Received: 28 March 2022 | Revised: 3 June 2022 | Accepted: 6 June 2022

DOI: 10.1111/liv.15335

Liver INTERNATIONAL WILEY

REVIEW

One size does not fit all; practical, personal tailoring of the diet to NAFLD patients

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Handling Editor: Dr. Luca Valenti

Abstract

Different dietary regimens for weight loss have developed over the years. Since the most evidenced treatment for non-alcoholic fatty liver disease (NAFLD) is weight reduction, it is not surprising that more diets targeting obesity are also utilized for NAFLD treatment. However, beyond the desired weight loss effects, one should not ignore the dietary composition of each diet, which may not necessarily be healthy or safe over the long term for hepatic and extrahepatic outcomes, especially cardio-metabolic outcomes. Some of these diets are rich in saturated fat and red meat, are very strict, and require close medical supervision. Some may also be very difficult to adhere to for long periods, thus reducing the patient's motivation. The evidence for a direct benefit to NAFLD by restrictive diets such as very-low-carb, ketogenic, very-low-calorie diets, and intermittent fasting is scarce, and the long-term safety has not been tested. Nowadays, the approach is that the diet should be tailored to the patient's cultural and personal preferences. There is strong evidence for the independent protective association of NAFLD with a diet based on healthy eating patterns of minimally-processed foods, low in sugar and saturated fat, high in polyphenols, and healthy types of fats. This leads to the conclusion that a Mediterranean diet should serve as a basis that can be restructured into other kinds of diets. This review will elaborate on the different diets and their role in NAFLD. It will provide a practical guide to tailor the diet to the patients without compromising its composition and safety.

KEYWORDS
fatty liver, Mediterranean diet, time-restricted eating, ketogenic diet, low-carb diet, low-fat diet

Abbreviations: CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HFC, hepatic fat content; EASL, the European association for the study of the liver; EASD, the European association for the study of diabetes; EASO, the European association for the study of obesity; ESPEN, European society of clinical nutrition and metabolism; ALT, alanine aminotransferase; MRI, magnetic resonance imaging; RCT, randomized clinical trial; AHA, American heart association; PUFA, polyunsaturated fat; WHO, world health organization; VLCKD, very low-carb ketogenic diet; AcAc, acetoacetate; BHB, β-hydroxybutyrate; OMTF, obesity management task force; LDL-c, low-density lipoprotein cholesterol; MUFA, monounsaturated fat; TRE, time-restricted eating; TRF, time-restricted feeding; US, ultrasound; HCC, hepatocellular carcinoma; BMI, body mass index; UPFs, ultra-processed foods.

1 | INTRODUCTION

The prevalence of obesity is increasing worldwide, with a third of all adults currently defined as people with overweight or obesity.[1] Higher levels of adiposity are associated with several co-morbidities, including hypertension, stroke, cardiovascular disease (CVD), and type-2 diabetes mellitus (T2DM),[2,3] as well as with all-cause mortality.[4] Obesity-associated morbidities are strongly associated with fat accumulation in body pools that are not physiological storage areas (ectopic fat), such as intra-abdominal organs, including the liver, pancreas, heart, kidney, and muscle.[5] Non-Alcoholic Fatty Liver Disease (NAFLD) is the hepatic manifestation of obesity and the metabolic syndrome. NAFLD can progress to non-alcoholic steatohepatitis (NASH), liver fibrosis and cirrhosis, and liver cancer and is independently associated with increased risk for T2DM and CVD.[6] NAFLD is the most common liver disease worldwide, affecting as many as a quarter of the global adult population.[6] NAFLD prevalence is very high in people with obesity, who have a 3.5-fold increased risk of developing NAFLD compared to those with normal weight.[7] Similarly, the prevalence of NAFLD among T2DM patients is 60%, more than two-fold higher than the general population.[8]

Current recommendations for the treatment of NAFLD and visceral fat suggest at least 5% weight loss and a greater reduction of 10% to regress fibrosis in most patients. However, improvements in NASH and fibrosis can also be seen with moderate weight reduction.[9] Unfortunately, weight loss also reduces lean mass,[10,11] and losing weight and maintaining weight loss in the long term is a complex process and remains a major public health challenge.

Currently, there is no effective drug therapy for NAFLD, although several compounds are under development. Therefore, lifestyle modifications are considered the first-line treatment.[12] The approach nowadays is that the type of diet should be tailored to the patient's cultural and personal preferences. Patients are exposed to various diet regimens (e.g., on the media and social networks) and wish to try them or have gained experience knowing which diet works for them. In this review, we will illustrate the efficacy and applicability of five main common dietary strategies for the treatment of NAFLD: low-fat diet, Mediterranean diet, low-carbohydrate (carb) diet, ketogenic (keto) diet, and time-restricted eating (TRE).

Lay summary

- The most beneficial treatment for NAFLD is weight reduction, achieved by a Mediterranean diet combined with physical activity. Other types of diets are also possible (such as low-fat or low-carb diets, ketogenic diet, and intermittent fasting), but the long-term efficacy and safety has not been tested.
- NAFLD patients should keep a healthy eating pattern, including: minimally processed or unprocessed foods, which are low in sugar and saturated fat, high in polyphenols and healthy types of fats as omega-3 fatty acids and olive oil. The Mediterranean diet is based on these principles.
- The exact type of diet in terms of macronutrient composition, food choices, and timing of eating can be tailored to the patient's preferences, as long as the healthy eating principles are followed.

Key Points

- The evidence for the benefit of restrictive diets like ketogenic, very-low-calorie diets, and intermittent fasting in NAFLD is scarce.
- A diet based on healthy eating patterns of minimally or unprocessed foods, low in sugar and saturated fat, high in polyphenols, and healthy fats (mono- and omega-3 polyunsaturated fats) is evidenced-based for the treatment of NAFLD.
- The Mediterranean diet and similar patterns should serve as a basis that can be restructured into other kinds of diets.
- The type of diet can be tailored to the patients' experience and preferences as long as the healthy dietary composition principles are followed.

2 | THE TREATMENT OF NAFLD BY DIETARY MODIFICATION AND WEIGHT REDUCTION

Weight reduction achieved by caloric restriction and a healthy diet improves serum liver enzymes, liver fat, hepatic inflammation, and fibrosis in a dose-dependent manner.[9,13,14] The European Association for the Study of the Liver (EASL)/diabetes (EASD)/obesity (EASO) Clinical Practice Guidelines and the European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines recommend, a 7%–10% weight loss to improve steatosis and liver biochemistry in NAFLD patients with overweight or obesity and >10% to regress fibrosis.[13,15]

However, NAFLD can also develop in subjects with BMI within the ethnic-specific cut-off, defined as normal weight NAFLD.[16] It has been suggested that the normal weight NAFLD phenotype might be consistent with obesity resistance, where individuals are prone to develop steatosis in response to an obesogenic environment.[17] In addition, normal weight NAFLD patients have a greater waist circumference than normal-weight controls.[18] Therefore, normal-weight patients can benefit from reducing visceral fat through diet and physical activity, without major weight loss.[15] It has been demonstrated that normal weight NAFLD patients can achieve remission of steatosis even with 3%–5% weight reduction[19] and may benefit from a healthier diet similarly to patients with obesity.

Even NAFLD patients with genetic determinants may benefit from dietary modifications, since PNPLA3 rs738409 G-allele seems to be a predisposing genotype amplifying dietary intake influence. Few human observational studies suggested liver fat accumulation is positively associated with the interaction between PNPLA3 rs738409 G-allele and diet rich in carbohydrates (especially sugar) or with a high omega-6/omega-3 polyunsaturated fat (PUFA) ratio.[20,21] Furthermore, the relationship between specific dietary nutrients and the risk of fibrosis is stronger for individuals carrying the rs738409 G-allele as compared to CC genotype; having a stronger risk with high carbohydrate intake and a more significant lower risk with an intake of omega-3 PUFAs, total isoflavones, methionine, and choline.[22] More importantly, few studies (small trial and post-hoc analysis of a larger trial) have reported that lifestyle modification and weight loss reduce liver fat to a greater extent in patients with the rs738409 G-allele as compared to CC genotype,[23,24] thus these patients should also be encouraged to perform lifestyle modification.

But the questions remain: What is the best way to achieve and maintain weight loss and liver fat, NASH, and fibrosis reduction?

2.1 | Low-fat versus low-carb diets

The most commonly compared diets are low-carb diets versus low-fat diets. However, the definition of the low-carb diet is variable in different studies. Low-carb diets can be classified into three categories depending on carbohydrate intake. A "moderate-carb diet" or "reduced-carb diet" could be defined as a 26%–45% carbohydrate intake to the total calorie intake per day, or >130 g/day (and lower than about 250 g/day in 2000 calories diet, for example). When the carbohydrate intake ratio is <26%, or >30 g/day, it is classified as a "low-carb diet." One step further is when the carbohydrate intake ratio is <10%, or <30 g/day, it can be categorized as the "ketogenic diet" or a "very-low-carb diet"[25] (Figure 1). Of course, as the ratio of carbohydrate intake decreases, the proportion of fat and protein increases, so diets called high-protein[26] or high-fat diets are usually reduced- or low-carb diets. Generally, despite the superiority of the low-carb diet in the short term, in the long term, both appear to be similarly effective in liver fat and alanine aminotransferase (ALT) reduction as long as a 7% weight loss is achieved.[27] A meta-analysis concluded no significant difference between a low-carb diet and a low-fat diet in improving hepatic fat content and transaminases in NAFLD.[25] However, the number of trials is small, and they are based on small sample size and a short-term follow-up; only a few of them evaluated hepatic fat by magnetic resonance imaging (MRI), and none used liver biopsy. Therefore, they do not show convincing results to determine the superiority of any of the diets (detailed in Table 1). A body of evidence indicates that specific types of fat and carbohydrates are important determinants in liver fat accumulation.[28] Therefore, the question about the role of fats and carbohydrates distribution in diets for the treatment of NAFLD should be refined to specific fats and carbohydrates and specific food. The Mediterranean dietary pattern demonstrates such an approach.

2.2 | Mediterranean dietary pattern and overlapping dietary patterns

Mediterranean dietary pattern is characterized by a high intake of olive oil, vegetables, fruits, nuts, legumes, whole grains, fish, and seafood, and a low intake of red meat, mainly processed meat. Mediterranean dietary pattern is the most studied diet. It has been repeatedly shown to provide hepatic and extra-hepatic, especially cardiovascular[29–31] health benefits, even beyond weight loss. Therefore, this is the preferred dietary pattern recommended to treat NAFLD by the EASL–EASD–EASO Clinical Practice Guidelines[13] and the ESPEN guidelines.[15] However, other largely overlapping (most notably, low in sugar and saturated fat and high in vegetables) healthy dietary patterns, including some low-fat diets, were also beneficial.[29,32] Interestingly, the Mediterranean diet is also characterized by reduced-carb intake (40% of the calories vs. 50%–60% in a typical low-fat diet; Figure 1), especially reduced sugars and refined carbohydrates, meaning that this is also a reduced-carb diet that may partially explain its beneficial effect in liver fat reduction. Three recent randomized clinical trials (RCT) support this notion. In a cross over RCT of patients with T2DM, 12 weeks of treatment with a carb-reduced high-protein diet (30% energy as carbohydrate) led to a more remarkable improvement in liver fat compared to a conventional diabetes diet consisting of 50% energy as carbohydrate, despite minor similar weight reduction under both treatments.[33] A

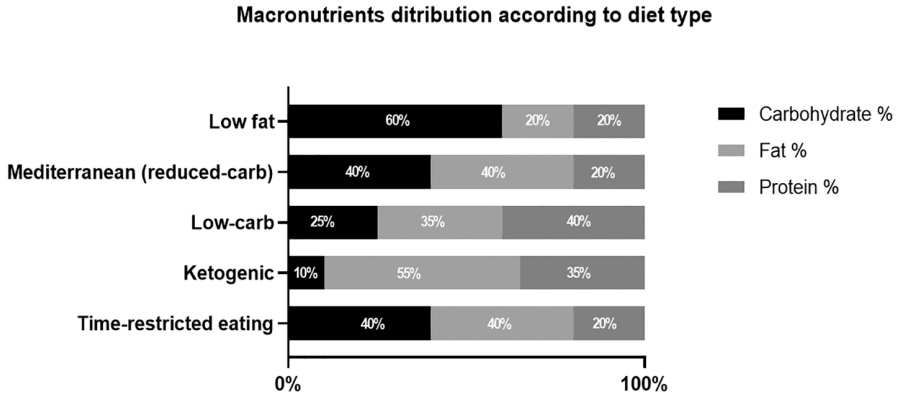

FIGURE 1 Distribution of macronutrients across different diet types. Macronutrients are presented as a relative percentage of total energy. We recommend that the macronutrient distribution of the time-restricted eating will be in accordance with the Mediterranean diet, but it may differ in different studies.

TABLE 1 Clinical trials testing the effect of restrictive diets on NAFLD

Author, year of publication, country (ref)	Study design and duration	Study population and sample size (number of participants who completed the intervention)	Dietary intervention	Main outcomes
Reduced- or low-carb diets				
Thomsen MN., 2022, Denmark[34]	RCT 6 weeks	67 subjects with T2DM Group A: carb-reduced high-protein diet ($n = 34$) Group B: conventional diabetes diet ($n = 33$)	Group A: CHO 30%, fat 40%, protein 30%. Group B: CHO 50%, fat 33%, protein 17%. All meals were provided to the subjects (prepared in the metabolic kitchen). Energy deficit individualized to each subject to achieve a 6% weight loss.	Bodyweight decreased by 5.8 kg (5.9%) in both groups after 6 weeks, without significant differences between the groups ($p = .83$). %HFC (MRI) was reduced significantly by 51% and 64% in group B and group A, respectively, with the relative difference between groups reaching borderline significance (−26%, $p = .051$).
Goss AM., 2020, USA[134]	RCT 8 weeks	25 children/adolescents (age 9–17) with obesity and NAFLD Group A: LCD ($n = 14$) Group B: LFD ($n = 11$)	Group A: CHO <25%, fat >50%, protein 25%. Limited SFA <10% + daily multivitamin. Group B: CHO 55%, fat 20%, protein 25%. Based on the USDA MyPlate Daily food plan for teenagers.	No significant difference between group A and B in %HFC (MRI) −6.2% (LCD) vs. −1.0% (LFD), ($p = .12$).
Gepner Y., 2018, Israel[40]	RCT 18 months	278 subjects with abdominal obesity/dyslipidemia Group A: LFD without PA ($n = 76$) Group B: LFD with PA ($n = 63$) Group C: MED/LCD without PA ($n = 73$) Group D: MED/LCD with PA ($n = 66$)	Group A + B: limited total fat intake 30%, SFA 10%, cholesterol 300 mg/day, and increased dietary fibres. Group C + D: restricted CHO intake to 40 g/day in the first 2 months (induction phase), and after that, a gradual increase up to 70 g/day. Protein and fat intake according to MED diet + 28 g of walnuts/day after induction phase. Both diets with restricted intake of trans-fats and refined carbohydrates and an increased intake of vegetables.	Similar moderate weight loss (−5.8% and −3.1% after 6 and 18 months, respectively). A similar reduction in HFC between PA groups. Groups C + D induced a greater %HFC (MRI) reduction than Groups A + B. −7.3% (MED/LCD) vs. −5.8% (LFD), after 6m ($p = .079$), and −4.2% vs. −3.8% after 18 months ($p = .036$).
Skytte, MJ., 2019, Denmark[33]	RCT 12 weeks (6+6 crossover design)	28 subjects with T2DM Group A: conventional diabetes diet ($n = 14$) Group B: carb-reduced high-protein ($n = 14$)	Group A: CHO 50%, fat 33%, protein 17%. Group B: CHO 30%, fat 40%, protein 30%. All meals were provided to the subject, with 5 meals/day to fully cover daily energy needs (iso-energetic).	Significant reduction in %HFC (MRI) by −2.4% [−7.8% to −1.0%] in group B vs. 0.2% [−2.3% to 0.9%] in group A ($p < .01$).
Jang EC., 2018, Korea[135]	RCT 8 weeks	106 subjects with NAFLD Group A: moderate LCD ($n = 52$) Group B: LFD ($n = 54$)	Group A: CHO 50%–60%, fat 20%–25%, protein 20%–25%. Group B: CHO 60%–70%, fat 15%–20%, protein 15%–20%. Recommended calorie intake for both groups: approximately 25 kcal/kg according to ideal body weight to reduce weight.	A significant similar decrease in body weight in both groups. Intrahepatic fat accumulation (CT) decreased significantly in group A compared to group B. Normalization of ALT activity at 8 weeks was 38.5% for group A and 16.7% for group B ($p = .016$).

TABLE 1 (Continued)

Author, year of publication, country (ref)	Study design and duration	Study population and sample size (number of participants who completed the intervention)	Dietary intervention	Main outcomes
Otten J., 2016, Sweden[67]	RCT 2 y	58 overweight women Group A: Paleolithic diet ($n = 33$) Group B: LFD ($n = 25$)	Group A: CHO 30%, fat 40%, protein 30%. Based on fish, seafood, lean meat, eggs, nuts, fruits, and vegetables (high intake of MUFA and PUFA). Cereals, dairy products, legumes, added salt, and sugar were excluded. Group B: CHO 55%–60%, fat 25%–30%, protein 15%. LFD is based on the Nordic Nutrition Recommendations: increased intake of fruit, vegetables, whole grain, fish, low-fat meat and dairy products. Energy intake in both diets was ad libitum.	Liver fat decreased after 6 months by 64% (95% CI: 54%–74%) in group A and by 43% (27%–59%) in group B ($p < .01$ between groups). After 24 months, liver fat decreased by 50% (25%–75%) in group A and 49% (27%–71%) in group B.
Kani AH., 2014, Iran[136]	RCT 8 weeks	45 subjects with NAFLD Group A: Low-calorie diet ($n = 15$) Group B: Low-calorie, LCD ($n = 15$) Group C: low-calorie, soy-containing LCD ($n = 15$)	In all diet groups: −200 kcal/day for normal and overweight participants and −500 kcal/day for obese participants. Group A: CHO 55%, fat 30%, protein 15%. Group B: CHO 45%, fat 35%, protein 20%. Group C: CHO 45%, fat 35%, protein 20% + 30 g of soy nut incorporated instead of 30 g of red meat.	Weight changes were not significantly different between the three groups. Significant serum ALT (IU/L) reduction (group C −15.2 ± 12.1 vs. −6.8 ± 4.6 in group B, and −6.4 ± 4.4 in group A; $p = .02$), Serum fibrinogen (g/L) reduction (−49.1 ± 60.1 vs. −12.9 ± 8.1 and −17.4 ± 8.4 g/L, respectively; $p = .01$). Reductions in AST(IU/L) were significantly higher in group C ($p = .05$).
Browning JD., 2011, USA[61]	RCT 2 weeks	18 subjects with obesity and NAFLD Group A: LCD ($n = 9$) Group B: low-calorie diet ($n = 9$)	Group A: limited CHO <20 g/day, protein, and fat intake according to subjects' individual preferences. Group B: 1200 kcal/day for women and 1500 kcal/day for men. A dietary composition according to subjects' individual preferences.	Weight loss was similar between groups A and B (−4.6 ± 1.5 kg LCD vs. −4.0 ± 1.5 kg low-calorie diet; $p = .363$). %HFC (MRS) decreased significantly more in group A −55 ± 14% than in group B −28 ± 23% ($p = .008$).
Haufe S., 2011, Germany[137]	RCT 6 months	102 subjects with overweight/obesity Group A: LCD ($n = 52$) Group B: LFD ($n = 50$)	Group A: CHO ≤90 g, 0.8 g protein per kg body weight, and a minimum of 30% fat. Group B: fat ≤20%, 8 g protein per kg body weight, and remaining provided by CHO. Total energy intake was reduced in both groups (−30% of energy intake before diet intervention, to a minimum of 1200 kcal/day).	A significant similar decrease in body weight in both groups, group A (95.0 ± 15.9 to 89.5 ± 15.9 kg) compared to group B (93.6 ± 17.3 to 89.4 ± 17.0 kg) ($p = .078$). %HFC (MRS) decreased from 7.6 ± 8.2 to 4 ± 4.6% (−47%) in group A and from 9.6 ± 9.8% to 5.6 ± 6.4% (−42%) in group B, (non-significant between interventions, $p < .001$ compared with baseline for both).

(Continues)

TABLE 1 (Continued)

Author, year of publication, country (ref)	Study design and duration	Study population and sample size (number of participants who completed the intervention)	Dietary intervention	Main outcomes
Kirk E., 2009, USA[66]	RCT 48 h, and follow up after 7% body weight loss (average 6 ± 1 weeks)	22 subjects with obesity Group A: Hypocaloric LCD (n = 11) Group B: Hypocaloric HCD (n = 11)	Group A: CHO ~10% (≤50 g), fat 75%, protein 15%. Group B: CHO ~65% (≥180 g), fat 20%, protein 15%. Average total daily energy intake in both diets ~1100 kcal/day.	At 48 h, IHTG (MRS) decreased more in group A compared to group B (29.6 ± 4.8% vs. 8.9 ± 1.4%; p < .05) but was similar in both groups after 7% weight loss (group A, 38.0 ± 4.5%; group B, 44.5 ± 13.5%).
Lin WY., Taiwan, 2009[138]	RCT 12 weeks	93 obese subjects (from those 83 with NAFLD) Group A: VLCD 450 Kcal/day (n = 46) Group B: VLCD 800 Kcal/s (n = 47)	For all subjects, the first two weeks with 1200 Kcal/day. Group A: 450 Kcal/day for 10 weeks. Group B: 800 Kcal/day for 10 weeks. All subjects were asked to drink at least 2 L of non-caloric fluid per day. No alcohol was permitted.	Similar significant weight reduction in group A (−8.37 ± 0.70 kg, p < .001) and B (−8.42 ± 0.70 kg, p < .001), (p = .962). The proportions of NAFLD subjects (semi-quantitative liver US, 4 levels) who achieved improvement (moving from a higher level to a lower level) was 41.5% in group A and 50.0% in group B.
Ryan MC., 2007, USA[139]	RCT 16 weeks	52 subjects with obesity and IR (high risk for NAFLD) Group A: low-calorie, moderately LCD (n = 26) Group B: low-calorie LFD (n = 26)	Group A: CHO 40%, fat 45%, protein 15% and 7% SFA (1595 ± 262 kcal/day). Group B: CHO 60%, fat 25%, protein 15% and 7% SFA (1699 ± 334 kcal/day). Calorie deficit for both diets 750 kcal/day. Both diet choices included complex carbohydrates with high fiber content, lean protein, and low SFA.	A significant similar decrease in body weight in both groups (−7.0 ± 3.8 kg in group A [p < .001] vs. −5.7 ± 4.1 kg in group B [p < .001]). Serum ALT decreased twice as much in group A vs. group B (−9.5 ± 9.4 vs. −4.2 ± 8.3; p = .02).
Ketogenic diets				
Luukkonen PK., Finland, 2020[64]	Single-arm trial 6 d	10 subjects with NAFLD	The diet provided ~1440 kcal/day. CHO ~6% (≤25 g/day), fat ~64%, protein 28%. All meals were prepared in a catering kitchen.	Significant reduction in weight (~ −3%), IHTG (^{1}H-MRS) (−31%, p < .001) and hepatic IR (−58%, p < .010).
Ministrini S., Italy, 2019[65]	Single-arm trial 25 days	52 obese subjects (candidates for bariatric surgery)	Caloric restriction (<800 kcal/day). CHO <50 g/day (corresponding to <200 kcal/day), protein 1.4 g/kg of ideal weight. The remaining caloric intake was composed of fat (<250 kcal/day, corresponding to <30 g/day).	The proportion of liver steatosis Grade 3 (liver US) decreased from 43.1% at baseline to 23.5% at the end of the intervention (p < .001).

TABLE 1 (Continued)

Author, year of publication, country (ref)	Study design and duration	Study population and sample size (number of participants who completed the intervention)	Dietary intervention	Main outcomes
Tendler D., North Carolina, 2007[63]	Single-arm trial 6 months	5 obese subjects with biopsy-proven NAFLD	CHO <20 g/day. The diet consisted of unlimited amounts of meats and eggs, cheese (4 oz/day), salad vegetables (2 cups/day), and low-carb vegetables (1 cup/day). There was no predetermined limit on the amount of caloric intake.	Significant weight reduction (−10.9%, $p = .036$). Four out of 5 posttreatment liver biopsies showed improvements in steatosis ($p = .020$), necroinflammatory grade ($p = .020$), and fibrosis ($p = .070$).
High protein diets				
Xu C., 2020, Germany[140]	RCT 3 weeks	29 subjects with morbid obesity Group A: low protein diet ($n = 10$) Group B: high protein diet ($n = 9$) Group C: reference-protein diet ($n = 10$)	Group A: CHO 55%–65%, fat 25%–35%, protein 10%. Group B: CHO 35%–45%, fat 25%–30%, protein 30%. Group A and B with hypocaloric (1500–1600 kcal/day) diet. Group C: hypocaloric diet (1200–1500 kcal/day) with a moderately increased protein intake (10%–22% protein), as a reference group.	Significant similar decrease in BMI in all groups (group A: −4.4%, group B: −4.6%, group C: −4.9%, $p = .895$). Reduction in %HFC (MRS) by 42.6% in group B and by 36.7% in group C. No significant decrease in group A. The differences in %HFC between group A and group B and between group A and group C were significant ($p = .001$ and $p = .001$, respectively).
Markova M., 2017, Germany[26]	RCT 6 weeks	37 subjects with T2DM and NAFLD Group A: animal protein diet ($n = 18$) Group B: plant protein diet ($n = 19$)	Group A: diet rich in animal protein, mainly from meat and dairy foods. Group B: diet rich in plant protein, mainly from legume. Without calorie restriction. The diets were isocaloric with the same macronutrient composition (CHO 40%, fat 30%, protein 30%).	Both groups had a similarly moderate but significant reduction of BMI (animal protein: $-0.8 \pm 0.1\ kg/m^2$; plant protein: $-0.5 \pm 0.1\ kg/m^2$). Significant reduction of %HFC (MRS) in both groups, by 48.0% ($p = .0002$) and 35.7% ($p = .001$) in animal protein and plant protein, respectively. It was not significantly different between the groups.
Time-restricted eating/Intermittent fasting diets				
Holmer M., 2021, Sweden[91]	RCT 12 weeks	74 subjects with NAFLD Group A: LCHF ($n = 25$) Group B: 5:2 diet ($n = 25$) Group C: standard-of-care dietary instructions ($n = 24$)	Group A: an average daily calorie intake of 1600 kcal/day for women and 1900 kcal/day for men. CHO 5%–10%, fat 50%–80%, protein 15%–40%. Group B: on 2 non-consecutive days; 500 kcal/day for women and 600 kcal/day for men. For the remaining 5 days; a limit of 2000 kcal/day for women and 2400 kcal/day for men. CHO 45%–60%, fat 25%, protein 10%–20%. Group C: guidance for a healthy diet.	The proportions of subjects who achieved a weight loss of >7% were higher in group A (73%) and B (63%) vs. C (19%). The absolute reduction of fat (MRS) was significantly higher in both group A (−3.9) and B (−2.6) vs. C. No significant difference between group A vs. B. Significant reduction in liver stiffness (TE) in group B (−1.5 kPa) and C (−1.2 kPa) vs. A.

(Continues)

TABLE 1 (Continued)

Author, year of publication, country (ref)	Study design and duration	Study population and sample size (number of participants who completed the intervention)	Dietary intervention	Main outcomes
Johari MI., Malaysia 2019[107]	RCT 8 weeks	43 subjects with NAFLD Group A: modified alternate-day calorie restriction ($n = 33$) Group B: control (no intervention) ($n = 10$)	Group A: modified alternate-day calorie restriction; on a fasting day, restriction of 70% of calorie requirement per day and on the non-fasting day, eating ad libitum. Diet was self-selected using detailed individualized food portion lists, meal plans, and recipes. Group B: no specific dietary advice was provided.	Significant reduction in weight ($p = .001$) in group A vs. B. ALT was reduced only in group A ($p = .02$). Both liver steatosis and fibrosis (SWE) scores were significantly reduced in group A vs. B (both $p < .010$).
Cai H., China 2019[141]	RCT 12 weeks	271 overweight subjects with NAFLD Group A: alternate-day fasting ($n = 90$) Group B: time-restricted eating (TRE) ($n = 95$) Group C: control ($n = 79$)	Group A: 25% of energy in a fast day (one meal a day). CHO 55%, fat 30%, protein 15%. Ad libitum feeding in feed day. Group B: 8 h of feeding and 16 h of fasting. There were no additional instructions or recommendations. Group C: consumed 80% of their energy needs every day without any further recommendations.	Significant reduction in weight in group A (-4.04 ± 0.54 kg) and B (-3.25 ± 0.67 kg) compared to group C (-1.85 ± 0.65 kg) ($p < .001$). No significant difference between groups A vs. B. Changes in liver stiffness (TE) did not differ between the groups.

Abbreviations: RCT, randomized clinical trial; T2DM, type 2 diabetes mellitus; CHO, carbohydrates; HFC, hepatic fat content; MRI, magnetic resonance imaging; USA, united states; NAFLD, non-alcoholic fatty liver disease; LCD, low-carb diet; LFD, low-fat diet; SFA, saturated fatty acids; MED/LCD, Mediterranean/low-carb diet; PA, physical activity; CT, computed tomography; ALT, alanine aminotransferase; MUFA, monounsaturated fats; PUFA, polyunsaturated fats; CI, confidence interval; AST, aspartate aminotransferase; MRS, magnetic resonance spectroscopy; HCD, high carbohydrate diet; IHTG, intrahepatic triglyceride; VLCD, very low-calorie diet; US, ultrasound; ^{1}H-MRS, proton magnetic resonance spectroscopy; IR, insulin resistance; BMI, body mass index; LCHF, low-carb high fat; TE, transient elastography; SWE, Shear wave elastography; TRE, time-restricted eating.

parallel RCT also supports this finding in adults with T2DM, treated for six weeks with energy restriction (all foods were provided) with either a carb-reduced high-protein diet (percentage of total energy intake [E%]: carbs 30/protein 30/fat 40) or a conventional diabetes diet (E%: carbs 50/protein 17/fat 33). After 6 weeks, both groups' body weight decreased by 5.8 kg (5.9%). However, the reduced-carb diet improved liver fat to a greater extent.[34] The third RCT adds information on the long-term effects of a 2-year treatment with two personalized energy-restricted dietary strategies among 98 overweight/obese participants with NAFLD. The American Heart Association (AHA) diet was based on 3–5 meals/day with a conventionally balanced distribution of macronutrients; E%: carbs 55/protein 15/fat 30, healthy fatty acid profile). The Mediterranean-like diet was based on a higher meal frequency (7 meals/day) and macronutrients distribution of; E%: carbs 40–45 preferring those with low glycemic index/25 protein predominantly from vegetable sources/30–35 fat favoring extra virgin olive oil and omega-3 PUFA on account of saturated and trans fats. The Mediterranean-like diet group showed a more significant decrease in body weight (−7.6% vs. −4.8%), ALT, liver stiffness, and liver fat at 24 months compared to the AHA group. These findings indicate that both strategies are suitable alternatives for NAFLD management, yet, the Mediterranean diet seems easier to maintain.[35]

An earlier study compared two high-protein diets rich in either animal protein or plant protein without calorie restriction for 6 weeks in subjects with T2DM and NAFLD. In fact, both diets were reduced-carb diets with the same macronutrient composition; E%: carbs 40/protein 30/fat 30, and both reduced liver fat similarly, independently of body weight.[26]

Observational prospective studies support the inverse association of NAFLD with the Mediterranean diet or the overlapping dietary patterns.[36,37] A prospective study of the elderly population has suggested that adherence to the World Health Organization (WHO) healthy nutritional pattern was related to regression of NAFLD (vegetables and fruit intake of ≥400 g/day, added sugar intake of <10 g/day, E% fat <30%, E% saturated fat <10%, E% trans fatty acid <1%, and salt intake of <5 g/day).[38] Similarly, in the Multiethnic Cohort study, keeping a Healthy Eating Index pattern was related to lower risks for high visceral fat and NAFLD.[39] Moreover, in the Framingham Heart Study cohort, improved diet quality by closer adherence to Healthy Eating Index or Mediterranean diet pattern was associated with a reduction in liver fat and lower risk for new onset of NAFLD over 6 years of follow-up.[37]

Accordingly, clinical trials testing the effect of classical or modified (low-carb or enriched with polyphenols) Mediterranean diets support its beneficial effect on liver fat. The two largest and longest RCTs (18- months) provide the best evidence for the valuable role of two modified Mediterranean diets. The first showed the superiority of a Mediterranean diet, which was also low-carb, over a low-fat diet in decreasing intrahepatic fat.[40] The second revealed that a Mediterranean diet enriched with polyphenols and more strictly restricted in red/processed meat led to a two-fold liver fat loss than an isocaloric regular Mediterranean diet, despite similar weight reduction. Both were better than standard nutritional counseling.[41] Indeed, observational studies have shown that red and processed meat intake are risk factors for NAFLD or NAFLD-related cirrhosis[42,43] and that the dietary polyphenols subgroup (phenolic acids, abundantly present in foods such as berries, nuts, coffee, tea, and whole grains) have a protective association with NAFLD, liver fibrosis markers (FibroTest) and insulin resistance.[44] However, importantly, no liver histology was obtained in either of the RCTs, and thus, the effect of the Mediterranean diet on NASH and fibrosis is unknown.[40] In contrast, such evidence exists for weight reduction by a standard low-fat diet (E%: carbs 64/protein 14/fat 22/saturated fat <8), leading to NASH and fibrosis regression in a one-year intervention. This diet shares common principles with the Mediterranean diet; dietary fiber >20 g/day, cholesterol <150 mg/1000 kcal, carbohydrate-rich foods with a low glycemic index, and high amounts of fruits, vegetables, and whole grains.[9] Table 2 summarizes the primary RCTs testing the efficacy of the Mediterranean diet in NAFLD.

2.3 | Very low carbohydrate ketogenic diets

Very low-carb ketogenic diet (VLCKD) pattern is characterized by carbohydrate restriction of <30–50 g/day (13%–25% of total calories), high fat (60%–70%), with an amount of protein equivalent to 0.8–1.2 g/day per kg of ideal body weight.[45] When carbohydrate consumption is limited or fatty acid concentration increases, there is an upregulation of the ketogenic pathway and an increased production of ketone bodies during the first 14 days.[46] Although the liver is the primary site that produces ketone bodies, it does not use ketone bodies because it lacks the necessary enzyme beta ketoacyl-CoA transferase. There are three central ketone bodies: acetoacetate (AcAc), β-hydroxybutyrate (BHB), and acetone, though only AcAc and BHB are important in terms of energy substrate, of which the latter is the most abundant ketone body in the blood (and frequently measured).[47] The predominant substrates for ketone synthesis are fatty acids, although a small proportion of ketones are synthesized from leucine and in phenylalanine-tyrosine metabolism.[48]

The VLCKD was first introduced as an alternative treatment for patients with refractory epilepsy, and its adapted versions later became widely popular in treating obesity due to their excellent ability to induce satiety and weight loss. In fact, the VLCKD is an emerging technique to induce a significant, well-tolerated, and rapid loss of body weight in morbidly obese patients.[49] Compared with the standard calorie-restricted low-fat diets, the VLCKD yielded faster weight loss, while the subsequent weight gain was similar between the diet types.[50,51]

Several studies investigated the efficacy of VLCKD in patients with overweight and obesity; however, long-term and high-quality evidence is limited. VLCKD was an effective strategy in some studies in terms of weight loss, reduction of visceral fat, and improvement of metabolic parameters and inflammatory markers.[52–56] Yet, other studies found similar results in bodyweight reduction[57,58] following VLCKD compared to regular or low-fat diets. In a meta-analysis of

TABLE 2 Randomized clinical trials testing the effect of the Mediterranean diet on NAFLD

Author, year of publication, country (ref)	Study design and duration	Study population and sample size (Number of participants who completed the intervention)	Dietary intervention	Main outcomes
Yaskolka Meir A., 2021, Israel[41]	RCT 18 months	294 participants with abdominal obesity/dyslipidemia Group A: MED ($n = 84$) Group B: green-MED ($n = 89$) Group C: control ($n = 91$)	Group A: MED+ 28 g/day walnuts. Group B: green-MED+ 28 g/day walnuts+ 3–4 cups green tea+ 100 g/day Mankai + restricted in red/processed meat. Group C: healthy diet guidelines. All groups performed PA. Both MEDs 1500–1800 kcal/day for men and 1200–1400 kcal/day for women.	Despite similar moderate weight loss in group A (−2.7 ± 5.6 kg) and B (−3.7 ± 6.3 kg), group B achieved almost double %HFC loss as compared with group A (^{1}H-MRS) (−38.9% vs. −19.6%, $p = .035$).
Marin-Alejandre, BA., 2021, Spain[35]	RCT 24 months	58 overweight or obese subjects with NAFLD Group A: MED-like ($n = 32$) Group B: AHA guidelines ($n = 26$)	Group A: 7 meals/day, CHO 40%–45% (low glycemic index), fat 30%–35% (extra virgin olive oil and Omega-3 fatty acids), protein 25% (mainly from vegetable sources). Group B: AHA guidelines: 3–5 meals/day, CHO 50%–55%, fat 30%, protein 15%. Both diets applied a 30% energy restriction.	Both groups significantly reduced weight (−7.6% in group A vs. −4.8% in group B, $p = .684$). Group A had a greater decrease in ALT ($p = .038$), liver stiffness (TE) ($p = .016$), and FLI ($p = .021$), compared to group B.
Properzi C., 2018, Australia[32]	RCT 3 months	48 subjects with NAFLD Group A: MED ($n = 24$) Group B: a low-fat diet, based on AHA guidelines ($n = 24$)	Group A: CHO 40%, fat 35%–40% (with <10% SFA), protein 20%, Group B: CHO 50% fat 30% (with <10% SFA), protein 20%.	Similar weight reduction in both groups (−2.3% vs. 2.1%, in group A vs. group B, respectively). HTGC (MRS) reduced significantly in both groups, relative change of −32.4% in group A and −25.0% in group B ($p < .01$ within groups, no difference between groups $p = .32$).
Katsagoni CN., 2018, Greek[142]	RCT 6 months	63 overweight or obese subjects with NAFLD Group A: MED ($n = 21$) Group B: MED + healthy lifestyle ($n = 21$) Group C: control ($n = 14$)	Group A: MED + nutritional counselling program. Group B: MED+ nutritional counselling program+ healthy lifestyle: PA (30 months/day) + sleeping habits (≥7 and ≤9 h/day) Group C: general written dietary guidelines for a healthy lifestyle. In all diets, 1800 Kcal/day for men and 1500 Kcal/day for women; CHO 45%, fat 35%, protein 20%.	Greater weight loss in group A (−5.4%, $p = .010$) and B (−6.3%, $p = .010$) vs. group C (−2.1%). The percentage of subjects who reached normal ALT levels was higher in group B than C (71.4% vs. 38.1%, $p < .050$), with no significant difference from group A. The percentage of subjects reaching liver stiffness ≤6.6 kPa (TE) was higher in group A and B vs C (57.1% vs 55% vs 28.6%, $p < .050$).
Misciagna G., 2017, Italy[143]	RCT 6 months	98 subjects with NAFLD Group A: Low Glycemic Index-MED ($n = 50$) Group A: control ($n = 48$)	Group A: Low Glycemic Index-MED rich in MUFA+PUFA, SFA <10%. Group B: Standard WHO recommended diet. No advice was given for the total calories to be consumed.	No significant weight change. Group A had a reduced NAFLD score (US) in the sixth month (−4.43, 95%CI −7.15, −1.71).

TABLE 2 (Continued)

Author, year of publication, country (ref)	Study design and duration	Study population and sample size (Number of participants who completed the intervention)	Dietary intervention	Main outcomes
Abenavoli L., 2017, Italy[144]	RCT 6 months	50 overweight subjects with NAFLD Group A: MED ($n = 20$) Group B: MED + antioxidant supplementation ($n = 20$) Group C: control ($n = 10$)	Group A: low-calorie MED (1400–1600 kcal/day). CHO 50%–60%, MUFA+PUFA <30%, SFA <10%, cholesterol <300 mg/day, protein 15%–20%, fibers 25–30 g/day. Group B: MED (as detailed above) + antioxidant supplementation. Group C: no diet or lifestyle intervention.	Significant reduction in BMI in group A (−6%, $p < .001$) and B (−7%, $p = .030$) vs. C (−0.5%). FLI significantly reduce in group A (−19%, $p = .017$) and B (−27%, $p < .001$) vs. C (+4.7%). Liver stiffness (TE) significantly improved in group A (−21%, $p = .001$) and B (−27%, $p < .001$) vs. C (+8.7%).
Cueto-Galán R., 2017, Spain[145]	RCT 6 y	276 subjects Group A: MED + olive oil (1 l/week) ($n = 117$) Group B: MED + 30 g/day of nuts ($n = 65$) Group C: control ($n = 94$)	Group A: MED + 1 extra liter of virgin olive oil per week). Group B: MED+ 15 g of walnuts, 7.5 g of hazelnuts, and 7.5 g of almonds per day. Group C: advised to follow a low-fat diet.	FLI increased significantly over time in group C, with 1.13 ± 0.41 points per year ($p = .006$). The change in FLI in group A was -3.90 ± 1.9 points lower than in group C ($p = .038$). In group B the change was significantly lower than in group C (-1.63 ± 0.62; $p = .009$).
Abenavoli L., 2015, Italy[146]	RCT 6 months	30 overweight or obese NAFLD subjects Group A: hypocaloric MED ($n = 10$) Group B: hypocaloric MED+ Realsil complex (2 pills per day) ($n = 10$) Group C: control ($n = 10$)	Group A: 1400–1600 kcal/day, CHO 50%–60%, MUFA & PUFA <30%, SFA <10%, cholesterol <300 mg/day, fibers 25–30 g/day, proteins 15%–20%, (of which about 50% were vegetable proteins). Group B hypocaloric MED + silybin 94 mg, phosphatidylcholine 194 mg, vitamin E acetate 50% (a-tocopherol 30 mg) per day. 89.28 mg) Group C: no diet or lifestyle intervention	Significant reduction in BMI in group A (−9%, $p = .001$) and B (−9%, $p = .001$) vs. C (−0.5%). HOMA-IR reduced significantly in group A (−6%, $p = .043$) and B (−38%, $p = .007$) vs C (+ 51%). FLI improved significantly in group A (−28%, $p = .009$) and B (−28%, $p = .002$) vs. group C (+4.6%).
Ryan MC., 2013, Australia[147]	Cross over RCT 6 weeks (each diet)	12 subjects with biopsy-proven NAFLD Group A: MED ($n = 12$) Group B: LF/HCD ($n = 12$)	Group A: CHO 40%, fat (MUFA+ PUFA) 40%, protein 20%. Group B: CHO 50%, fat 30%, protein 20%.	No significant change in weight. Significant %HFC (^{1}H-MRS) reduction in group A vs group B ($-39 \pm 4\%$ vs. $-7 \pm 3\%$, $p = .012$).

Abbreviations: RCT, randomized control trial; MED, Mediterranean diet; HFC, hepatic fat content; ^{1}H-MRS, proton magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; CHO, carbohydrates; AHA, American heart association; ALT, alanine aminotransferase; TE, transient elastography; FLI, fatty liver index; SFA, saturated fatty acids; HTGC, hepatic triglyceride content; MRS, magnetic resonance spectroscopy; PA, physical activity; MUFA, monounsaturated fats; PUFA, polyunsaturated fats; WHO, world health organization; US, ultrasound; CI, confidence interval; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; LF/HCD, low-fat high carb diet.

13 RCTs among obese patients that tested the long-term effect of VLCKD versus low-fat diets, those treated with VLCKD lost ~1 kg more at 12–24 months.[59] A more recent meta-analysis (of prospective studies, RCTs and other study designs)[60] by the Obesity Management Task Force (OMTF) of the EASO found more significant improvement in body weight, waist circumference (central adipose tissue), total fat mass, and glycemic control (improvement in insulin sensitivity and fasting plasma glucose) with very-low-calorie VLCKD intervention compared to other weight loss interventions, as well as significantly greater reductions in triglycerides, total cholesterol and low-density lipoprotein cholesterol (LDL-c). The very low-calorie VLCKD is characterized by a low carbohydrate content (<50 g/day), 1–1.5 g of protein/kg of ideal body weight, 15–30 g of fat/day, and a daily intake of about 500–800 calories. This is a highly restrictive diet, and the guidelines state that the very low-calorie VLCKD phase should be under a health professional's supervision and limited to 8–12 weeks, followed by a gradual increase of calories, carbohydrates, and food variety.

To date, no long-term RCTs allow conclusions regarding the effect of VLCKD on NAFLD and NASH and its efficacy in reducing fibrosis. Several short-term and small trials among NAFLD patients found a significant reduction in hepatic fat content and liver total volume following the VLCKD diet compared to standard caloric restriction[61,62] or in non-controlled trials.[63–65] In an RCT study of 22 obese subjects, VLCKD was superior in liver fat reduction at 48 h, compared to a low-fat diet (30% fat vs. 9%), but was comparable after achieving 7% weight loss at 11 weeks follow-up.[66] In a recent 6-day single-arm trial, 10 obese subjects that received stable isotope infusions decreased hepatic fat content by 31%, along with a 3% decrease in body weight.[64] In conclusion, no practical recommendations can be drawn at this stage regarding the use of VLCKD in NAFLD (Table 1).

2.4 | Plant-based diets versus meat-based diets

While the Mediterranean diet is mainly based on plant protein, some of the versions of low-carb-high-fat/high-protein diets are rich in meat, like the Paleolithic diet.[67] The paleolithic diet (also known as the Hunter-Gatherer or Paleo diet) is based on lean meats (but some people also include a high intake of red meat and animal fat), roots, vegetables, seasonal fruits, nuts, and seeds (limiting foods such as dairy, grains, and legumes).[67,68] There are very few clinical trials testing the effect of the Paleolithic diet versus other diets on liver fat; none are specific for NAFLD patients or tested NASH or fibrosis. In RCT of obese women, ad libitum Paleolithic diet was more effective at six months for liver fat reduction than ad libitum conventional low-fat diet (E%: carbs 55–60/protein 15/fat 25–30). Still, both diets had a similar effect at twenty-four months.[67] The Paleolithic diet in this study was based on fish, seafood, lean meat, eggs, nuts, fruits, and vegetables, whereas cereals, dairy products, legumes, added salt, and sugar were excluded. It provided 40 E% as fat with a high intake of monounsaturated fat (MUFA) and PUFA, and 30 E% from carbohydrates, making it a reduced-carb-high-protein diet (30 E% from protein). So, in fact, this diet shares some common features with the Mediterranean diet.

Plant-based diets emphasize a high intake of plant and plant-derived food (i.e., grains, legumes, vegetables, and fruits) and a low intake of animal-derived food. A vegetarian diet overlaps partially with a plant-based diet, while a vegan diet is characterized by abstinence from animal products. Plant-based diets confer the benefit of preventing chronic diseases, but their effect on NAFLD has not been demonstrated in long-term RCTs and was tested only in a few observational studies.[69] A 16-week RCT, including 44 participants with overweight or obesity, found that a low-fat vegan ad libitum diet, as compared to no diet, led to reduced energy intake, weight reduction, and a liver fat reduction by 34.4%, while no changes occurred in the control group.[70]

If done correctly in terms of balanced and varied nutrition, these diets are probably safe in the long term. Interestingly, the "EAT-Lancet Commission on healthy diets from sustainable food systems" recommended a global diet pattern that is moderately plant-based, and its principles share similarities with the Mediterranean diet; consisting of a diversity of plant-based foods, low amounts of animal source foods, unsaturated rather than saturated fats, and small amounts of refined grains, highly processed foods and added sugars.[71] In contrast, a Paleolithic diet that includes a daily high meat intake has an undemonstrated potential to be harmful to NAFLD patients in the long term. Several studies have shown an association between high meat intake and NAFLD risk,[72] specifically red and processed meat.[43] In a large population-based study of ethnically diverse populations, higher intakes of red meat, processed red meat, poultry, and cholesterol were risk factors for NAFLD or NAFLD-related cirrhosis.[73] Moreover, a recent prospective cohort of the general population from six states in the United States and 16-year follow-up data indicated that high intake of total meat, processed and unprocessed red meat (beef, lamb, and pork), and nitrite from processed meat were associated with liver disease-related mortality.[74] These findings are supported by another cohort study from the United States, including 77 795 women. Red meat consumption, both unprocessed and processed, was associated with a significantly increased risk of developing NAFLD in a dose-dependent manner.[75] In addition, high red[76,77] and processed[78] meat intake, high saturated fat-rich dairy,[79] and cholesterol[80] intake have been associated with hepatocellular carcinoma.

2.5 | Time-restricted eating

Time-restricted eating (TRE, for humans) or time-restricted feeding (TRF, for mice) is a nutritional strategy in which calories are consumed in a defined time window,[81] also called intermittent fasting, and involves several forms of time- restriction. Studies have found that the median time window for eating lasts 14 h and includes 3–10 meals/day, with a median of 3 h between meals.[82] TRE limits the daily period of food intake to 8–10 h on most days of the

week.[83,84] This nutritional strategy changes the daily ratio between feeding and fasting periods without necessarily reducing the total daily calorie intake.[85] However, in some trials (two RCTs and one single-arm trial), an unintentional energy intake reduction of 250–600 calories was observed.[86–88] Several recent RCTs have examined the optimal daily fasting schedule, mildly favouring TRE based on daytime eating schedules.[86,89,90] Mice fed with different obesogenic diets during a restricted time frame gained less weight and body fat than mice with more extended feeding periods. The effect of TRE on health outcomes has been extensively studied, mainly in mouse models, and resulted not only in reduced body weight but also in increased total energy expenditure and an improvement in glycemic and lipid profiles and hepatic fat content.[85,91] Several mechanisms may explain the potential benefits of TRE on liver fat accumulation. First, TRE reduces pyruvate carboxylase and glucose 6-phosphatase and increased glucokinase,[92] potentially underpinning reductions in hepatic glucose production and increased glucose utilization.[93] Such a shift in liver metabolism, referred to as the metabolic switch, leads the body periodically switches from liver-derived glucose to adipose cell-derived ketones during fasting periods. Second, several genes involved in glucose homeostasis in the liver, such as glut2, pyruvate kinase, glucokinase, and glycogen synthase, are inhibited following prolonged (>12 h) fasting. On the other hand, it was found that TRE overexpressed lipid homeostasis genes, such as acylCoA dehydrogenase acetyl CoA carboxylase, and diacylglycerol-O-acyltransferase in the liver, which leads to a reduction in fat accumulation in the liver.[94] TRE also reduced the fluctuation of genes fatty acid synthase, stearoyl CoA desaturase, and fatty acid elongase during the active phase, and increased the fluctuation of hepatic triglyceride lipase during the inactive phase, which was associated with reduced lipid storage and increased triglyceride hydrolysis.[92]

Over the past few years, an increasing number of interventional studies and protocols have tested the effect of TRE in normal,[88,95–98] over-weight, and obese humans,[10,11,97,99–102] or metabolically unhealthy participants.[87,103] Among overweight/obese people without additional co-morbidities, a 2.6%–3.8% weight loss was achieved in studies of TRE intervention with no intended calorie restriction.[10,11,100,104] However, in a recent RCT comparing time-restricted eating (eating only between 8:00 a.m. and 4:00 p.m.) with calorie restriction or daily calorie restriction alone for 12 months, a regimen of time-restricted eating was not more beneficial with regard to reduction in body weight, body fat, or metabolic risk factors than daily calorie restriction.[105]

The results regarding metabolic effects are somewhat controversial, with some studies reporting no effect on fasting glucose, insulin, and lipids,[11,96] while others noted significant improvements in glycemic control,[10] blood pressure,[100] respiratory quotient, and metabolic flexibility.[102] Inconclusive results were also observed when assessing the effect of TRE on insulin sensitivity, lipid profile, and inflammatory markers.[87,89,103] Importantly, late-night eating was associated with a higher risk for coronary heart disease in a prospective study.[106]

There is currently very weak evidence for a beneficial effect of TRE on hepatic fat in NAFLD patients,[91,107] and none of these studies examined the long-term impact of TRE. In an 8-week RCT, intervention with alternate-day calorie restriction (fasting day; 30% of calorie requirement/non-fasting day; ad libitum), compared with a normal habitual diet (no intervention) as control, resulted in a greater reduction of steatosis and fibrosis as measured by ultrasound (US) and elastography.[107] A more recent RCT among 74 patients with NAFLD compared three interventions for 12 weeks. The TRE was in the form of a 5:2 diet in which, on 2 non-consecutive days per week, participants consumed 500 kcal/day for women and 600 kcal/day for men and kept a generally healthy diet on the remaining 5 days of the week. TRE was superior to standard- of care dietary instructions in reducing weight and steatosis but was equally effective as a regular low-carb, high-fat diet.[91] In conclusion, TRE is a relatively new strategy that can be considered an alternative option for patients who find it easier to maintain (Table 1).

2.6 | Core principles that need to be kept in any diet

In diets such as intermittent fasting, patients may get the impression that during the eating time, also called sometimes the "feast day/time," they can eat whatever they want regardless of its healthiness. That may lead to overconsumption of sugars, saturated fats, and ultra-processed foods (UPFs). Furthermore, there may be an excess of saturated fat, and meat, specifically red and processed meat, in low-carb and ketogenic diets. At the least, unprocessed or minimally processed fish and poultry should be preferred.

In various feeding trials, saturated fat (e.g., butter/palm oil) has consistently increased liver fat, in contrast to PUFA and MUFA.[28,108,109] It is also well evidenced that overconsumption of fructose-containing sugars leads to NAFLD,[110–112] and a little evidence also indicates increased risk for NASH.[113] In a recent meteanalysis of cross-sectional and case-control studies, consumption of both red meat and soft drinks was positively associated with NAFLD, while nut consumption was negatively associated with NAFLD.[114] Prospective cohort study supports these findings, by showing a dose-response association between soft drink consumption (mainly sugar-containing carbonated beverages) and NAFLD diagnosed by US; a consumption of 4 or more servings per week was related with 45% increased risk to develop NAFLD.[115] Importantly, high sugar consumption is also related to the risk for liver cancer.[116] This is emphasized explicitly for sugar-sweetened beverages consumption, which is strongly related to the risk of hepatocellular carcinoma (HCC).[117,118] Therefore, any type of diet should have a low intake of sugars and saturated fats.

The polar opposite of the Mediterranean diet, which advocates home-based cooking and fresh local foods, omega-3 fatty acids, vitamins, and polyphenols which are important for NAFLD prevention,[44,119] is UPFs. UPFs and drinks (e.g., sugar-containing beverages) are often characterized by lower nutritional quality, high energy

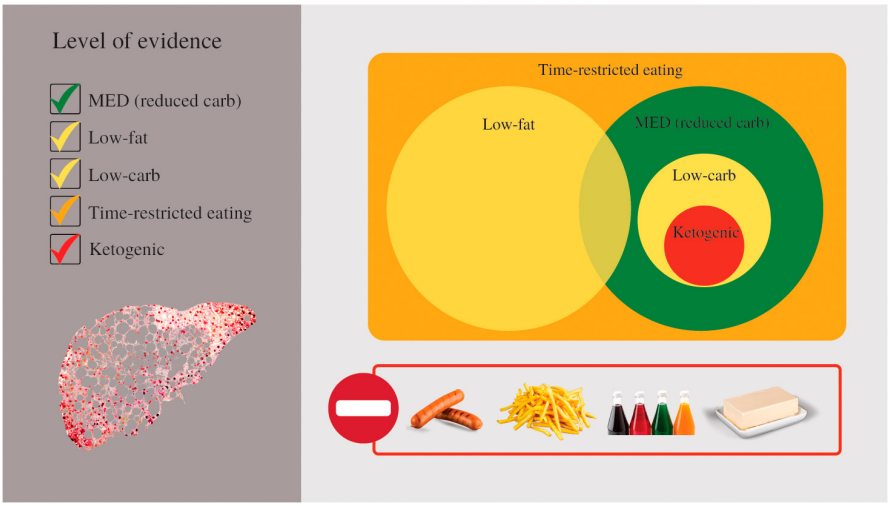

FIGURE 2 A conceptual summary of the level of evidence of each type of diet for NAFLD treatment and suggested combinations. The colours represent the level of evidence of each type of diet in the treatment of NAFLD; the most evidence-based treatment is in green, and the lowest is in red. Low-fat and Mediterranean diets share common principles (e.g., both are low in saturated fat and sugar). Both are effective for liver fat reduction, but the Mediterranean diet is superior in some studies. Therefore, all other types of low-carb diets should probably adopt the Mediterranean diet principles as much as possible. The level of evidence for a low-carb diet is similar to the low-fat diet and higher than the ketogenic diet that cannot be currently recommended. Intermittent fasting/time-restricted eating can be used with all types of diets. All diets should minimize ultra-processed foods and meat, sugary foods and drinks, and saturated fat. The exact type of diet and timing of eating can be tailored to the patient's preferences.

TABLE 3 Sample menu of a low-carb diet in Mediterranean diet style

	Foods	Quantity
Breakfast 'Tzaziki'	Natural yogurt 3% fat	150cc
	walnut	Four halves
	Cucumber	1 unit
	Olive oil	One tbl
	Green herbs (can choose, e.g., dill, mint, coriander)	Few leaves
	Chia seeds or ground flax seeds	1 tsp
Lunch 'Baked lemon fish fillet'	Baked or steamed fish fillet with olive oil	One portion, 150 gr
	Black or green olives	Eight units
	Tomato and lemon	Few slices
	Olive oil	One tbl
	Cooked greens (can choose, e.g., green beans, broccoli, spinach)	1 cup
4 pm 'Fresh snack'	Fruit (can choose, e.g., apple, pear, banana)	1 medium unit/1 cup
	Almonds, raw	Ten units
Dinner 'Israeli dinner'	Boiled egg	1 unit
	Roasted eggplant	1/2 cup
	Fresh vegetable salad: tomato, cucumber, pepper, green herbs (can choose, e.g., mint, parsley, lettuce)	2–3 veg units/2 cup
	Tahini, whole sesame (sesame-based spread)	Two tbl of raw past/3 TBL of tahini salad mixed with lemon and water
	Chickpeas, cooked	1/2 cup
Night 'Lettuce wraps'	Lettuce	Three pieces
	Low-fat feta cheese 5%	Two tbl
	avocado	1/2 a unit
	Green herbs (can choose, e.g., dill, mint, coriander)	Few leaves

Note: ~1600 kcal, ~17% of energy from carbohydrates, ~58% of energy from total fat, ~10% of energy from saturated fat, and ~21% of energy from protein. ~67 g/day carbohydrates, ~38 g/day fibers.

TABLE 4 Sample menus of intermittent fasting (5:2 ~2000: 500 kcal) diet in Mediterranean diet style - Maintenance phase

	Foods	Quantity
Breakfast 'Classic breakfast'	Whole wheat bread	Two units
	Low-fat white cheese 5% fat	Two tbl
	Cucumber and tomato	Few slices each
	Boiled egg	1 unit
Lunch 'Chicken and rice'	Cooked or roasted chicken thigh	One portion, 150 g
	Rice, cooked	1 1/2 cup
	Cooked vegetable mix (can choose, e.g., carrot, zucchini, celery)	1 cup
	Olive oil	1 tsp
4 pm 'Yogurt bowl'	Natural yogurt 3%	150cc
	Fruit (can choose, e.g., apple, pear, banana)	1 medium unit/1 cup
	Oat flakes	Three tbl
Dinner 'Soup and salad'	Tuna fish preserved in oil	Two tbl
	Fresh vegetable salad: tomato, cucumber, pepper, green herbs (can choose, e.g., mint, parsley, lettuce)	2–3 veg units/2 cup
	Olive oil	1 tsp
	Legume soup: lentil, peas, or beans	1 1/2 cup
Night 'Peanut butter sandwich	Whole wheat bread	1 unit
	Natural peanut butter	1 tsp

Note: ~2000 kcal, ~41% of energy from carbohydrates, ~26% of energy from total fat, ~7% of energy from saturated fat, ~24% of energy from protein, ~209 g/day carbohydrates, ~52 g/day fibers.

TABLE 5 Sample menus of intermittent fasting (5:2 ~2000: 500 kcal) diet in Mediterranean diet style - Fasting phase

	Foods	Quantity
Breakfast 'Green smoothie'	lettuce	1 cup
	Mixed greens (can choose, e.g., spinach, kale, mint, basil)	½ a cup
	Cucumber	1 unit
	Lemon juice	Two tbl
	Apple or pear	One small unit
	Nut or almond natural spread	1 tsp
Lunch 'Vegetable omelet'	Egg	2 unit
	Cooked vegetable mix (can choose, e.g., carrot, zucchini, celery)	1 1/2 cup
	Olive oil	1 tsp
Dinner 'Cheese dip with Vegetables'	Low-fat white cheese 3%	Three tbl
	Green herbs (can choose, e.g., dill, mint, coriander)	1 tsp
	Fresh vegetable (can choose, e.g., tomato, cucumber, pepper, carrot, kohlrabi, celery)	3–4 veg units

Note: ~500 kcal, ~35% of energy from carbohydrates, ~38% of energy from total fat, ~10% of energy from saturated fat, ~23% of energy from protein, ~45 g/day carbohydrates, ~13 g/day fibers.

density, added sugars and saturated fat, additives, and compounds formed during processing and storage.[120,121] In a cross-sectional study, UPFs and drinks have been related among NAFLD diagnosed subjects with a higher prevalence of the metabolic syndrome, NASH, and significant fibrosis measured by markers (FibroMax).[122] In addition, in an RCT, UPFs led increased caloric intake and weight gain as compared to minimally processed food,[123] and an association has been demonstrated between the dietary share of UPFs and the risk of obesity and chronic diseases highly related to NAFLD; T2DM, CVD, and cancer, in several observational studies including prospective cohorts.[124–127] Therefore, whatever diet is chosen for a patient, the consumption of UPFs should be kept to a minimum (Figure 2).

Last but not least, is the incorporation of physical activity to any lifestyle modification plan.

In NAFLD treatment, exercise is recommended by clinical-practice guidelines.[13,15] The recommendations are established upon the findings that exercise overall, without weight loss, produces a 20%–30% relative reduction in hepatic fat content,[128,129] with similar effects of different modalities of exercise (aerobic exercise, resistance exercise, or high-intensity intermittent exercise). Although most exercise trials among NAFLD patients to date were relatively small and based on short-term interventions, between 8 and 12 weeks, the positive effects on liver fat reduction are consistent.[130,131] Even low-volume, low-intensity aerobic exercise can decrease liver fat without clinically significant weight loss.[130] A recent meta-analysis using 16 RCTs of exercise intervention showed that exercise significantly reduced liver fat compared to the control group.[129] Studies reporting the effects of exercise in people with fibrosis are limited. A 12-week aerobic exercise non-controlled intervention led to reduced fibrosis by one stage, according to repeated liver biopsy, in about 60% of patients.[132] A randomized trial indicated that a 12-weeks high-intensity interval aerobic training reduced liver stiffness measured by transient elastography.[133]

3 | CONCLUSIONS

A general recommendation for reducing total fat or total carbohydrates intake should be replaced with specific recommendations for the different types of fat, carbohydrates, specific food groups like meats, vegetables, oils, and specific categories of food processing levels. The evidence for a direct benefit to NAFLD by restrictive diets like low-carb, ketogenic, very-low-calorie diets, and intermittent fasting is scarce, and the long-term safety has not been tested. Taking into account the existing evidence, the approach of a diet based on healthy eating patterns of minimally processed or unprocessed foods, low in sugar and saturated fat, high in polyphenols, omega-3 PUFA, and MUFA, leads to the conclusion that ideally, a Mediterranean diet, or other overlapping dietary patterns, should serve as a basis which can be restructured into different types of diets. The exact type of diet in terms of macronutrient composition, food choices, and timing of eating can be tailored to the patient's preferences to increase long-term adherence, as long as these principles are kept (Figure 2). From a practical point of view, Tables 3–5 provide sample menus of a low-carb diet and an intermittent fasting diet in the Mediterranean dietary pattern style.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Zelber-Sagi S, Grinshpan LS, Ivancovsky-Wajcman D, Goldenshluger A, Gepner Y. One size does not fit all; practical, personal tailoring of the diet to NAFLD patients. *Liver Int*. 2022;42:1731-1750. doi: 10.1111/liv.15335