


The use of very low-calorie diets in subjects with obesity complicated with nonalcoholic fatty liver disease: A scoping review

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Abstract

This scoping review synthesizes the existing research on the use of very low-calorie diets (VLCDs) in subjects with nonalcoholic fatty liver disease (NAFLD) and end-stage liver disease (ESLD). 19 studies were included, of which 5 were clinical trials, 11 were cohort studies, 1 was a case-control study, and 2 were case series totaling 968 subjects. About 17 studies were focused on patients with NAFLD while the two case series described in patients with ESLD on the transplant list or post-liver transplant. Six studies included subjects managed with VLCDs prior bariatric surgery. Most studies were short term and demonstrated acute improvement of diverse liver biomarkers including liver function tests, indices of hepatosteatosis and reduction in liver size. Adherence rates in these studies were between 69% and 93%. Eight studies did not report any adverse events and four subjects were reported to have discontinued VLCD due to adverse effects in two different studies. Aggregated adverse events were mild. Treatments based on VLCD in subjects with NAFLD seem to be safe and tolerable but can result in mild adverse effects. The findings of this scoping review suggest that the use of VLCD in patients with obesity complicated with NAFLD and potentially in ESLD appear to be effective to induce weight loss and to acutely reduce hepatosteatosis.

KEYWORDS

liver disease, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, very-low calorie diet

1 | INTRODUCTION

The rise in the prevalence of liver disease is thought to be occurring as a direct consequence of obesity and secondary to increases in ectopic adipose tissue in the liver leading to

inflammation, fibrosis, and subsequent organ failure. Weight loss is known to decrease the fat content of the liver and reduce inflammation. Nonalcoholic steatohepatitis (NASH) is predicted to eclipse hepatitis C as the leading indication for liver transplant.^{1,2}

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Very low-calorie diets (VLCD) have been used since the 1920s but became more popular in the sixties.³ The definition of VLCD has shifted over the years but in 1979 an expert panel working for the Life Sciences Research Office of the Federation of American Societies of Experimental Biology defined VLCD as those containing less than or equal to 800 kilocalories per day.⁴ The current definition of a VLCD is a hypocaloric diet comprising 800 kcal per day or less that meets all the vitamin, mineral, electrolyte, and essential fatty acid needs of the individual.

VLCDs have been demonstrated to be effective and safe for short-term weight loss under medical supervision^{4,5} and are commonly used to aid in weight loss and to reduce liver volume prior to bariatric surgery.⁶ Studies have described the effect of VLCD-based treatments on reduction of hepatosteatosis.^{7,8} However, this effect has not been systematically studied in this population.

Scoping review is a form of knowledge synthesis that addresses an exploratory research question aimed at mapping key concepts, types of evidence, and gaps in research related to a defined area or field by systematically searching, selecting, and synthesizing existing knowledge.⁹ The aim of this scoping review is to summarize in a descriptive way the literature evaluating the efficacy, adherence, and safety of VLCD in individuals with NAFLD and chronic liver disease.

Given the paucity and heterogeneity of manuscripts addressing this topic, it was not possible to conduct a systematic review with meta-analysis. Furthermore, we aggregated studies that included subjects undergoing both clinical and surgical management of obesity complicated with NAFLD. Although the inclusion of both clinical and presurgical VLCD interventions add variability to our descriptive results, short-term presurgical studies can provide an insight of the acute effectiveness and safety of VLCD in bariatric surgery patients with NAFLD regarding liver outcomes.

2 | METHODS

2.1 | Protocol

Our review protocol was conducted using the methodological framework described by Arksey and O'Malley and reported using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Protocols Extension for Scoping Reviews.

2.2 | Eligibility criteria

The following parameters aided the search of relevant articles and defined the inclusion criteria for reviewing abstracts: adults (≥ 18 years) with obesity who must either be liver transplant candidates or diagnosed with NAFLD, NASH, or chronic liver

disease. Studies could consist of inpatients or outpatients, but the trials must report on weight loss. The articles must be written in English, Spanish, French, or Italian. All clinical trials, observational trials, cohort studies, case series, and case reports were included. The intervention being reviewed was VLCD, which encompassed any type of planned manipulation of dietary intake that induced an energy deficit, given the intake was no greater than 900 kcal (3700 kJ) per day. We increased the caloric cutoff to 900 kcal/day (as opposed to the VLCD definition of 800 kcal/day) to include more studies that were borderline between a VLCD and low-calorie diet (LCD).

To focus on the research of VLCD in chronic liver disease patients, the following exclusion criteria were agreed upon: studies on pregnant women, subjects < 18 years, subjects with acute medical illnesses or terminally ill. Dietary interventions that included energy intake greater than 900 kcal (3700 kJ) per day, studies that did not include weight loss outcomes or liver disease outcomes, and studies in any language other than English, Spanish, French, or Italian were also excluded. Any publications in the form of editorials, letters to the editor, and comments were excluded.

2.3 | Search methods

The searches were developed and conducted by a health sciences librarian trained in systematic literature searching (HSH). Search strategies employing subject headings and keywords were created for Ovid MEDLINE, Embase (Elsevier), Scopus (Elsevier), and Cochrane CENTRAL (Wiley). The MEDLINE and Embase strategies were peer reviewed by another librarian trained in systematic searching. These strategies were then translated for the remaining two databases. Searches were conducted on 7 February 2020 and updated on 16 November 2020. Search results for Ovid MEDLINE and Embase were limited to references in English, Italian, French, and Spanish. No date limits were applied to any databases. Database records were de-duplicated in EndNote.¹⁰ The search strategies are available in the appendix.

2.4 | Study selection and data management

All abstracts of studies retrieved for selection after de-duplication were split in two and each half reviewed by two reviewers. The reviewers were to independently decide which studies should be included based on the pre-agreed inclusion and exclusion criteria. If a study was included by one reviewer but not the other, it would remain for review of full text. If disagreement occurred, a third reviewer would make the final decision by reviewing the full text. The reviewers were not blinded to institutions, authors, or journals of publication. Excluded studies and reasons for exclusion were documented. An open-source systematic review web-based

software (Rayyan®) was used to support the review screening process. The results of the screening process can be found in Figure 1.

After thoroughly selecting the studies, data extraction was performed, and the following variables were recorded: author(s), year of publication, research design, sample size, location, and outcomes. The primary outcomes of interest included timing and effect measures (length of time on diet), degree of weight loss, change in liver disease burden and eligibility for liver transplant. The percentages of patients who dropped out of studies and patients experiencing major side effects when starting VLCD were carefully noted. Data were collected on many different subgroups based on their age, race, body mass index (BMI), dietary intervention, and transplant candidate status. Data collection was conducted by one reviewer and verified by a second reviewer.

We organized the included manuscripts by study design and number of participants in each category to give a better idea of the hierarchical relevance and contribution of a particular study in the current aggregate knowledge about this topic.

3 | RESULTS

3.1 | Types of studies and participant description

The four databases yielded 2620 records, which after abstract screening left 197 full text studies to review. Of these, 178 were excluded for the following reasons: 63 studies did not have a VLCD (<900 kcal/day), 37 studies did not include participants with chronic liver disease or liver transplant candidates, 34 studies were the incorrect study types (i.e., reviews, commentaries, etc.), 15 studies were poster abstracts without full text, 21 studies were duplicates, 4 studies were incomplete or unpublished clinical trials, and 4 studies were in another language (i.e., not English, Spanish, French, or Italian).

This screening yielded 19 studies that met our inclusion criteria (Figure 1). These studies included 5 randomized trials, 11 cohort studies, 1 case-control study, and 2 case series. About 17 of the studies were focused on subjects with NAFLD and NASH, while two case reports included patients with end-stage liver disease (ESLD) on

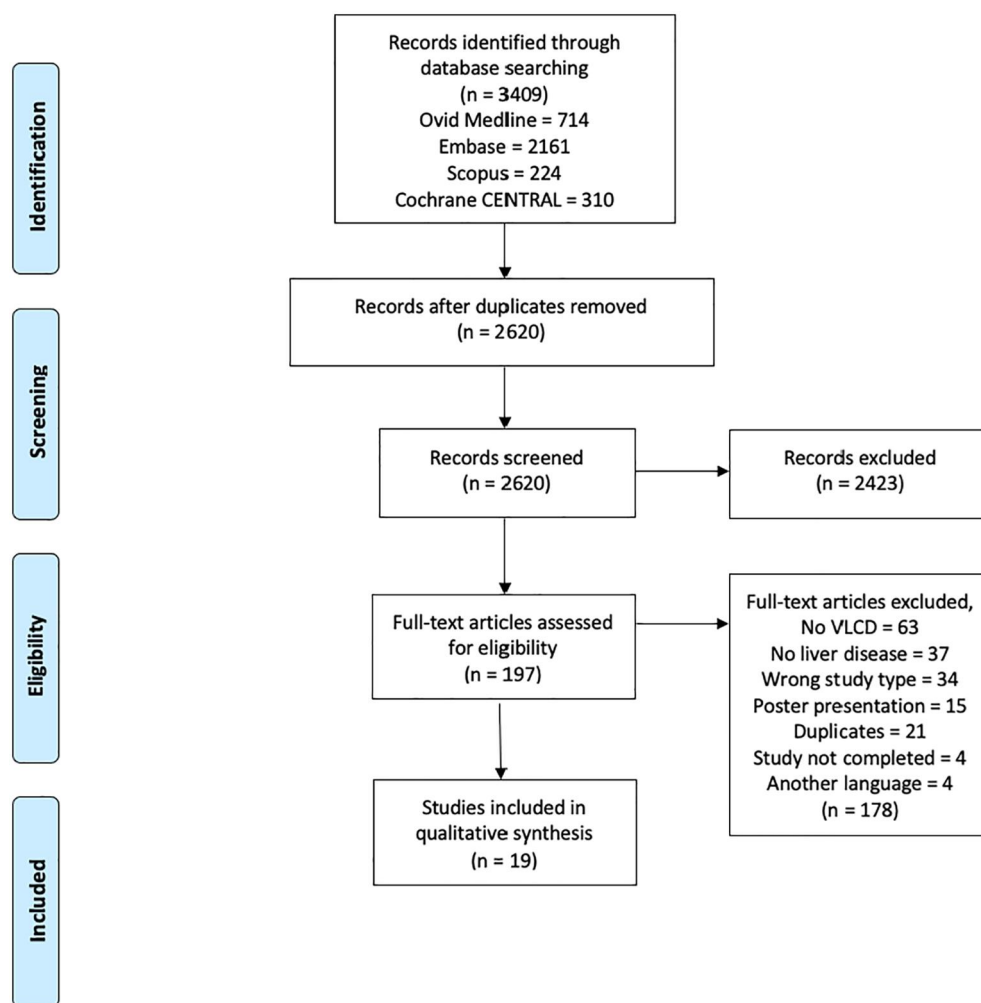


FIGURE 1 Flow diagram of scoping review

the transplant list or post-transplant. A summary of these studies is presented in Tables 1-3.

All five randomized clinical trials included participants with NAFLD. Three of those trials recruited subjects with obesity and NAFLD, and two studies enrolled bariatric surgery candidates (Table 1). The trial by Lin et al. investigated Taiwanese subjects with BMI ≥ 30 kg/m² undergoing VLCD but excluded subjects with type 1 or 2 diabetes and individuals with aspartate transaminase (AST) or alanine transaminase (ALT) more than two times above the upper limit of normal. Abdominal ultrasound revealed NAFLD in 89.2% of the participants.¹¹

Another trial by Contreras et al. recruited men and women with a BMI ≥ 35 kg/m² with associated comorbidities (i.e., type 2 diabetes, hypertension, dyslipidemia, sleep apnea) or BMI ≥ 40 kg/m² and in whom conservative treatment was not successful. These patients were all bariatric surgery candidates. They excluded subjects with BMI < 35 , pregnant women, persons receiving insulin, with severe illness, or presenting eating disorders.¹²

A trial by Chong et al. in New Zealand recruited subjects who had either been diagnosed with NAFLD based on liver biopsy or had a high likelihood of having NAFLD with a BMI ≥ 27 kg/m², elevated ALT (male > 40 U/L, female > 30 U/L), and type 2 diabetes or metabolic syndrome as defined by WHO criteria. They excluded subjects who consumed more than 20 g of ethanol per day for at least three consecutive months, individuals with cirrhosis, hepatitis C, or another liver disease.¹³

In the trial by Baldry et al.¹⁴ they recruited subjects with obesity and BMI ≥ 40 kg/m² who were enrolled in a bariatric surgery program in the United Kingdom and had liver biopsy performed during the surgery.

In the trial by Cunha et al.⁷ subjects were recruited with a BMI ≥ 30 kg/m² while exclusion criteria were diabetes diagnosis during the study, inability to complete the program, history of alcohol abuse, or contraindications to MRI.

Of the 11 cohort studies, 9 were prospective cohorts and 2 were retrospective cohort studies (Tables 2 and 3). The study conducted by Schwenger et al.¹⁵ included subjects who had been confirmed for bariatric surgery and underwent variable periods of weight loss prior to the procedure to improve surgical access. In the study by Hohenester et al.¹⁶ subjects with BMI ≥ 30 kg/m² were recruited while active in a lifestyle intervention program. In the study by D'Abbondanza et al., the subjects had a BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² with obesity related comorbidities (i.e., metabolic disorders, respiratory disease, cardiovascular disease, and osteoarthritis). Exclusion criteria were type 1 diabetes, severe chronic kidney disease (estimated glomerular filtration rate < 30 ml/min), psychiatric disorders, severe liver failure, severe heart failure, excessive alcohol consumption, and chronic hepatitis.¹⁷ In the study by Watanabe et al.,¹⁸ the subjects were required to have BMI ≥ 30 kg/m², stable body weight over 3 months, and a positive screening for fatty liver based on hepatic steatosis index above 36. Exclusion criteria were type 1 diabetes, previous bariatric surgery, or severe cardiac, liver, renal, or hepatic diseases.

In the prospective study by Colles et al., the subjects were recruited if weight was stable over 3 months, with total weight < 155 kg, and BMI was ≥ 40 kg/m² for men and ≥ 50 kg/m² for women. Exclusion criteria included severe hepatic, renal, cardiac diseases, or excessive alcohol intake.¹⁹ In the trial by Scragg et al., participants were required to have a clinically significant diagnosis of NAFLD (i.e., imaging evidence of steatosis and indeterminate or high NAFLD fibrosis scale) and BMI > 27 kg/m². Subjects were excluded if they had a coexisting liver disease, decompensated NASH cirrhosis, eating disorder, excessive alcohol consumption (i.e., > 21 units/week for men or > 14 units/week for women), insulin use, cancer, recent myocardial infarction, or pregnancy.⁸ The study by Lewis et al.²⁰ included subjects on the waiting list for laparoscopic adjustable gastric banding, who were monitored for NAFLD with MRI. In the study by Haas et al.,²¹ the subjects were recruited if they had type 2 diabetes mellitus, BMI > 30 kg/m², and a recently stable weight prior to the study. The small study by Yu et al.²² recruited nondiabetic subjects and BMI ≥ 30 kg/m², who had elevated liver fat content of $> 5.6\%$ as determined by liver MRI and proton magnetic resonance spectroscopy.

In the retrospective cohort study by Schwasinger-Schmidt et al., they included individuals taking part in a physician-directed, community-based weight management program. Subjects were required to have a clinical diagnosis of NAFLD and the average BMI was 45.²³ The retrospective cohort study by Doyle et al.²⁴ included all potential liver donors with hepatic steatosis $\geq 10\%$ at baseline, who were placed on a VLCD, and had liver biopsies at follow up.

One case-control and two case series studies were included (Table 3). The case-control study by Ministrini et al. examined subjects with obesity referred to a bariatric surgery with BMI ≥ 35 kg/m² and obesity-related comorbidities or BMI ≥ 40 kg/m². The control group comprised of 20 healthy, normal-weight subjects. Another group of 20 subjects with grade 1 obesity and no related comorbidities were used as a sham control group. These patients were given nutritional and lifestyle advice at the moment of enrollment.²⁵

In the case series by Bhatti et al.²⁶ inclusion criteria included a BMI ≥ 30 kg/m², either a liver biopsy indicating hepatosteatosis or biopsy confirmed NAFLD, at least 6 months post-liver transplant and not taking corticosteroids. Temmerman et al. reported two cases of patients with obesity who needed to lose weight to make it to the liver transplant list. One patient was a man with alcohol-related cirrhosis, whereas the second patient was a woman with NASH. The BMI goal for both patients was < 37 kg/m² for transplant eligibility.²⁷

3.2 | Interventions

The interventions implemented in the manuscripts were heterogeneous with varying caloric targets and duration of VLCD. In the clinical trial by Lin et al., participants were randomized to either 450

TABLE 1 Description of clinical trial studies

Author (Country)	Study design	Sample % (completed)	Patients included	Intervention	Clinical outcomes	Weight loss outcomes	Liver disease outcomes	Safety
Lin 2009 (Taiwan)	Randomized open -label, parallel trial	95 (72%)	Obesity, NAFLD	Randomized 12 weeks of 450 or 800 kcal/day	Change in body weight, body composition, waist circumference, lipids, liver ultrasound	Average weight loss of 9.2% and 8.9% in 450 kcal/day and 800 kcal/day, respectively	16% of participants with NAFLD on ultrasound returned to normal by 12 weeks	103 adverse events (60 may be treatment related); no serious adverse events
Contreras 2018 (Spain)	Randomized open -label, parallel trial	84 (98%)	Obesity, LAGB candidates, NAFLD	Randomized to 21 days of 800 kcal/day of meal replacement versus 1200 kcal diet prior to bariatric surgery	Body weight change, body composition, liver volume, surgical complications	Weight loss of 5.8% in VLCD compared to 4.2% in LCD	Liver volume reduced by 15.6% \pm 11.2% in VLCD and 12.3% \pm 10.6% in LCD (not significant)	More participants in VLCD had dizziness (39.5% vs. 12%) and weakness (37.2% vs. 21%) than LCD
Chong 2020 (New Zealand)	Randomized double-blind placebo-controlled trial	56 (93.3%)	NAFLD	4 weeks of 600 kcal/day, then randomized into three groups (MI, PI, PP) for 12 weeks	Maintaining \geq 7% weight loss at 16 weeks, changes in ALT, glycemia, lipids, elastography, gut microbiome	Maintenance of \geq 7% weight loss was 55%, 53%, and 35% for the MI, PI, and PP groups, respectively	MI group had a significant reduction in ALT of 19.6 U/L	No adverse events
Baldry 2016 (UK)	Randomized open -label, parallel trial	54 (90%)	Bariatric surgery candidates, NAFLD	Randomized 2 weeks of 800 kcal/day (food-based or meal replacement shake)	Liver biopsy histological assessment at end of diet, weight loss, inflammatory markers, and difficulty of surgery	Weight loss of 3.6% in the food group and 3.4% in the meal replacement groups (not significant)	50% of food group and 64% in the meal replacement group had steatosis (not significant)	1 adverse event and 1 serious adverse event likely unrelated to intervention
Cunha 2020 (Brazil)	Randomized open -label, parallel trial	39 (84.8%)	Obesity, NAFLD	Randomized to 2 months of either low carbohydrate (<50 g) 600-800 kcal/day	Body weight change, abdominal MRI to measure visceral adipose tissue area and liver PDFF,	Average weight loss of 9.6% \pm 2.9% in the VLCKD and 1.9% \pm 2.4% in the lower calorie group	Liver PDFF mean reduced 38.5% on VLCKD. Liver steatosis (PDFF>5.4%) decreased from 70%	No adverse events

TABLE 1 (Continued)

Author (Country)	Study design	Sample % (completed)	Patients included	Intervention	Clinical outcomes	Weight loss outcomes	Liver disease outcomes	Safety
				diet or diet with 15% deficit (1400–1800 kcal/day)	elastography for liver stiffness		to 30% in the VLCKD group	

Abbreviations: ALT, alanine transaminase; LAGB, laparoscopic adjustable gastric banding; LCD, low calorie diet; NAFLD, nonalcoholic fatty liver disease; MI, metronidazole/inulin, PI, placebo/inulin, PP, placebo/placebo; PDFF, proton density fat fraction; VLCD, very low calorie diet; VLCKD, very low calorie ketogenic diet.

or 800 kcal/day for 12 weeks. They also performed ultrasound for NAFLD and assessed a host of measures including waist circumference, hip circumference, body composition with electrical impedance, resting metabolic rate, fasting glucose, and lipid profile at baseline and at week 12.¹¹

In the trial by Contreras et al., subjects were randomized to 21 days of either 800 kcal/day meal replacements or 1200 kcal/day diets prior to bariatric surgery. They measured body weight change and composition, liver volume, and surgical complications during bariatric surgery.¹²

In the trial by Chong et al., participants were allowed 600 kcal/day for 4 weeks and were then randomized into three groups (i.e., metronidazole and inulin, placebo and inulin, and double placebo) to investigate whether metronidazole and/or inulin would further reduce ALT and maintain weight loss after the VLCD.¹³ The outcomes of this study included maintenance of weight loss $\geq 7\%$ at 16 weeks, changes in ALT, elastography, and gut microbiome in response to the dietary and pharmacological interventions.¹³

In the trial by Baldry et al., participants consumed an 800 kcal/day diet for 2 weeks but were randomized to consume these calories as either meal replacements or through natural foods. Weight loss, technical challenges of surgery, and liver biopsies were assessed in this clinical trial.¹⁴

In the trial by Cunha et al., participants were randomized to 2 months of either low carbohydrate (i.e., < 50 g/day) 600–800 kcal/day diet or a diet with a 15% caloric deficit from calculated requirements resulting on a calorie intake of 1400–1800 kcal/day. They measured body weight change, abdominal MRI, and elastography to assess liver stiffness.⁷

In the prospective cohort study by Schwenger et al., each participant was given replacement meals as shakes consisting of 900 kcal/day, lasting 1 week for every 100 lbs of body weight. The mean duration of the intervention was of 2.6 weeks. Besides insulin resistance evaluation, liver histology, and metabolic biomarkers including HbA1c, insulin, glucose, liver enzymes, lipid profile, and platelets were measured in this cohort.¹⁵

In the cohort study by Hohenester et al., participants were on an 800 kcal/day diet for 12 weeks followed by a normal diet for a total of 52 weeks. Response to therapy was defined as a 5% weight loss for BMI < 35 kg/m² and a 10% weight loss for BMI ≥ 35 kg/m². Measurements of LFTs and abdominal ultrasound were used to calculate the fatty liver index (FLI).¹⁶

In the study by D'Abbondanza et al., participants were placed on a low carbohydrate diet with 800 kcal/day for 25 days. They measured changes in body weight, body composition, abdominal ultrasound, liver enzymes, hemoglobin A1c, and homeostatic model assessment for insulin resistance (HOMA-IR).¹⁷

In the cohort by Watanabe et al., participants were given an 800 kcal/day diet for 45 days with a subsequent 1150 kcal/day diet for another 45 days. Outcomes included changes in the hepatic steatosis index, body weight, liver enzymes, and metabolic markers like hemoglobin A1c.¹⁸

TABLE 2 Description of prospective cohort studies

Author (Country)	Study design	Sample (%completed)	Patients included	Intervention	Clinical outcomes	Weight loss outcomes	Liver disease outcomes	Safety
Schwenger 2018 (Canada)	Prospective cohort study	139 (N/A)	Bariatric surgery candidates, NAFLD	Meal replacement 900 kcal/day for a median of 2.6 weeks	Liver biopsy histological assessment, weight loss, waist circumference, lipids, LFTs, HOMA-IR	Weight loss per week was 3.7 kg (9.6 kg total)	NAFLD diagnosed in 76.3% of patients (18.9% NASH), ALT and AST increased on VLCD	No adverse events reported
Hohenester 2018 (Germany)	Prospective cohort study	121 (79.6%)	Obesity, NAFLD	12 weeks of 800 kcal/day followed by normal diet to 52 weeks	Therapy response is 5% weight loss in BMI <35 and 10% in BMI of ≥ 35 , LFTs, abdominal ultrasound, fatty liver index	With ITT analysis, 67.8% had a treatment response and 85.1% had per protocol response	FLI declined from 98.1% to 54.3% of patients; abnormal ALT declined from 81% to 50.5% of patients	No adverse events reported
D'Abbondanza 2020 (Italy)	Prospective cohort study	70 (96%)	Obesity, NAFLD	25 days of low carbohydrate diet (<50 g) 800 kcal or less per day	Body weight, waist circumference, body composition via bioimpedance, abdominal ultrasound, LFTs, hemoglobin A1c, HOMA-IR	Average weight loss of 13 kg for males and 10 kg for females	Grade 3 steatosis decreased from 58.3% of male participants to 18.8% and from 41.7% of females to 18.2%	No adverse events reported
Watanabe 2020 (Italy)	Prospective cohort study	45 (69%)	Obesity, NAFLD	45 days of 800 kcal/day with meal replacements then 45 days of 1150 kcal/day	HSI, body weight changes, waist circumference, body composition, lipids, hemoglobin A1c, LFTs	Average weight loss of 8.6% \pm 2.5% after the first phase and 12.5% \pm 3.7% at the end	HSI decreased from 47.5 \pm 7.5 to 33.5 \pm 4.6, ALT decreased from 22 to 16.	No adverse events reported
Colles 2006 (Australia)	Prospective cohort study	32 (86%)	Obesity, LAGB candidates, NAFLD	12 weeks of 450-680 kcal/day meal replacement with non-starchy vegetables	Body weight changes, BMI, waist circumference, liver volume, VAT, LFTs, hemoglobin A1c, lipids	Average weight loss of 14.8 \pm 7.2 kg	Liver volume decreased 18.7%, VAT decreased 16.9%, and LFTs did not change	Four patients had taste intolerance, nausea and vomiting
Scragg 2020 (UK)	Prospective cohort study	27 (90%)	Obesity, NAFLD	8-12 weeks of 800 kcal/day with 4 weeks of food reintroduction and 20-week	Feasibility and 10% weight loss at follow up, body weight, LFTs, glucose, lipids, hemoglobin A1c, elastography	34% of patients had $\geq 10\%$ weight loss at 9 months. At the end of VLCD, 53% achieved $\geq 10\%$ weight loss.	AST reduced from 35 \pm 18 to 24 \pm 14, ALT reduced from 47 \pm 30 to 23 \pm 10, and GGT reduced from 82 \pm 74 to 35 \pm 20 by 9 months	No adverse events reported

TABLE 2 (Continued)

Author (Country)	Study design	Sample (%completed)	Patients included	Intervention	Clinical outcomes	Weight loss outcomes	Liver disease outcomes	Safety
Lewis 2006 (Australia)	Prospective cohort study	18 (85.7%)	LAGB candidates, NAFLD	weight maintenance phase 6 weeks of 450–800 kcal/day meal replacement	Liver size/fat content, weight loss, and ease of operative access	Mean weight loss was 9.7% ± 5.8%. LSM improved between baseline and post-VLCD (13.0 ± 6.7 to 7.9 ± 2.9 kPa) that was maintained at 9-month (7.0 ± 2.0 kPa)	Relative reduction in liver fat and volume were 43% and 14.7%, respectively	3 patients did not tolerate VLCD
Haas 2020 (Sweden)	Prospective cohort sub-study	10 (90%)	Obesity, diabetes, NAFLD	7 weeks of 800 kcal/day followed by 2-week reintroduction and weight maintenance for a year	Body weight change, body composition, elastography to estimate hepatic steatosis, ALT, hemoglobin A1c	Average weight loss of 15 kg over 7 weeks	ALT reduced from 0.57 to 0.40 mmol/L	1 participant had gastro-intestinal adverse effects and dropped out after 3 weeks
Yu 2014 (China)	Prospective cohort study	8 (N/A)	Obesity, NAFLD	8 weeks of 800 kcal/day	Weight loss, body composition, liver fat, hepatic glucose production	Average weight loss of 7% (6.8 kg)	Relative liver fat percentage decreased 67% and HGP decreased 22%	No adverse events reported

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; FLI, fatty liver index; GGT, gamma-glutamyl transferase; HGP, hepatic glucose production; HOMA-IR, homeostatic model assessment of insulin resistance; HSI, hepatic steatosis index; ITT, intention to treat analysis; LAGB, laparoscopic adjustable gastric banding; LFT, liver function test; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; VAT, visceral adipose tissue; VLCD, very-low-calorie diet.

TABLE 3 Description of retrospective cohort, case-control and case series studies

Author (Country)	Study design	Sample (% completed)	Patients included	Intervention	Clinical outcomes	Weight loss outcomes	Liver disease outcomes	Safety
Schwasinger-Schmidt 2017 (USA)	Retrospective cohort study	97 (N/A)	NAFLD	12 weeks of 800 kcal per day in meal replacements	Reductions in LFTs, weight loss, waist circumference	Average weight loss of 13% of body weight	44% reduction in ALT and 41% reduction in AST observed at 12 weeks	No adverse events reported
Doyle 2016 (Canada)	Retrospective cohort study	16 (88.9%)	Liver donors, NAFLD	≥4 weeks of 900 kcal/day meal replacement (median 7.3 weeks)	Change in BMI, post-diet liver biopsies, diet tolerability, donor/recipient outcomes	BMI was reduced from 32.7 to 28.3.	Steatosis decreased from 29.3% to 4.75% in patients with prior biopsy	Two adverse events (constipation)
Ministrini 2019 (Italy)	Case control study	52 (N/A)	Bariatric surgery candidates, NAFLD	25 days of 800 kcal/day	Weight loss, liver steatosis on ultrasound, lipids, glucose, lysosomal acid lipase	Average weight loss of 7 kg	Grade 3 steatosis decreased from 43.1% to 23.5% of patients	No adverse events reported
Bhatti 2015 (USA)	Case series	3 (N/A)	Obesity, NAFLD, post-liver transplant or pre-liver transplant	500–800 kcal per day diet for 6 months	Weight loss, body composition, BMI, LFTs	Patient 1 lost 31 lb, patient 2 lost 81 lb, patient 3 lost 53 lb	Reduction in ALT from 108 to 38 and AST from 40 to 24 in patient 3, otherwise LFTs unchanged	No adverse events reported
Temmerman 2013 (USA)	Case series	2 (N/A)	ESLD, Obesity, liver transplant candidates	Patient 1 on 800 kcal/day for 28 weeks, patient 2 on 800 kcal/day for 30 weeks	Weight loss, need for transplant, safety	Patient 1 lost 44.1 kg, patient 2 lost 39.7 kg	Patient 1 was taken off the transplant list while patient 2 had stable MELD scores	No adverse events reported

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; ESLD, end-stage liver disease; LFT, liver function test; MELD, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease.

In the cohort study by Colles et al., the participants were on a 450–680 kcal/day diet with meal replacements and non-starchy vegetables for 12 weeks. Outcomes included body weight changes, BMI, visceral adipose tissue changes, liver volume, liver enzymes, and hemoglobin A1c.¹⁹

In the study by Scragg et al., subjects received 8–12 weeks of 800 kcal/day with 4 weeks of food reintroduction and 20 weeks of weight maintenance. Outcomes includes percent of subjects with 10% weight loss, body weight changes, liver enzymes, and metabolic markers like hemoglobin A1c.⁸

In the cohort study by Lewis et al., participants were on a 450–800 kcal/day diet for 6 weeks. Liver size and fat content measured via MRI/nuclear magnetic resonance spectroscopy and ease of operative access were evaluated.²⁰

In the study by Haas et al., the participants were on an 800 kcal/day diet for 7 weeks with a 2-week reintroduction with a subsequent goal of weight maintenance for 1 year. Outcomes included body weight changes, elastography to estimate steatosis, ALT, and hemoglobin A1c.²¹

In the prospective cohort study by Yu et al., patients were put on an 800 kcal/day diet for 8 weeks. The outcomes of interest included weight loss, body composition, liver fat content, and hepatic glucose production.²²

In the retrospective study by Schwasinger-Schmidt et al., participants were placed on an 800 kcal/day diet for 12 weeks. Outcomes included reductions in liver enzymes, weight changes, and waist circumference.²³ In the retrospective cohort study by Doyle et al., participants were on a 900 kcal/day diet for a median of 7.3 weeks. Changes in BMI, post-intervention liver biopsies, and donor/recipient outcomes were recorded.²⁴

In the case-control study by Ministrini et al., 52 patients with obesity were on a ketogenic 800 kcal/day diet for 25 days. Liver steatosis on ultrasound and other metabolic markers (i.e., lysosomal acid lipase, blood count, gamma glutamyl transpeptidase, lipid profile, fasting glucose, and insulin) were assessed.²⁵ In the case series by Bhatti et al., participants were on a 500–800 kcal/day diet for 6 months and outcomes included weight loss, body composition changes, and liver enzyme changes.²⁶ In the case report by Temmerman et al., both patients were on an 800 kcal/day ketogenic diet for 28 and 30 weeks, respectively. The safety of the intervention, and the need for transplant were reviewed in this case report.²⁷

3.3 | Weight loss and liver disease outcomes

Our focus in this scoping review is to explore how effective VLCD is in facilitating weight loss and improvements in liver fatty infiltration in subjects with chronic liver disease and in candidates for liver transplant. While studies reported variable weight loss and liver outcomes, they all reflect that VLCD is effective in assisting patients lose weight and reduce NAFLD burden. In the clinical trial by Lin et al., the average weight loss was 9.18% and 8.98% in the 450 and 800 kcal/day groups, respectively. Ninety three participants had two

abdominal ultrasound examinations at the beginning and end of the study. Nonalcoholic fatty liver disease (NAFLD) was detected in 83 (89.2%) of these participants and there were 15 (16.1%) participants whose NALFD resolved by the end of the 12-week dietary intervention.¹¹

In the clinical trial by Contreras et al., the participants in the VLCD group lost 5.81% of their body weight and those in the LCD group lost 4.19% of their body weight which was significantly different. Liver volume was reduced in both groups (i.e., $15.6\% \pm 11.2$ in the VLCD and $12.3\% \pm 10.6$ in the LCD groups) but this was not statistically different.¹²

In the clinical trial by Chong et al., maintenance of $\geq 7\%$ of body weight loss at 16 weeks was observed in 55%, 53%, and 35% for the metronidazole/inulin (MI), placebo/inulin (PI), and placebo/placebo (PP) groups, respectively. At 28 weeks, a sustained weight loss of $\geq 7\%$ was reached by 42% in group MI, 35% in group PI, and 25% in group PP. These results suggest that the metronidazole and inulin can promote weight maintenance after a VLCD intervention. The only significant liver disease outcome in this trial was a mean reduction in ALT in the MI group by 19.6 U/L. Otherwise between groups there was no significant difference in the changes in ALT, glycemia, lipids, or elastography.¹³

In the Baldry et al. clinical trial, participants lost 3.6% of their bodyweight in the natural food group and 3.4% in the meal replacement group over 2 weeks. It was noted that 12 of 28 (43%) of the participants in the natural food group and 18 of 28 (64%) of the participants in the meal replacement groups exhibited liver steatosis after the dietary interventions with no significant difference between groups. There was no significant difference between groups in steatosis grade, liver cell injury, portal inflammation, lobular inflammation, or fibrosis stage. These results suggest that these diets are equivalent in reducing body weight and do not appear to have any difference in reducing liver fat.¹⁴

In the trial by Cunha et al., average weight loss was $9.59 \pm 2.87\%$ in the very low-calorie ketogenic diet (VLCKD) group and $1.87 \pm 2.4\%$ in the LCD group. Liver proton density fat fraction was reduced on average 38.5% in the VLCKD group and 2.7% in the LCD group. Liver steatosis decreased from 70% to 30% in the VLCKD group whereas the LCD group decreased from 63.2% to 52.6%.⁷

In the prospective cohort study by Schwenger et al., the mean weight loss was 9.59 kg over the course of 2.6 weeks of VLCD.¹⁵ NAFLD was diagnosed via liver biopsy during bariatric surgery in 76.3% of participants after the diet. Eighty one percent of patients diagnosed with NAFLD had simple steatosis and 18.9% had NASH. It was also noted that ALT and AST increased slightly while on the VLCD. Aspartate aminotransferase increased an average of 8.71 U/L and ALT increased an average of 10 U/L.¹⁵ This observation has been previously reported in the literature associated with transient weight loss, notably in women. Of note, in this study, 73.4% of participants were women. Importantly, ALT has also been shown to normalize during a eucaloric diet.^{28,29}

In the prospective cohort study by Hohenester et al., 85.1% of participants responded to the VLCD for 12 weeks. Presence of

steatosis by ultrasound declined from 86.6% to 38.6% of participants. Eighty one percent of participants exhibited an elevated ALT before the intervention, which declined to 50.5% after VLCD.¹⁶

In the prospective study by D'Abbondanza et al., there was an average weight loss of 13 kg for men and 10 kg for women. Grade 3 steatosis decreased from 58.3% to 18.8% in men and from 41.7% to 18.2% in women.¹⁷

In the cohort study by Watanabe et al., there was an average weight loss of $8.6 \pm 2.5\%$ after the first phase of the diet and $12.5 \pm 3.7\%$ at the end of the LCD. The hepatic steatosis index decreased from 47.5 ± 7.5 to 33.5 ± 4.6 at the end of the study. Mean ALT decreased from 22 to 16 U/L and AST was not changed.¹⁸

In the cohort by Colles et al., there was an average weight loss of 14.8 ± 7.2 kg and liver volume decreased 18.7%, visceral adipose tissue decreased by 16.9%, and LFTs were unchanged.¹⁹

In the cohort by Scragg et al., 34% of patients had $\geq 10\%$ weight loss at 9 months. At the end of the VLCD, the mean weight loss percentage was $9.7 \pm 5.8\%$. AST was reduced from 35 ± 18 to 24 ± 14 IU/L, ALT reduced from 47 ± 30 to 23 ± 10 IU/L, and GGT reduced from 82 ± 74 to 35 ± 20 IU/L by 9 months.⁸ In the Lewis et al. prospective cohort study, 61% of participants had fatty liver and there was an average weight loss of 9.1 kg over the 6 weeks. Weight loss was associated with a reduction in liver volume and fat content of 14.7% and 43%, respectively, whereas liver fat was reduced by 72.5% in participants with hepatic steatosis.²⁰

In the prospective cohort by Haas et al., participants lost an average of 15 kg over 7 weeks and ALT was reduced from 0.57 mmol/L to 0.40 mmol/L.²¹ In the prospective cohort study by Yu et al., the participants lost an average of 7% (6.8 kg) of their body weight over 8 weeks. The reduction of liver fat content was 67% and hepatic glucose production decreased by 22%.²²

In the retrospective cohort by Schwasinger-Schmidt et al., there was an average weight loss of 13% of body weight, 44% reduction in ALT, and 41% reduction in AST over 12 weeks.²³ In the Doyle et al. retrospective cohort study, BMI was reduced from 32.7 to 28.3 kg/m², whereas liver steatosis decreased from 29.3% to 4.75% per liver biopsies before and after VLCD. ALT decreased on average by 9 IU/L and AST decrease on average 4 IU/L.²⁴

In the Ministrini et al. case-control study there was an average weight loss of 7 kg, and the proportion of participants with grade 3 steatosis decreased from 43.1% to 23.5%.²⁵ In the case series by Bhatti et al., patient #1 lost 31 lbs, patient #2 lost 81 lbs, and patient #3 lost 53 lbs. Only one patient had significant reduction LFTs as patient #3 ALT reduced from 108 to 38 and AST from 40 to 24.²⁶ In the Temmerman et al. case report, the man with alcohol-related cirrhosis lost 44.1 kg over 28 weeks and the woman with NASH lost 39.7 kg over 30 weeks. The male patient transitioned to a balanced diet after weight loss and his model for end-stage liver disease (MELD) score reduced from 14 to 10. Importantly, with this improvement in MELD score the patient no longer required transplant listing for 6 months after the VLCD. The female patient also transitioned to a balanced diet but her MELD score that went up

slightly from 16 to 19. She was still awaiting transplant by the time of the case report publication.²⁷

Altogether, these results confirm VLCD-dependent weight loss in subjects with NAFLD and suggest improvement in liver steatosis. Body weight losses of 5% or more are common with VLCD lasting at least 2 weeks.

3.3.1 | Safety

Eight of the reviewed studies did not mention or report on any adverse events during VLCD. In the Lin et al. clinical trial, 103 adverse events were reported and 60 of those were considered to be related to the VLCD. However, no serious adverse events were reported.¹¹ In the Contreras et al. trial, more participants in the VLCD group had dizziness (39.5% vs. 12%) and weakness (37.2% vs. 21%) than in the LCD group.¹² In the Chong et al. clinical trial, they reported no adverse events. In their clinical trial, Baldry et al. reported 1 adverse event and 1 serious adverse event but neither were related to the VLCD.¹⁴ In the prospective study by Colles et al., four patients noted taste intolerance causing nausea and occasional vomiting.¹⁹ In the prospective cohort study by Lewis et al., three participants could not tolerate the VLCD. In the prospective cohort study by Haas et al., one participant had gastro-intestinal adverse effects and dropped out of the study. In the retrospective cohort study by Doyle et al., two participants reported constipation related to the VLCD.^{20,21,24} In the Ministrini et al. case-control study, the case series by Bhatti et al., and in the Temmerman et al. case report no adverse events to VLCD were observed.

4 | DISCUSSION

According to the American Association for the Study of Liver Diseases, the primary treatment for NAFLD is lifestyle interventions, which include diet and physical activity aiming at weight loss. Apart from weight loss medicines, specific pharmacological treatments are typically not recommended for NAFLD but can be attempted in biopsy-proven NASH. Pioglitazone can be used to treat NASH in patients with or without type 2 diabetes in which it may improve liver histology. Vitamin E has been shown to improve liver histology in patients without diabetes. However, there is little evidence of the efficacy of vitamin E in the treatment of NASH in other patient populations.³⁰ Of note, none of these medicines are approved by the FDA for management of NAFLD.

In the absence of effective pharmacological treatments specifically targeting the liver disease, interventions that promote substantial weight loss can be helpful in the management of NAFLD and NASH. Bariatric surgery is the most effective intervention for weight loss and has been associated with improvement of liver steatosis and fibrosis.³¹ However, bariatric surgery is not widely available and might be contra-indicated in patients with portal hypertension and advanced liver dysfunction. Furthermore, short- and long-term

morbidity and mortality in patients with cirrhosis undergoing bariatric surgery seems to be higher as compared with patients without this condition.³² VLCDs can yield substantial weight loss amongst most patients. However, the potential benefits of VLCD for patients with NAFLD and NASH before progression to cirrhosis, and in patients with ESLD are insufficiently studied.

This scoping review included five randomized clinical trials, nine prospective cohort studies, two retrospective studies, one case-control study and two case series, totaling 968 subjects. The randomized clinical trials were mostly open label, used 450–800 kcal diets, lasted between 4 and 16 weeks, and enrolled 328 subjects, ranging from 95 to 39 subjects per study. The three longest trials lasting between 8 and 16 weeks with 190 subjects reported an approximate 7%–9% weight loss. Two of these studies reported reductions in liver steatosis parameters (i.e., steatosis per ultrasound and proton density fat fraction) and one study showed reductions in plasma ALT only.

The prospective cohort studies used 450–900 kcal diets and lasted between 2.6 and 12 weeks with participation of 470 subjects. The three longest trials lasting 12 weeks with 180 participants reported weight loss greater than 10% in a substantial number of participants, which was associated with reductions in fatty liver index, liver volume or LFTs.

Two retrospective cohort studies reported results from 113 subjects that consumed 800–900 kcal diets for 7.3–12 weeks. In the largest retrospective study with 97 subjects, an average weight loss of 13% was accompanied by reductions of more than 40% in AST and ALT. The other study reported an average decrease in BMI by 4.4 units. Importantly, the latter study reported a reduction in biopsy-proven steatosis from 29.3% to 4.75%. In one case-control study, results from 52 cases compared with 40 controls were reported after an average of 25 days of an 800-kcal diet, which produced a 7 kg weight loss. In this study, grade 3 steatosis per ultrasound decreased from 43.1% to 23.5%. Among the five patients described in the case series, it is worth reporting that one patient listed for liver transplantation no longer needed the procedure after losing 44.1 kg.

Collectively, the manuscripts listed in this review are in line with publications reporting the impact of weight loss on NAFLD. For example, in a meta-analysis of 8 randomized controlled trials showed that $\geq 5\%$ weight reduction improved hepatic steatosis in participants with NASH, and $\geq 7\%$ weight reduction resulted in improved histological disease activity.³³ These results are supported by a prospective cohort study that assessed lifestyle modification in 293 patients with NASH for 52 weeks. Weight loss was an independent predictor of improvements in NASH histological parameters.³⁴ Patients with $\geq 5\%$ weight reduction were more likely to have NASH resolution as well as lower NAFLD activity scores. Furthermore, patients losing $\geq 10\%$ weight exhibited more dramatic changes: 45% had regression in fibrosis, 90% had NASH resolution, and all had reduction in NAFLD activity score. None of the studies described above implemented VLCD but used caloric restriction for weight loss.

Regarding weight loss efficacy, VLCD studies incorporating lifestyle modifications and lasting 3–4 months have demonstrated weight loss ranging from 15% to 25%.⁵ Several studies reported in this scoping review confirmed that VLCD can promote substantial weight loss associated with improvement of both NAFLD and liver function. It is possible that some selected patients with ESLD associated with NASH might be removed from liver transplantation lists similar to one patient described in the case series by Temmerman et al.²⁷ However, our scoping review could not find studies showing liver fibrosis improvement with weight loss promoted by VLCD.

While a Western diet rich in carbohydrates and saturated fats are strongly associated with the development of NAFLD, a meta-analysis has shown that Mediterranean and Prudent diets rich in fruits, vegetables, nuts, whole grains, legumes, low-fat dairy products, fish, and lean cuts of meat, are protective against this condition.³⁵ Another meta-analysis studying diverse dietary interventions for NAFLD, but not VLCDs, has shown that Mediterranean and hypocaloric diets rich in unsaturated fatty acids result in improvements in hepatosteatosis independent of weight loss, whereas hypocaloric diets with weight loss are necessary for reductions in transaminases. These studies were confounded by physical activity and the diet effects alone remain to be defined. Importantly, the effects of dietary interventions on liver fibrosis are poorly studied. The authors concluded that the optimal dietary intervention in NAFLD remains to be defined.³⁶

Short term VLCD is utilized before bariatric surgery for reduction of liver volume that may technically facilitate the intervention. These studies can also give insight about the short-term liver outcomes and safety in bariatric surgery patients with NAFLD. Six studies in this review (i.e., two clinical trials, three prospective cohort studies, and one case-control study comprising 379 subjects) reported results of pre-operative VLCD in the setting of NAFLD.

Three studies reported reductions in liver volume ranging from 14.7% to 18.7% and one study reported a reduction of grade 3 steatosis by approximately 50%. Intraoperative liver biopsy was performed in two studies after 3 weeks of VLCD and showed a prevalence of NAFLD in 64% and 76.3% of participants who lost 3.4% and 5.4%, respectively. Weight loss and liver size reductions are in line with the results reported in a systematic review of pre-bariatric surgery VLCD treatment in nonselected patient cohorts. The pre-operative VLCD treatment did not significantly reduce perioperative or intraoperative complications and the long-term liver disease prognosis was not reported.³⁷ Whereas bariatric surgery seems to resolve or improve NAFLD and NASH overtime,^{38,39} the impact of pre-operative VLCD on these outcomes is unknown.

In 13 of the 19 studies of this scoping review reported completion rates that ranged from 72% to 90% of the participants, suggesting good adherence to the intervention among subjects with NAFLD. However, VLCD-based interventions typically last only 3–4 months and sustained weight loss is a concern. In one study

listed in this scoping review, 53% of participants lost more than 10% of their weight after 8–10 weeks of VLCD, whereas only 34% of participants sustained weight loss greater than 10% after 9 months.⁸ Nevertheless, it has been shown that complementary interventions such as intermittent meal replacements and anti-obesity medicines can improve sustainability of weight loss after dietary interventions with less than 1000 kcal daily.⁴⁰ Whether VLCD-dependent weight loss is sustainable in subjects with NAFLD concomitantly treated with anti-obesity medications is a matter of future investigation.

In 12 of the 19 studies, no adverse events were reported, even though it is not clear whether this information was omitted, or subjects did not in fact experience adverse effects. In the largest randomized clinical trial reported in this review counting with 95 participants, 72% completed the trial. The authors reported no serious adverse events but decided that 60 of the 103 adverse events were related to the dietary intervention. In addition, two patients developed asymptomatic gallstones by the end of the study.

The other studies also cited constipation and VLCD intolerance, but serious adverse events were rare. In the trial by Contreras et al., dizziness and weakness occurred more frequently in the VLCD group. In the studies by Colles et al. and Haas et al. participants experienced gastro-intestinal side effects. Thereby, this review suggests that VLCD-based treatments in subjects with NAFLD, although safe and tolerable, can result in mild adverse effects. This highlights the importance of medical supervision, screening appropriate patients, and education of potential expected symptoms prior to starting VLCD.

Limitations of this scoping review include great heterogeneity between studies including liver disease measurements and dietary interventions. The studies tended to have small number of participants and the patient populations varied between participants with NAFLD, bariatric surgery candidates, liver donor candidates, and persons with ESRD. While all the studies were required to have a VLCD below 900 kcal per day, the duration and daily caloric target varied between studies. While most studies reported weight loss as percent body weight loss or in total weight lost, the liver outcomes had a lot of variation. Liver outcomes included diagnosis with ultrasound, elastography, liver function tests, liver biopsy, and fatty liver index.

Outcome measures in the setting of liver disease are challenging because the gold standard is liver biopsy which is not frequently performed. Of note, no studies involving liver biopsy before and after the VLCD-based intervention are currently available. With the variation between study design and outcomes, it is difficult to directly compare results between studies. Further research on this topic needs to be conducted to better characterize the effectiveness and sustainability of VLCD in the setting of NAFLD and chronic liver disease regarding liver clinical outcomes and safety. Importantly, better clinical trials are necessary addressing the hypothesis that NAFLD can be successfully and safely managed with aggressive weight management promoted by a combination of intensive lifestyle modifications, anti-obesity medicines and VLCDs.

5 | CONCLUSIONS

The findings of this scoping review suggest that VLCD in patients with NAFLD and potentially with ESLD appear to be effective and safe to induce weight loss and short-term reductions in hepato-steatosis. However, the impact of VLCD on liver fibrosis is unknown. Adherence rates in these studies ranged between 69% and 93% and over longer time periods, we would expect adherence to decrease. However, it is expected that combination therapies including intensive lifestyle modifications, anti-obesity pharmacotherapy and VLCD might extend the sustainability of weight loss and reduced hepato-steatosis. Limitations of the scoping review include great heterogeneity between studies including dietary interventions and liver disease outcome measurements. VLCDs seem to improve liver disease markers and may allow selected patients to be removed from transplant list.

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AUTHOR CONTRIBUTIONS

Grant J. Herrington, Heather S. Healy, Marcelo L. G. Correia contributed with the design of the study.

Heather S. Healy performed literature search and ascertained that the manuscript strictly followed the methodological precepts of a scoping review.

Joshua J. Peterson, Linhai Cheng, Benjamin M. Allington, Renato D. Jensen performed the initial selection of abstracts, conducted full revision of selected manuscripts and produced the tables.

Grant J. Herrington reconciled discrepancies of abstract and manuscript selection, consolidated the data, wrote the first draft of the manuscript and produced Figure 1.

Grant J. Herrington, Joshua J. Peterson, Linhai Cheng, Benjamin M. Allington, Renato D. Jensen, Heather S. Healy, Marcelo L. G. Correia revised the drafted manuscript.

Grant J. Herrington and Marcelo L. G. Correia wrote the final version of the manuscript.

CONFLICT OF INTEREST

Marcelo Correia is a consultant to Novo Nordisk Inc. and receives research grants from Stead Family, Eli Lilly & Co., Novo Nordisk Inc., and Novartis. However, these conflicts of interest are unrelated with the topic of this scoping review. The other authors have no conflicts of interest to disclose.

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