Received: 13 May 2021 | Revised: 9 July 2021 | Accepted: 23 July 2021

DOI: 10.1111/eci.13659

REVIEW

WILEY

Is there an 'ideal' diet for patients with NAFLD?

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Funding information
LV was supported by Gilead_IN-IT-989-5790; Ricerca Finalizzata Ministero della Salute: RF-2016-02364358 and CV PREVITAL; the Innovative Medicines Initiative 2 joint undertaking of European Union's Horizon 2020 research and innovation programme and EFPIA for the project LITMUS under grant agreement No. 777377; the European Union (EU) Programme Horizon 2020 Programme 'Photonics' under grant agreement '101016726' for the project 'REVEAL'; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico 'Ricerca Corrente', and Fondazione Sviluppo Ca' Granda for the project 'Liver-BIBLE' (PR-0391), Fondazione IRCCS Ca' Granda '5permille' for 'COVID-19 Biobank' (RC100017A)

Abstract

Nonalcoholic fatty liver disease (NAFLD) is a growing epidemic that encompasses three distinct clinical phenotypes: uncomplicated fatty liver, nonalcoholic steatohepatitis (NASH) and NASH-related cirrhosis with its complications, including hepatocellular carcinoma. To date, no pharmacological treatments have been approved and lifestyle modifications including reduced caloric intake targeting a 7%-10% weight loss from baseline assessment represent the standard approach. Mediterranean diet has been recommended as the best dietary pattern since it is easy to follow and, independently of caloric intake its nutritional components have beneficial metabolic effects that not only improve steatosis but also risk factors for cardiovascular events, the leading cause of morbidity/mortality in individuals with NAFLD. Other dietary patterns such as ketogenic diet and Dietary Approach to Stop Hypertension (DASH) diet can be used in patients with NAFLD. Recently, intermittent fasting diets have gained popularity among healthy individuals and have been proposed as a safe and effective treatment for the metabolic syndrome in experimental and in a few human studies. In this narrative review, we aim to summarize the evidence for the available dietary approaches for patients with NAFLD.

KEYWORDS
chronic liver disease, diet, dietary regimen, lifestyle intervention, nonalcoholic steatohepatitis

Nicola Pugliese and Maria Corina Plaz Torres contributed equally to this work. All the authors have given substantial contribution to the completion of this work and have seen and approved the text in the current version.

1 | INTRODUCTION

In recent years, the clinical relevance of nonalcoholic fatty liver disease (NAFLD) has progressively increased, and this disease is currently deemed a major public health issue. NAFLD can be considered in the majority of cases the hepatic manifestation of the metabolic syndrome, and in turn, it contributes to metabolic alterations. NAFLD consists of excessive fat accumulation in the liver in individuals without excess of alcohol consumption (daily alcohol consumption ≤30 g for men and ≤20 g for women), other known causes of hepatic fat storage, or other aetiologies of liver disease. The spectrum of NAFLD includes several pathological entities: from simple steatosis to nonalcoholic steatohepatitis (NASH) with different degrees of fibrosis, up to cirrhosis and end-stage liver disease.[1,2]

Global prevalence of NAFLD is estimated at 24%; the highest rates are reported from South America and the Middle East, followed by Asia, the United States and Europe.[3] The prevalence of NAFLD in Europe ranges from 5% to 44% in different countries and increases in 'at risk' groups such as patients with type 2 diabetes (T2D) and/or obesity.[3] The strong link between NAFLD and metabolic alterations led to a scientifical trend suggesting to rename NAFLD in metabolic (dysfunction)-associated fatty liver disease (MAFLD).[4] In view of the progressive increase in the prevalence of this disease, it is estimated that NASH-related cirrhosis will become the leading cause for end-stage liver disease, hepatocellular carcinoma and liver transplantation in the foreseeable future.[3]

In addition, NAFLD has become, in parallel with the increasing prevalence of obesity, the most common cause of chronic liver disease during the developmental age in Western countries.[5] This is a worrying trend as paediatric NAFLD has been associated with an increased risk of developing cardiometabolic diseases and cirrhosis in adulthood.[6]

NAFLD is also present in 7% of normal-weight (lean) people, more frequently in female and Asian subjects.[7] The pathogenesis of 'lean-NAFLD' seems to be related to multiple factors including dysfunctional fat, altered body composition and genetic predisposition.[7,8] Lean subjects with NAFLD have milder features of the metabolic syndrome when compared with obese patients, but they have a higher prevalence of metabolic derangements compared with healthy controls, above all diabetes and higher plasma triglycerides.[9] Data on long-term prognosis of 'lean-NAFLD' patients are scarce and controversial but suggest that, in contrast to what has been believed for years, lean NAFLD is not a 'benign' disease as these subjects can develop the full spectrum of liver disease associated with NASH.[10,11]

The management of NAFLD, according to the European Association for the Study of the Liver (EASL) guidelines, should be based on lifestyle changes through diet and habitual physical activity. In fact, at present, the only treatment which has robustly been proved to ameliorate liver damage in patients with NAFLD without severe liver fibrosis is represented by weight loss achieved through diet. EASL guidelines recommend diets that have a 500-1000 kcal/d deficit, exclusion of NAFLD-promoting components and macronutrient composition adjusted according to the Mediterranean diet. Diet should be combined with physical activity, the EASL guidelines recommend 150-200 min/wk of moderate intensity aerobic exercise or resistance training in 3-5 sessions. The goal is, in overweight or obese patients, to achieve a 7%-10% weight reduction, which results in improvement of liver enzymes and histology.[12]

In cases of morbid obesity, bariatric surgery, including sleeve gastrectomy and Roux-en-Y gastric bypass, remains one of the most effective methods of producing sustained weight loss in patients with NAFLD by either restricting the volume of food that can be consumed, creating malabsorption or a combination of both.[13-15]

There are currently no drugs approved for the treatment of NAFLD, but several phase 2 and 3 clinical trials are underway. The EASL guidelines for NAFLD suggest the use of pioglitazone (off-label in nondiabetic patients) or vitamin E as they improve steatohepatitis in patients with a histologically proven diagnosis of NASH; however, data on long-term safety and efficacy in these patients are lacking.[12]

Here, we will review the dietary regimens that have been proposed over the years as a therapeutic approach for NAFLD (Figure 1). The purpose of this review is to describe the current scientific evidence supporting the use of specific dietary regimens in adults with NAFLD in the hypothesis that they improve liver damage independently of the overall caloric intake (Table 1).

2 | LITERATURE SEARCH

We performed a comprehensive literature search on PubMed, Scopus and EMBASE up to December 2020 in order to identify all studies assessing efficacy of diet in patients with NAFLD. The following search terms matched to "Non-alcoholic fatty liver disease" or "Non-alcoholic steatohepatitis" or related acronyms were used: "diet", "dietary regimen", "Mediterranean diet", "ketogenic diet", "intermitting fasting", "very low carbohydrate diet", "low carbohydrate diet", "low energy diet", "DASH diet". We focused on full-text articles published in English, but abstracts were considered if relevant. Additional studies were identified through the careful analysis of the reference lists of the included studies.

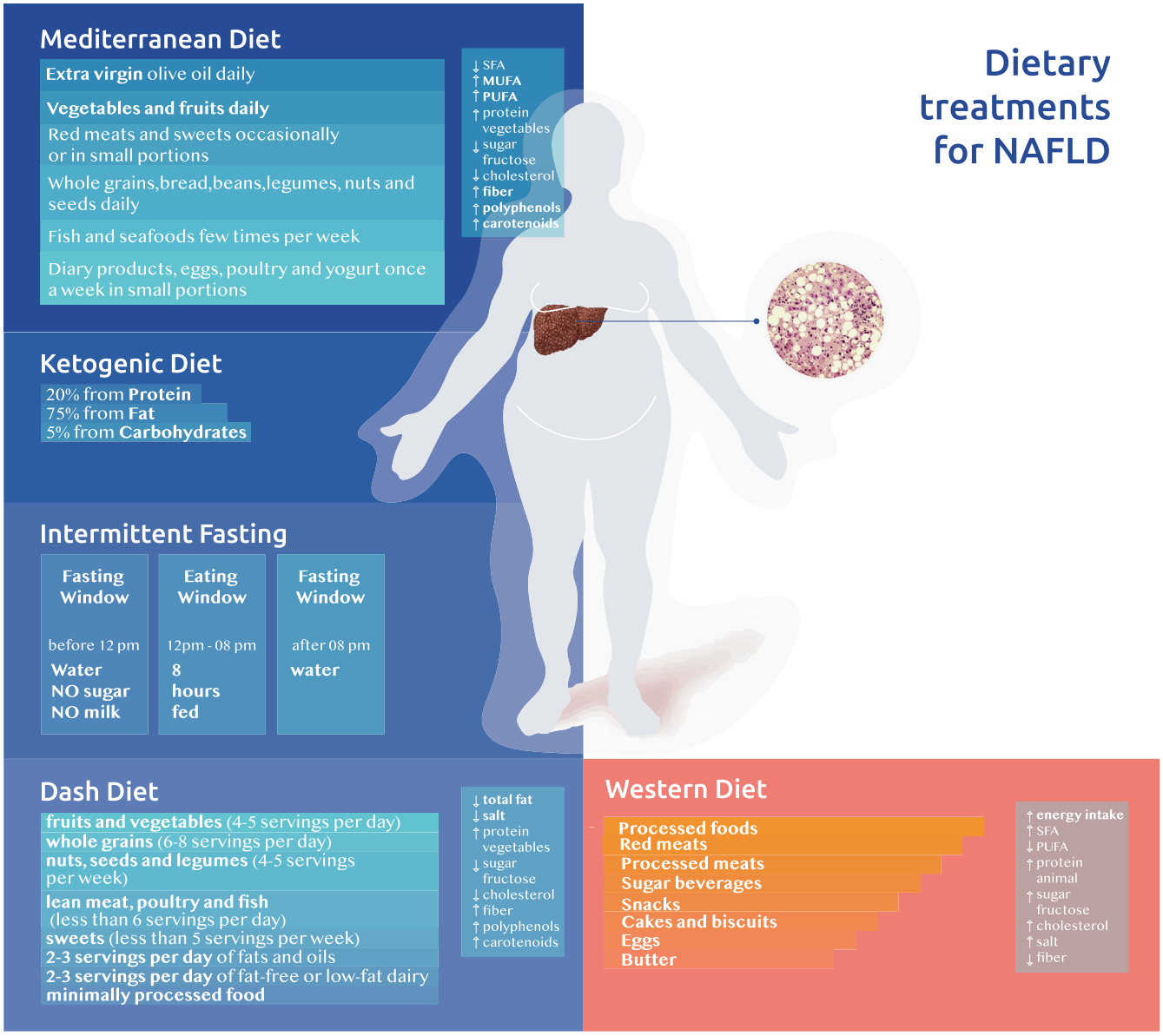

FIGURE 1 Dietary treatments for NAFLD

3 | MEDITERRANEAN DIET AND ITS VARIANTS

The Mediterranean diet (MD) is based on the daily consumption of cereals, vegetables, fresh fruits, dairy products, olive oil and nuts. In addition, it includes the consumption of 1 or 2 glasses of wine/day, whereas fish and white meats are consumed in moderation and the intake of red and processed meats and desserts is usually allowed only on a one monthly basis. MD is a diet with a high fat content; in fact, fat constitutes 35%-45% of the total daily energy intake but the proportion of saturated fatty acids and cholesterol is low whilst that of mono-unsaturated fatty acids (MUFAs) and poly-unsaturated fatty acids (PUFAs) is high, with a balanced omega-6 to omega-3 ratio. Carbohydrates and proteins, respectively, represent 35%-40% and 15%-20% of the daily energy intake.[16] Several studies have shown that dietary regimes rich in omega-3 PUFAs can reduce insulin resistance and intrahepatic triglyceride content, resulting in an amelioration of steatohepatitis: it seems to be important that a low omega-6/omega-3 ratio is maintained in order to obtain benefit from omega-3 PUFA.[16] Moreover, PUFAs have been shown to be advantageous in preventing cardiovascular events through an improvement of insulin sensitivity, an anti-inflammatory effect and a reduction in oxidative stress.[17] An additional benefit of the MD on fatty liver disease is related to its low content of refined sugars and high content of complex carbohydrates and fibres. Epidemiologic studies have identified a directly proportional association between refined sugar, particularly high-fructose corn syrup, and the risk for NAFLD.[18,19] Moreover, the MD is rich in whole grains, which have a high content of fibres that may be beneficial

TABLE 1 Studies evaluating effects of diet on liver-related outcomes in NAFLD and NASH

Reference	Type of diet	Study design	Study aim	N of patients	NAFLD diagnosis and assessment at follow-up	Main results
Kontogianni et al[29]	MD	Retrospective study	To investigate association between adherence to the MD (estimated with MedDietScore) and histological characteristics of NAFLD	73	Evidence of hepatic steatosis on ultrasound and/or compatible liver histology and/or elevated alanine aminotransferase (ALT) and/or γ-glutamyl-transpeptidase (GGT) levels	MedDietScore negatively correlated to ALT ($P = .03$) and severity of steatosis ($P = .006$) Patients with NASH exhibited lower adherence to MD (29.3 ± 3.2 vs 34.1 ± 4.4, $P = .004$) compared to those with simple fatty liver and had higher BMI ($P = .028$)
Aller et al[31]	MD	Cross sectional study	To investigate association between adherence to the MD (estimated with 14-item MD assessment tool) and histological characteristics of NAFLD	82	Evidence of hepatic steatosis on liver histology	Greater adherence to the MD was associated with lower grade of steatosis and presence of steatohepatitis
Properzi et al[32]	MD	Single blind RCT: randomization to MD vs Low-fat diet (LFD)	Investigate the effect of two ad libitum isocaloric diets (MD or LFD) on hepatic steatosis	48	NAFLD diagnosis was made by MRS	Hepatic fat content reduced significantly in both groups ($P < .01$), with no difference between groups ($P = .32$). Liver enzymes improved significantly in both groups
Abenevoli et al[34]	MD	RCT. Low-calorie MD was prescribed to Group A and B patients for 6 mo. Group B received also antioxidant complex. Group C received no treatment/advice	Evaluate the effects of antioxidant complex associated with MD on liver fat accumulation, BMI, glucose, and lipid metabolism	50	NAFLD was diagnosed by US. Steatosis degree was assessed by FLI and US using the Hamaguchi score	Significant reductions in BMI ($P = .0001$), lipid profile ($P < .001$) and in FLI ($P < .01$) and US-Hamaguchi score ($P = .0001$) were reported in groups A and B but not in the control group
Misciagna et al[35]	MD	Double blind RCT: LGIMD or INRAN (Italian National Research Institute for Foods and Nutrition) diet	To estimate the effect of a low-glycaemic variant of the MD (LGIMD) on steatosis	98	NAFLD diagnosis by US. Steatosis degree assessed by an US based scale	FLI and steatosis degree significantly decreased in both diets ($P < .05$) but the decrease was greater in the LGIMD group
Hekmatdoost et al[54]	DASH diet	Case-control study	To examine the association between adherence to the DASH diet and risk of NAFLD	306	NAFLD evaluation by Controlled Attenuation Parameter (CAP)	Inverse relationship between the DASH-style diet and risk of NAFLD
Razavi Zade et al[53]	DASH diet	Two-arm parallel randomized controlled clinical trial	To evaluate the effects of DASH diet on weight loss and metabolic status in patients with NAFLD	60	NAFLD diagnosis by US.	The DASH group showed a significantly reduction of BMI and steatosis degree and improvement of aminotransferases and metabolic markers
Drinda et al[61]	Intermittent fasting	Prospective, observational	Safety and effects on FLI and glucose metabolism	697	FLI was used as a surrogate parameter for NAFLD	FLI decreased significantly (-14.02 ± 11.67; $P < .0001$), with a larger effect in individuals with T2DM (-19.15 ± 11.0; $P < .0001$). Improvement of FLI correlated with the number of fasting days and with the magnitude of BMI reduction
Cai et al[62]	Alternate day fasting	Randomized controlled trial testing the effects of ADF vs TRF vs control	Evaluate effects of ADF on body weight and lipid profile in patients with NAFLD	271	NAFLD was diagnosed by means of US	ADF is effective in weight reduction and in amelioration of lipid metabolism but has no effect in steatosis regression

in NAFLD patients for different reasons. The first is that with their prebiotic effects they can modulate gut microbiota, which is known to play a role in the pathogenesis and progression of NAFLD. Additionally, they have a protective effect against the risk for dyslipidaemia, cardiovascular disease (CVD) and diabetes.[20-22] A minimal amount of red and processed meat intake is another characteristic of the MD: meat contains saturated fatty acids (SFAs) and cholesterol which are relevant in NAFLD pathogenesis as demonstrated by some case-control and cross-sectional studies.[23-25] Lastly, the typical Mediterranean dietary pattern also involves coffee consumption, which has been shown to be a protective agent for the development and progression of NAFLD.[26,27] Notably, Molloy et al[28] showed that coffee consumption was significantly associated with a reduced prevalence of steatosis and a lower severity NASH: comparing patients with bland steatosis/not-NASH to those with NASH stage 0-1 and also patients with NASH stage 0-1 to those with NASH stage 2-4, there was a significant difference in coffee consumption between the two groups ($P = .005$ and $P = .016$, respectively).

Based on the abovementioned benefits and in consideration of the current EASL clinical practice guidelines, several studies have been carried out in real-life settings in order to verify the actual effects of the MD on NAFLD.

Among the firsts to investigate the potential influence of the MD on NAFLD and its severity were Kontogianni et al.[29] The study investigators found that the adherence of 73 overweight/obese adult patients to the MD (verified through a MedDietScore food questionnaire) was associated with lower levels of serum alanine aminotransferase (ALT) and insulin resistance, as well as with a lower severity of liver steatosis as demonstrated by the liver biopsy samples obtained from 34 among the study participants.[29,30] Similar results were obtained by Aller et al, who conducted a study including 82 adult subjects with biopsy-proven NAFLD. Among those with greater adherence to the MD (determined through the 14-item MD assessment tool) the degrees of steatosis and NASH were less severe and insulin resistance more markedly decreased.[31]

The effectiveness of the MD in NAFLD has recently been confirmed in a randomized controlled trial (RCT) including 48 subjects with NAFLD diagnosed and quantified by magnetic resonance spectroscopy (MRS). Patients were randomized to a 12-week blinded dietary intervention (MD vs low-fat): at week 12, hepatic steatosis and liver enzymes were significantly reduced in both groups ($P < .001$) with an overall mean reduction of 25% in liver fat without differences between the two interventions.[32]

Further evidence on the validity of the MD in NAFLD comes from another recent RCT that enrolled 50 overweight patients with ultrasonography (US)-proven fatty liver disease, staged using the *Hamaguchi score* that includes hepatorenal echo contrast, bright liver, deep attenuation and vessel blurring.[33] Patients were randomized to three groups (MD alone/MD and antioxidant supplementation /control). After 6 months of intervention, a significantly ($P = .0001$) decreased hepatic fat content, assessed by US and compared to baseline, was reported for patients on the MD arms but not for controls. No significant difference between the two MD arms was detected in hepatic fat content decrease ($P = .626$). However, the group in which MD was associated with antioxidant intake showed a more consistent improvement in insulin sensitivity as well as in anthropometric parameters when compared with group of patients taking only MD, emphasizing the potential benefits of antioxidant supplementation in overweight patients with NAFLD.[34] Importantly, adherence to the MD also ameliorated liver stiffness as assessed by transient elastography[34] in accordance with previous results by Kontogianni et al.[29]

Other studies have analysed variants of the MD. As an example, a recent Italian RCT by Misciagna et al including 98 patients with moderate-to-severe US-proven NAFLD was conducted in order to test the low-glycaemic variant of the MD.[35] This dietary scheme has been shown to be effective in reducing the ALT levels and the fatty liver index (FLI), a validated algorithm based on body mass index (BMI), waist circumference, triglycerides and gamma-glutamyltranspeptidase values that predicts the presence of liver steatosis.[36,37] In this Italian cohort, the median values of the FLI significantly decreased from the baseline values of 82.28 (interquartile range (IQR) 70.31-90.38) to values of 57.72 (IQR 27.33-73.14, $P < .05$) at the 6-month follow-up visit. Similarly, ALT levels decreased from 48 to 39 U/L ($P < .05$).[36] This study has the limitation of assessing hepatic steatosis using a score, which, although validated, is not as reliable as a liver biopsy in proving regression of NASH. The same dietary regimen was investigated in another RCT involving 278 subjects with abdominal obesity or dyslipidaemia. The patients were randomized to low-fat or isocaloric Mediterranean/low-carbohydrate high-fibres content (MD/LC +28 g walnuts/d) diets with or without associated moderate physical activity. Hepatic fat content and abdominal fat depots were assessed using MRI. After a 6- and 18-month follow-up period, a greater decrease in liver fat content was evident ($P = .036$) in subjects randomized to the MD/LC diet, even after adjusting for visceral adipose tissue changes. Of note, after controlling for visceral adipose tissue loss, decreased hepatic fat content also remained independently associated with reductions in liver enzymes and glycated haemoglobin.[37]

Additional evidence for the benefit of the MD in fatty liver disease has been reported in a recent randomized clinical trial which was conducted on 294 obese patients whose NAFLD was assessed with MRS. Patients were randomized to three groups: healthy dietary guidelines (HDG), MD and

green-MD. Both isocaloric MD groups consumed 28 g/d walnuts; the green-MD group further consumed green tea (3-4 cups/d) and Mankai green shake, all polyphenol-rich foods. After 18 months, NAFLD prevalence declined to 54.8% (HDG), 47.9% (MD) and 31.5% (green-MD). Despite similar moderate weight loss in both MD groups, green-MD group achieved almost double intrahepatic fat loss, as compared with MD ($P = .035$) and HDG ($P < .001$), suggesting a crucial role for polyphenols.[38]

Finally, it is worth mentioning a recent study by Ma and collaborators, involving the second- and the third-generation cohorts of the Framingham Heart Study, which showed that improving diet quality leads to a reduction in the risk and severity of NAFLD in adults. Their focus was on the MD assessed by Mediterranean style diet score (MDS) and the Alternative Healthy Eating Index (AHEI) score. Greater adherence to this dietary pattern was associated with reduction in weight gain and hepatic fat with lower incidence of CVD. Moreover, it was suggested that adopting a healthier diet might blunt the genetic predisposition to NAFLD.[39]

Overall, these data suggest that adherence to a Mediterranean dietary pattern reduces the hepatic fat content and may ameliorate the degree of inflammation in NASH. Moreover, beneficial effects of the MD in terms of cardiovascular prevention have been largely documented. However, most data come from studies evaluating steatosis regression are based on radiological findings or surrogate markers of steatosis; consistent evidence with strong liver-related endpoints (NASH regression, fibrosis regression) based on histology are lacking.

4 | KETOGENIC DIET

Carbohydrates are known to play a key role in the synthesis of intrahepatic fat.[17] In these dietary patterns, carbohydrates should be less than 40% of the total daily energy intake.[40]

The most popular low-carbohydrate diet is the ketogenic diet (KD), which is based on a strict restriction of carbohydrates, which are taken in amounts of less than 20-50 g per day. Based on fat content, KD can be hypocaloric, normocaloric or unrestricted. This dietary pattern was introduced into clinical practice to treat patients with refractory epilepsy but became at the same time popular among obese patients due to its effectiveness in inducing satiety and, consequently, weight loss.[41-43] However, its effectiveness is contrasted by various side effects such as vomiting, headache, fatigue, constipation, irritability and lethargy; moreover, a limit to this approach is the difficulty in maintaining the adherence for long periods of time, as it is extremely restrictive.[44,45] KD, thanks to its very low carbohydrate content, decreases insulin levels resulting in an increase in fatty acids oxidation rate and in a reduction in lipogenesis which are important goals in the NAFLD treatment. Moreover, ketone bodies, produced as a reaction to carbohydrate restriction, induce satiety by a yet unknown mechanism, thereby promoting weight loss.[46,47] Hence, this diet has been tested as a treatment strategy for NAFLD patients in a few studies. The one performed by Perez-Guisado et al included 14 overweight male patients with metabolic syndrome and NAFLD, the latter, was diagnosed by means of a combination of a cut-off value of ALT levels >40 U/L with a bright liver at abdominal US. Patients were subjected to a Mediterranean high-fat KD, unrestricted in calorie intake and high in unsaturated fats, such as extra virgin olive oil and omega-3 fish oil. The results showed a significant ($P < .001$) improvement in body weight (from 109.79 to 95.86 kg), LDL (from 123.43 to 100.35 mg/dL), ALT (from 71.92 to 37.07 U/L), AST (from 47.71 to 29.57 U/L) levels and steatosis degree at US examination (an overall reduction was found in 92.86% of the patients with a complete fatty liver regression observed in 21.4% of the cohort).[48]

Additional evidence comes from a study by Mardinoglu et al who carried out a study of an isocaloric KD with increased protein content that was used as a 2-week dietary regimen in 17 obese patients with NAFLD. In this study, liver fat reduction (mean reduction 43.8%), as assessed by MRS, was detected despite a slight weight loss and, interestingly, the reduction was significant just 1 day after the beginning of the KD ($P = .027$).[49]

These findings suggest that KD is a potential therapeutic tool for addressing steatosis regression, weight loss and high cholesterol levels; however, again, data with solid endpoints associated with a reduced liver-related and overall mortality rate, such as regression of fibrosis and resolution of inflammation, are lacking, and therefore, we feel that further research in this field is needed.

5 | DASH DIET

The dietary approach to stop hypertension (DASH) is a low-glycaemic index and low energy-dense diet that was originally addressed to patients with hypertension as it is associated with a reduction in cardiovascular risk.[50,51] This diet is characterized by a high intake of fruits, vegetables, whole grains and low-fat products. It is low in added sugars, sugar-sweetened beverages and red and processed meats.[52] Hence, this diet similarly to the Mediterranean one induces an amelioration in glycaemic and lipid metabolism and helps obtaining weight reduction whilst decreasing the cardiovascular risk. All these effects are main goals of NAFLD treatment so that this diet gained interest among specialists taking care of NAFLD patients.

A RCT including 60 overweight or obese adults, aged 25-75 years with US-proven NAFLD and increased serum ALT levels were assigned participants to a DASH diet or a control

diet for 8 weeks. The DASH group showed a significantly greater reduction of BMI and steatosis degree and improvement of aminotransferases and metabolic markers such as insulin levels, HOMA (homeostatic model assessment) index, serum triglycerides, total-/HDL-cholesterol ratio.[53] Different results were obtained by a case-control study that was conducted to observe the association between adherence to the DASH diet and the risk of NAFLD development in 102 patients with newly diagnosed NAFLD and 204 controls. An inverse relationship between the DASH-style diet and the risk of NAFLD was found: subjects in the top quartile of DASH diet score (a score calculated based on the food and nutrients emphasized or minimized in DASH diet) were 30% less likely to have NAFLD (OR: 0.70; 95% CI: 0.61, 0.80). However, following adjustment for dyslipidaemia and BMI, the association was not significant (OR: 0.92; 95% CI: 0.73, 1.12).[54]

Based on these findings, DASH may be a promising good dietary option for subjects with NAFLD since weight loss, the amelioration of metabolic comorbidities and regression of steatosis are among the main goals of NAFLD treatment and surrogate markers of liver disease status. However, these studies were not specifically designed to assess the effects of the DASH diet on solid liver-related outcomes and liver histology was not assessed. Thus, we feel that also in this case, further studies are needed so as to identify the potential benefit of the DASH diet in NAFLD patients.

6 | TIME-RESTRICTED FEEDING AND INTERMITTENT FASTING

Intermittent fasting (IF) and time-restricted feeding (TRF) gained popularity in the past few years. Usually, intermittent fasting refers to diets that contemplate varying periods of fasting, generally ranging from 1 or 2 days/wk up to as many as 21 days. The term TRF, instead, is used to define eating patterns in which food intake is restricted to a time window of 8 hours or less every day, for variable time periods.[55] These dietetic approaches have shown several beneficial metabolic effects in overweight and obese subjects, including those with diabetes. The key feature of all these regimens is the so called 'metabolic switch' that refers to the body's preferential shift from utilization of glucose from glycogenolysis to fatty acids and fatty acid-derived ketones.[56] The metabolic switch occurs when glycogen stores in the liver are depleted, generally 12 hours after the cessation of food intake, and adipose tissue lipolysis increases to produce more fatty acids and glycerol.[56] The consequences of this swift are weight loss, reduced insulin resistance and lower levels of blood glucose together with a reduction of circulating leptin, an elevation of adiponectin levels and reduced risk factors for cardiovascular disease including total cholesterol, LDL cholesterol and triglyceride concentrations.[57-60] However, in most of the studies, a control group following a regular daily continuous energy restriction regimen was lacking; therefore, we cannot distinguish if the benefits of the IF regimens are a specific effect of fasting or a result of the overall energy restriction and weight loss. However, for some patients adhering to a TRF or to periodic periods of fasting may be easier than adhering to a standard continuous energy restriction.

The metabolic changes that have been demonstrated in studies among obese and overweight individuals following various IF patterns are targets for the dietary treatment of patients with NAFLD. Still, to the best of our knowledge, only two studies have tested the efficacy of intermittent fasting in this population. Particularly, Drinda et al performed a prospective observational trial aimed at investigating the effects and safety of periodic fasting in subjects with and without T2D and a diagnosis of steatosis as per FLI.[61] Six hundred and ninety-seven subjects (38 with T2D) were enrolled. The mean duration of fasting was 8.5 ± 4.0 days (range 6-38). FLI decreased significantly (-14.02 ± 11.67; $P < .0001$), with a larger effect in individuals with type 2 diabetes mellitus (-19.15 ± 11.0; $P < .0001$; $P = .002$ compared to nondiabetic subjects). After fasting, nearly half of the 264 subjects with FLI ≥ 60 (highest risk category) shifted to a lower risk category. The improvement of FLI correlated with the number of fasting days (Pearson's coefficient (r) $= -0.20$, $P < .0001$) and with the magnitude of BMI reduction ($r = 0.14$, $P = .0001$).[61] A limit of this study was that NAFLD was presumed only based on FLI.

In the second study, 271 NAFLD patients were randomized to an alternate day fasting (ADF) group, a TRF group or a control group and subjected to the respective diet for 12 weeks (62). NAFLD diagnosis was confirmed by abdominal US. Within 4 weeks, the body weight decreased significantly ($P < .001$) in the alternate day fasting group by 4.56 ± 0.41 kg ($6.1 \pm 0.5\%$) and the TRF group by 3.62 ± 0.65 kg ($4.83 \pm 0.9\%$) compared to the control group, and it decreased even more after 12 weeks in both groups. Accordingly, fat mass was significantly reduced by alternate day fasting (-3.49 ± 0.37 kg; $11 \pm 1.2\%$) and TRF (-2.91 ± 0.41 kg; $9.6 \pm 1.3\%$), with alternate day fasting leading to a further reduction in fat mass after 12 weeks (-3.48 ± 0.38 kg; $11 \pm 1.2\%$). Compared with the control group, also total cholesterol was significantly decreased at both time points in the alternate day fasting group (-0.91 ± 0.07 mmol/L; $18.5 \pm 1.5\%$) compared to the control and TRF groups. Conversely, both ADF (-0.64 ± 0.06 mmol/L; $25 \pm 1.9\%$) and TRF (0.58 ± 0.07 mmol/L; $20 \pm 1.7\%$) achieved a significant reduction in serum triglycerides ($P < .001$) after 12 weeks. Changes in fat free mass, HDL, LDL, fasting insulin, glucose, liver stiffness and systolic or diastolic blood pressure did not differ between the groups. Therefore, this study suggests that alternate day fasting appears to be an

effective dietary treatment for individuals with NAFLD with the aims of achieving weight loss and an amelioration of lipid metabolism but seems to have no additional direct effect in steatosis regression.[62]

In summary, even if TRF and IF undoubtedly lead to significant weight loss and metabolic improvements, data regarding its efficacy in the regression of steatosis and its severity and in the regression of fibrosis are lacking. Therefore, at present, we can assume that these diets might be of help for the NAFLD population as weight loss is strongly related to steatosis and NASH regression. However, until more evidence is available, no strong recommendation to the adherence to this type of diet can be given.

7 | CONCLUSIONS

The currently available literature demonstrates that weight loss is currently the best therapeutic approach for NAFLD. Combination of diet and exercise represent the backbone to achieve and maintain this goal. Although several dietary regimens have been tested, none is supported by solid efficacy data.

MD has been recommended as the diet of choice for NAFLD treatment due to its potential to improve hepatic fat content; however, most studies were limited in sample size, included few patients and differed in follow-up duration, inclusion/exclusion criteria and outcomes assessment.

The effectiveness of KD in NAFLD patients is still debated, although recent studies report a potential action of ketone bodies in reducing inflammation and metabolic complications involved in NAFLD pathogenesis and progression. With regard to IF and TRF, more research is needed in this field. Evidence regarding whether a reduction of steatosis grade may be achieved by means of IF or TRF is poor and inconsistent. However, these diets seem to be safe and well tolerated in the NAFLD population and could therefore represent a valid option to achieve weight loss for these patients.

In summary, all the studied diets share the efficacy on weight loss. Hence, considering that weight loss of around 5%-10% is a reliable marker of NAFLD/NASH regression and the target goal of NAFLD treatment, all these regimens might be suggested as possible dietary approaches to NAFLD. However, each diet has specific characteristics and additional metabolic effects. The MD is the only diet with consistent proven effects in NASH degree regression, besides having efficacy in lowering serum levels of LDL, triglycerides, insulin resistance. Moreover, adherence to this dietary regimen is easily maintainable in the long term thus prolonging its beneficial effects. Similar metabolic effects are achieved with the DASH and the ketogenic diets; however, these regimens are more difficult to adhere to in the long term, particularly the latter regimen is extremely restrictive, and therefore, the beneficial effects may be gradually lost. Moreover, evidence regarding the effects of these diets is heterogeneous and inconclusive. Of note, long-term data about the effects of the diets considered in this study are scarce.

Therefore, even if the MD seems to be the best dietary treatment for NAFLD as suggested by the EASL guidelines, due to the fact that weight loss is a reliable marker of disease regression and is achievable by several dietary regimens, we feel that more clinical studies are needed in order to understand if all the proposed dietary approaches are equivalent as long as they guarantee satisfactory weight loss, or if we may optimise and tailor the dietary treatment options for NAFLD. Future studies should aim to include homogeneous cohorts of patients based on metabolic comorbidities (normal BMI/overweight/obese, with or without DM, with or without hypertension, dyslipidaemia), as the presence of more metabolic comorbidities characterizes groups at higher risk of progression. Moreover, according to the presence or absence of obesity, dyslipidaemia or diabetes, the caloric amount and the dietary content of carbohydrates and fat might be optimized on a case by case basis. Finally, the diagnosis of and staging of NAFLD and NASH and their respective re-assessments after dietary interventions should ideally be made based on a histological evidence, including the assessment of fibrosis, as it is the strongest risk factor for liver-related and overall mortality in NAFLD.

CONFLICT OF INTEREST

AA: Advisory board: Gilead, Intercept, Abbvie, Sobi, Alfasigma, Speaker: Gilead, Mylan, Abbvie, Alfasigma. Research Grant: Gilead, Abbvie. SP: Speaker and/or Advisor for AbbVie, Echosens, Intercept, Gilead, Novonordisk, Pfizer. LV: advisory board for Gilead Sciences, Pfizer, Astra Zeneca, Novo Nordisk, Intercept pharmaceuticals, Diatech Pharmacogenetics, IONIS Pharmaceuticals, speaking and teaching for MSD, Gilead Sciences, AlfaSigma, AbbVie, Research grants for Gilead Sciences.

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How to cite this article: Pugliese N, Plaz Torres MC, Petta S, Valenti L, Giannini EG, Aghemo A. Is there an 'ideal' diet for patients with NAFLD? *Eur J Clin Invest*. 2022;52:e13659. https://doi.org/10.1111/eci.13659