed between baseline and 9 months (29 ± 5 kg vs 26 ± 6 kg, $P = 0.009$).

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 increase in liver enzymes 1 week into the VLCD that had returned to baseline by week 4. 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 ± 6.7 kPa to 7.9 ± 2.9 kPa; n = 22) and this was maintained at 9-month follow-up (7.0 ± 2.0 kPa; n = 18) $P = 0.001$.

Metabolic control. Metabolic control (glucose, HbA1c, and insulin; Table 1 and Figure 5) 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 5 other patients (16%) had their dosage reduced. At 9 months, 9 of 12 patients with diabetes had achieved good control of their diabetes (HbA1c <48 mmol/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 risk. Cardiovascular changes seen during the study period are summarized in Table 1 and Figure 5. Overall, there was a significant reduction in blood pressure from 144/86 to 133/81 mm Hg post-VLCD, which elevated slightly at 9-month follow-up but did not exceed baseline with a mean blood pressure of 138/83 mm Hg. 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 cardiovascular disease (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. Patients reported a significantly increased QoL 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-month follow-up (Figure 6). Weight-related symptoms score improved from 46 at baseline to 31 post-VLCD and 28 at 9-month follow-up. In addition, 30% of patients reduced the number of medications they were taking during the study.

DISCUSSION

Weight loss achieved through lifestyle behavior 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 study shows that a VLCD intervention is an acceptable and a 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 10.3 kg at 9-month follow-up consistent with previous studies of VLCD (17,36). This compares favorably 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

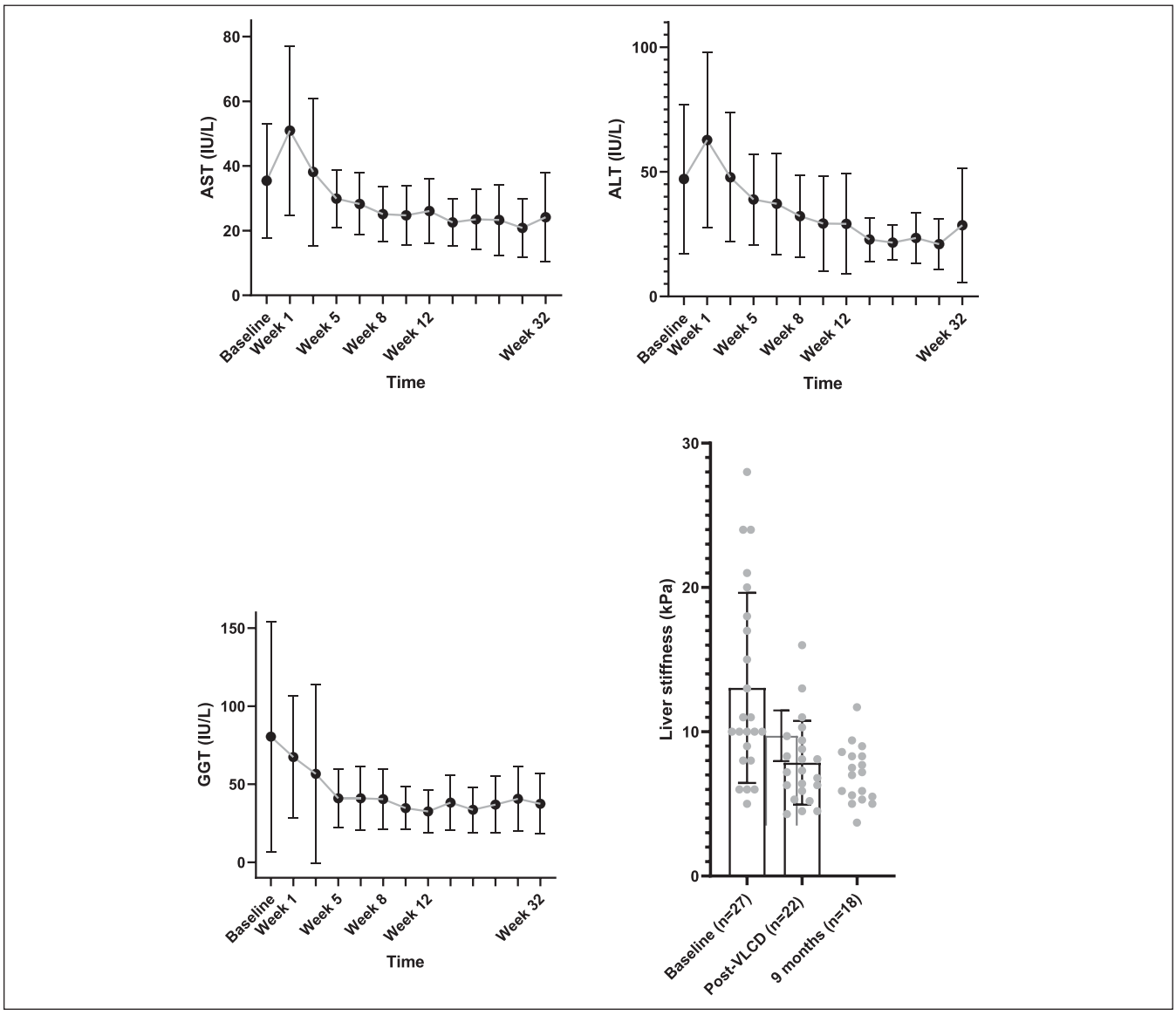

Figure 4. Liver health: AST, ALT, and GGT for the duration of the study (n = 30 at baseline, n = 28 at visit 3, n = 27 at visit 5, and n = 20 at visit 13). Liver stiffness (kPa) at baseline, post-VLCD and 9 months. Per-protocol analysis. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; VLCD, very low calorie diet.

site within 6 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). Although 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 patients with NAFLD 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 patients with NAFLD has not been explored. Therefore, it was important to establish these important outcomes before trialing the intervention to assess the impact on clinical outcomes. In this 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-month 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 this study, there were

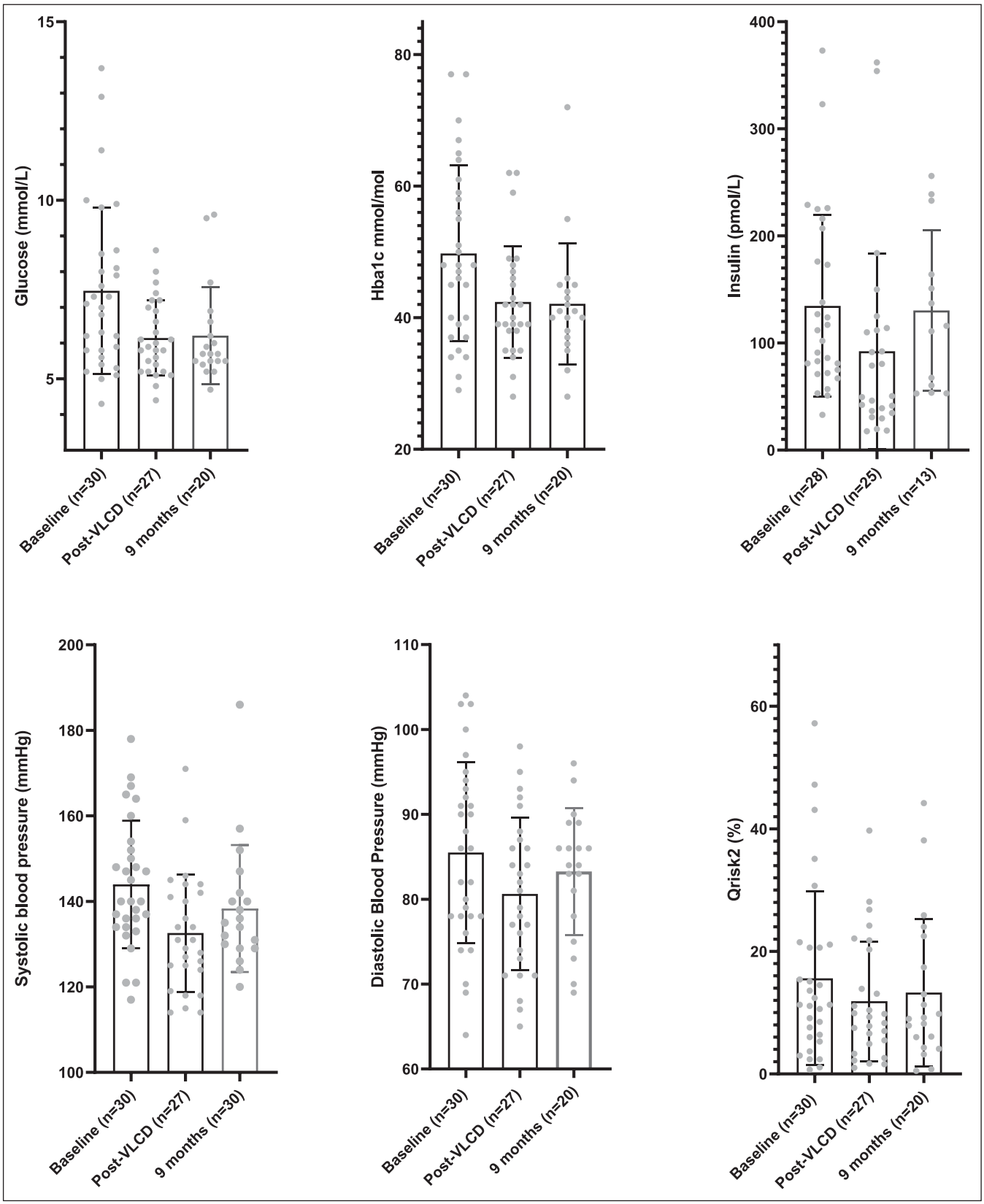

Figure 5. Cardiometabolic risk factor changes throughout study period: Per-protocol analysis. VLCD, very low calorie diet.

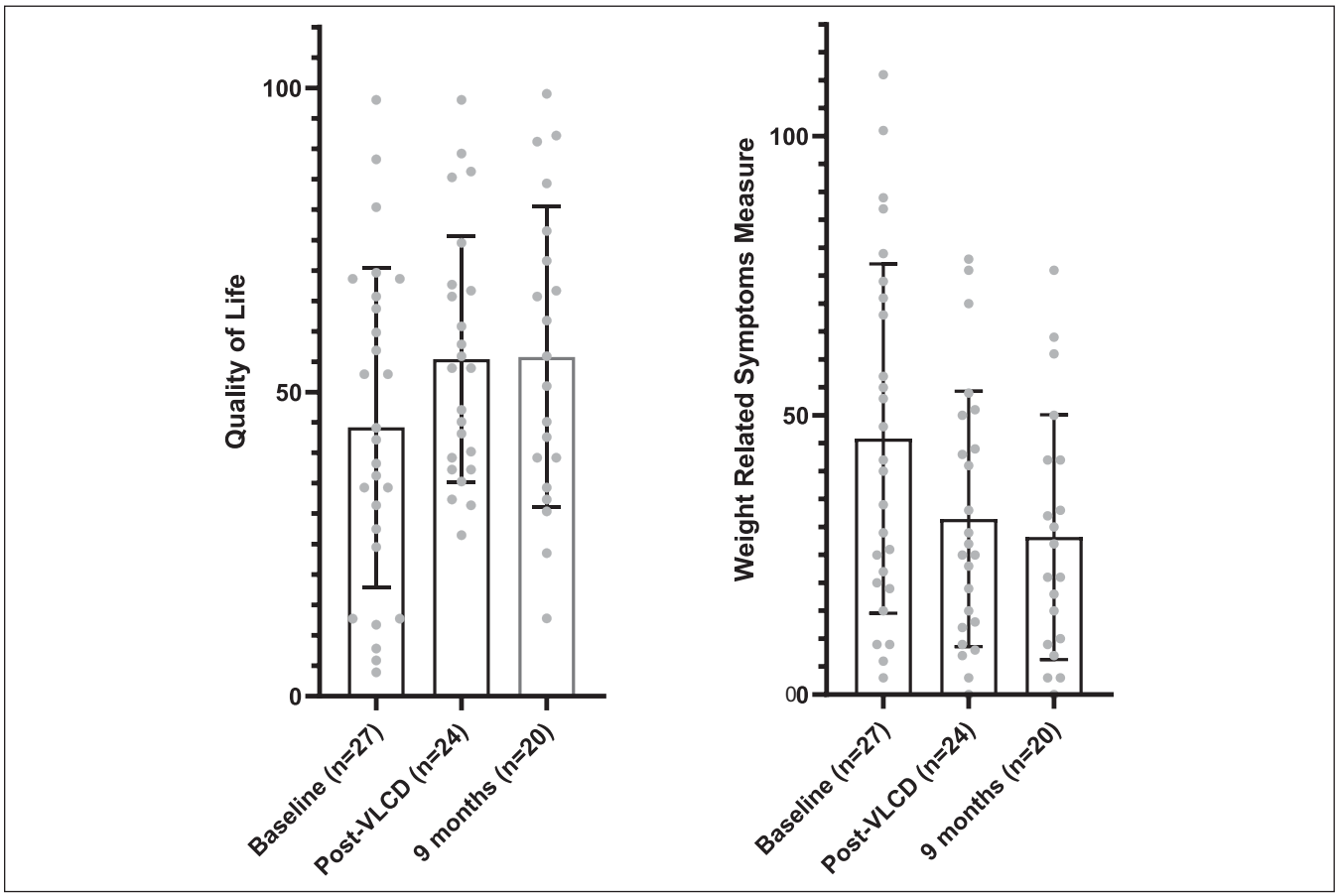

Figure 6. Quality of life (QoL) and weight-related symptoms at key time points in the study. An increase in QoL scores indicates better QoL and a decrease in weight-related symptoms indicates an improvement: Per-protocol analysis. VLCD, very low calorie diet.

improvements in the patients' cardiometabolic status after 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). By 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 an increase in low-density lipoprotein cholesterol and total cholesterol levels and a decrease in high-density lipoprotein cholesterol within the first month of treatment (42).

Interestingly, 1 week into the VLCD, there was a significant increase in serum ALT and AST in participants, which returned to baseline by week 4, and transaminases level fell thereafter. The cause of this acute increase in transaminases was not determined. One potential mechanistic explanation might 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 might cause lipotoxicity in hepatocytes leading to apoptosis and cell death and a consequent increase in liver enzymes. This pathophysiology of this phenomenon requires further investigation.

At baseline, the mean BMI of our cohort was 42 kg/m^2 (morbidly obese), and this reduced to 35 kg/m^2 9 months after the intervention, meaning most of the 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 might feel that reaching a normal BMI is unachievable. A weight loss target of >10%, with appropriate support, might be a more realistic goal that can have significant health benefits. Previously, there have been concerns that VLCD interventions might induce or increase sarcopenia among 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.

In addition to improving liver and cardiometabolic health, it would be advantageous for a treatment for NAFLD to improve QoL because 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 dyslipidemia in a population with NAFLD (44). Therefore, a treatment option that significantly reduced patients' weight to improve obesity and associated comorbidities would be worthwhile to improve QoL. Data have also shown that populations with NAFLD 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 this study, we found that there were significant improvements in QoL and there was a decrease in weight-related symptoms. Improvements in QoL after an intervention are very important, over and above improving liver and cardiometabolic health, because they might 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 might not necessarily be those who are most motivated who engage with this approach, but it might be a case of preference and the desire for rapid weight loss outcomes.

A feature of this 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 for treatment of their NAFLD. Moreover, by 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 might be more generalizable to real populations with NAFLD where patients frequently have multiple comorbidities, when compared with 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, that is, the study was uncontrolled and not powered to detect changes in secondary outcomes. Although it is acknowledged that a pilot randomized controlled trial design would have allowed us to explore estimates of variability, it was important to assess acceptability and feasibility before 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 randomized controlled trial to rehearse a future main trial. Second, noninvasive 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 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. Third, a significant proportion of patients (33%) were lost to follow-up at 9 months, and data on their outcomes were limited (although we did have follow-up data for weight). We were, therefore, unable to accurately describe all ITT outcomes for the whole population. Furthermore, if all outcomes for patients were included, overall cardiometabolic and liver outcomes might have been less pronounced. Fourth, patients on insulin for diabetes were excluded, which represents a significant proportion of the population with NAFLD. The decision to exclude patients on insulin was taken to ensure safety because rapid weight loss can cause hypoglycemia. Fifth, 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, it 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 standardized, and participants could extend the intervention from 8 to 12 weeks if there were mitigating circumstances, and this allowed some participants to optimize their weight loss outcomes. Given that intervention effects started to wear off toward the end of the follow-up period, it is likely that 6-month postintervention 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 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-month follow-up. A VLCD intervention offers a holistic treatment option that could be incorporated as part of clinical care for some patients with NAFLD.

CONFLICTS OF INTEREST

Guarantor of the article: Kate Hallsworth, PhD.

Specific author contributions: J.S.: participated in planning and conducting the study, collecting and interpreting the data, drafting the manuscript, and intellectual contribution. L.A.: participated in planning the study, drafting the manuscript, and intellectual contribution. S.C.: participated in planning the study, interpreting the data, drafting the manuscript, and intellectual contribution. G.T.: participated in data collection and intellectual contribution. L.H.: participated in the planning the study, drafting the manuscript, and intellectual contribution. M.B.: participated in conducting the study, drafting the manuscript, and intellectual contribution. M.T.: participated in planning the study, drafting the manuscript, and intellectual contribution. Q.M.A.: participated in planning and conducting the study, interpreting the data, drafting the manuscript, and intellectual contribution. S.M.: participated in planning and conducting the study, collecting and interpreting the data, drafting the manuscript, and intellectual contribution. K.H.: participated in planning and conducting the study, collecting and interpreting the data, drafting the manuscript, and intellectual contribution. All authors have approved the final draft of the manuscript submitted.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ A weight loss goal of ≥10% has been recommended as the primary treatment for nonalcoholic fatty liver disease (NAFLD).
- ✓ Only few 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 an 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 quality of life 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.

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