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Review Article

Current Evidence Concerning Effects of Ketogenic Diet and Intermittent Fasting in Patients with Nonalcoholic Fatty Liver

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is emerging globally, while no therapeutic medication has been approved as an effective treatment to date, lifestyle intervention through dietary modification and physical exercise plays a critical role in NAFLD management. In terms of dietary modification, Mediterranean diet is the most studied dietary pattern and is recommended in many guidelines, however, it may not be feasible and affordable for many patients. Recently, a ketogenic diet and intermittent fasting have gained public attention and have been studied in the role of weight management. This article reviews specifically whether these trendy dietary patterns have an effect on NAFLD outcomes regarding intrahepatic fat content, fibrosis, and liver enzymes, the scientific rationales behind these particular dietary patterns, as well as the safety concerns in some certain patient groups.

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Introduction

Nonalcoholic fatty liver disease (NAFLD), recently named as metabolic-associated fatty liver disease, is a major noncommunicable disease pandemic, currently affecting approximately 25% of the global population.[1] The trend of NAFLD incidence has been increasing worldwide together with those of obesity and metabolic syndrome.[2] Although the efficacies of various pharmacologic treatments in NAFLD management have been studied, no effective medication has been proven and recommended as a standard treatment of NAFLD; lifestyle intervention remains the mainstay of management.

Generally, clinical practice guidelines of major international hepatology associations concordantly recommend weight reduction ≥7–10% in overweight or obese patients with NAFLD via hypocaloric diet,[3] in combination with more physical exercise.[4–6] Notably, successful weight reduction is associated with a reduction in liver enzyme levels and an improvement in histological findings related to liver steatosis, inflammation, and fibrosis.[4–6] However, a 7–10% weight loss is not easily achievable or sustainable even in the context of clinical trials. Moreover, one-fifth of patients with NAFLD were classified as lean and 40% were non-obese;[7] hypocaloric diet may not be the most appropriate treatment for such patients. Therefore, the effect of exposure to dietary patterns on weight reduction, and its benefit beyond weight loss, has been studied in patients with NAFLD.

The Mediterranean diet is the most evaluated dietary pattern in patients with NAFLD; most NAFLD guidelines have established its beneficial effects.[4–6] The Mediterranean diet is characterized by a high intake of vegetables, nuts, legumes, olive oil, fruits, whole grains, and fish, with a low intake of red meat, sugars, and refined carbohydrates.[8] Nonetheless, in other parts of the world, such as low-income countries and those with food insecurity, that dietary pattern may not be feasible for many people with NAFLD because energy-dense, high-fat, high-sugar, or processed foods are more palatable and affordable than the Mediterranean-style diet.[9,10]

In recent years, there has been a paramount interest in two dietary patterns, ketogenic diets and intermittent fasting (IF), and their benefits in the management of various health conditions have been evaluated. In this review, we focus on the role of the aforementioned dietary patterns on liver-related outcomes in patients with NAFLD. In the current review, we performed a comprehensive search regarding the effectiveness of a ketogenic diet or IF on NAFLD using the search terms ("ketogenic diet" OR "intermittent fasting") AND "fatty liver" in PubMed and Web of Science database from inception to October 10, 2021. As we focused exclusively on liver outcomes, only studies including patients with documented NAFLD, not only overweight/obese patients, and available outcomes of liver fat/intrahepatic triglycerides or liver fibrosis were reviewed and summarized in this article. The details of the literature search for the studies included in Tables 1 and

Keywords: Nonalcoholic fatty liver disease; Ketogenic diet, Intermittent fasting; Lifestyle modification; Weight reduction.

Abbreviations: ADF, alternate-day fasting; ALT, alanine transaminase; BHB, β-hydroxybutyrate; BMI, body mass index; IF, intermittent fasting; IL, interleukin; MED/LC, Mediterranean plus low-calorie diet; NAFLD, nonalcoholic fatty liver disease; RCT, randomized controlled trial; RF, Ramadan fasting; SoC, standard of care; TRF, time-restricted fasting; VLCKD, very low carbohydrate ketogenic diet.

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Table 1. Characteristics of individual VLCKD studies and their outcomes in patients with NAFLD

Study	Type of study	No. of patients on VLCKD/ control	Control diet	Duration	VLCKD calories (Cal/d)	Control diet calories (Cal/d)	Weight reduction outcomes (estimated)	Liver fat or liver fibrosis outcomes	Liver enzymes outcomes
Tendler 2007[11]	Single arm	5	–	6 months	Not reported	–	weight −10.9%	↓ liver fat; ↓ fibrosis (p=0.07); by liver biopsy	↔
Pérez–Guisado 2011[21]	Single arm	14	–	12 weeks	Not reported	–	BMI −4 kg/m^2	↓ liver fat by USG	improved
Yu 2014[22]	Single arm	8	–	8 weeks	800	–	BMI −2.5 kg/m^2	↓ liver fat 67%	Not reported
Bian 2014[23]	Single arm	17	–	6 days	1,000	–	weight −3 kg	↓ liver fat 27%	↔
Mardinoglu 2018[12]	Single arm	10	–	2 weeks	3,115	–	weight −1.8%	↓ liver fat 43.8%	Not reported
Ministrini 2019[24]	Single arm	52	–	25 days	800	–	BMI −2.7 kg/m^2	↓ liver fat by USG	↑ AST/ ALT
Luukkonen 2020[25]	Single arm	10	–	6 days	1,440	–	weight −3%	↓ liver fat 31%; ↔ fibrosis	Not reported
D'Abbondanza 2020[26]	Single arm	70	–	25 days	800	–	BMI −4 kg/m^2	↓ liver fat by USG	↔
Wolver 2020[13] (abstract only)	Single arm	30	–	6 months	Not reported	–	BMI −4.4 kg/m^2	↓ liver fat by CAP 15%; ↓ fibrosis by liver stiffness measurement 12.3 to 6.8 kPa	↓ ALT
Browning 2011[27]	Comparative (non−RCT)	9/9	Low calorie diet	2 weeks	1,553	1,325	weight −5 kg VLCKD/−4 kg control	↓ liver fat 31% VLCKD vs. 28% control	↔
Kirk 2009[14]	RCT	11/11	High carbohydrate content, equal calories	11 weeks	1,100	1,100	weight −7.6% vs. −7.3%	↓ liver fat 45 % VLCKD vs. 55% control	↔
Cunha 2020[28]	RCT	20/19	Low calorie diet	2 months	600−800	1,400−1,800	weight −9.7 vs. −1.67 kg	↓ liver fat 38.5% VLCKD vs. −2.7% control; ↔ fibrosis	↔
Holmer 2021[15]	RCT	25/24	Standard of care	12 weeks	−184.1 from baseline	−282.9 from baseline	weight −7.7% vs. −2.6%	↓ liver fat by CAP 61.9 vs. 20.2 dB/m; ↔ fibrosis	↓ ALT both arms
Gepner 2019[16]	RCT but on VLCKD for only 2 months then up to 70 gm/d and Med/LC	139/139	Low fat diet	18 months	−26% from baseline	−22% from baseline	Not reported	↓ liver fat 4.2% (absolute unit) in Med/LC vs. 3.8% control	Not reported

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; Med/LC, Mediterranean plus low-calorie diet, NAFLD, nonalcoholic fatty liver disease; RCT, randomized controlled trial; USG, ultrasonography; VLCKD, very low carbohydrate ketogenic diet.

Table 2. Characteristics of individual IF studies and their outcomes in patients with NAFLD

Study	Type of study	No. of patients on IF/control	IF type	Control diet	Duration	IF calories (Cal/d)	Control diet calories (Cal/d)	Weight reduction outcomes (estimated)	Liver fat or liver fibrosis outcomes	Liver enzymes outcomes
Ebrahimi 2020[17]	Observational	42/41	Ramadan	Non–fasting	1 month	1,970	2,150	BMI −0.8 vs. −0.02 kg/m^2	↓ liver fat by USG in IF group	Improved
Hodge 2014[20] (abstract only)	RCT	17/15	TRF 8:16	Standard of care	12 weeks	Not reported	Not reported	BMI −1 vs. −1 kg/m^2	↓ liver fat by CAP (IF 287 to 263 dB/m, p=0.012; control=NS); ↓ fibrosis by TE (IF 7.33 to 5.84 kPa, p=0.0088; control=NS)	Not reported
Johari 2019[19]	RCT	33/10	ADF (70% calories)	Usual habitual diet	8 weeks	Not reported	Not reported	weight ↓ 3.06 kg more than control	↓ liver fat by USG in IF group; ↓ fibrosis by SWE 0.74 kPa more than control	Improved
Cai 2019[18]	RCT	95/79	ADF (25% calories)	80% calories	12 weeks	1,327 feed/330 fast	1,309	weight −6.1% IF vs. −2.54% control	No report liver on fat; But ↓ fat mass by DXA than control; ↔ fibrosis	Not reported
Cai 2019[18]	RCT	97/79	TRF 8:16	80% calories	12 weeks	1,358	1,309	weight −4.8% IF vs. −2.54% control	No report on liver fat; but ↓ fat mass by DXA than control; ↔ fibrosis	Not reported
Holmer 2021[15]	RCT	25/24	5:2	Standard of care	12 weeks	−587.8 from baseline	−282.9 from baseline	weight −7.4% IF vs. −2.6% control	↓ liver fat by CAP 63.8 vs. 20.2 dB/m; ↓ fibrosis by TE 1.8 vs. 1.5 kPa control	↓ ALT both arms

ADF, alternate-day fasting; ALT, alanine aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; DXA, dual-energy X-ray absorptiometry; IF, intermediate fasting; Med/LC, Mediterranean plus low-calorie diet, NAFLD, nonalcoholic fatty liver disease; NS, not significant; RCT, randomized controlled trial; SWE, shear wave elastography; TE, transient elastography; TRF, time-restricted fasting; USG, ultrasonography.

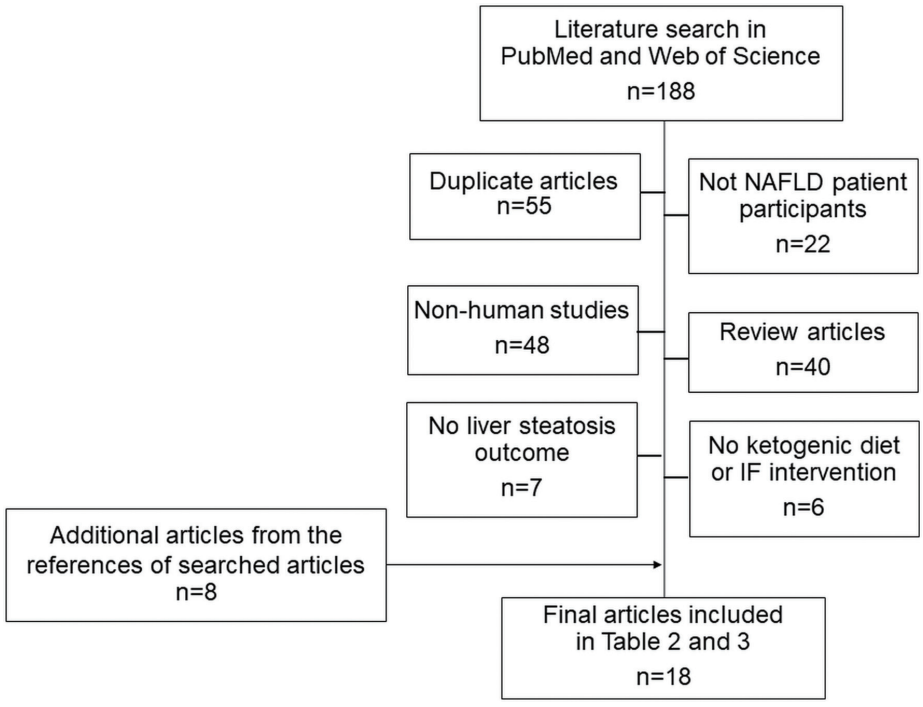

Fig. 1. Literature search for the studies included in Tables 1 and 2.

2 are shown in Figure 1.[11–28] Of the 18 studies included, two were available only in abstract form (see the Tables 1 and 2). PS performed the literature search and CB double checked the included studies. The outcomes beyond liver outcomes (e.g. cardiovascular, metabolic syndrome, and cancer including hepatocellular carcinoma) in patients with NAFLD were beyond the scope of this review and not included in this article.

Ketogenic Diet

Rationale

A ketogenic diet is one that induces ketosis. It can be a very low-calorie diet (<800 kcal/day) or very low carbohydrate diet that limits carbohydrate intake to <50 g/day and has an energy intake usually of >1,000 kcal/day).[29] Very low carbohydrate diets have gained much research interest in terms of health benefits and have become popular in lay public use and among some clinicians and nutrition scientists.[30,31] The current National Lipid Association Nutrition and Lifestyle Task Force classification of diets commonly confused with a ketogenic diet is shown in Table 3.[29] In this review, a very low carbohydrate ketogenic diet (VLCKD) is one that limits carbohydrate intake to <20–50 g/day or <10% of total energy intake, regardless of total daily energy intake.[32]

While emphasis is laid on carbohydrate intake, the types of fats and proteins that replace carbohydrates are less emphasized,[33] this usually results in a high intake of saturated fats and cholesterol, which is related to insulin resistance and cardiovascular risks.[29,34] The use of the ketogenic diet in patients with NAFLD stems from the notion that limiting carbohydrate intake results in relatively low blood glucose levels[34] leading to lower insulin levels, and thus in reduction of hepatic de novo lipogenesis.[35] Patients with NAFLD have high hepatic triglyceride levels resulting from three sources, de novo lipogenesis (mostly from glucose), lipolysis from adipose tissue, and dietary free fatty acids.[36] In healthy people, free fatty acids from adipose tissue contribute 60–80% of hepatic triglycerides, followed by dietary free fatty acids (15%), and de novo lipogenesis (5%).[36] On the other hand, the level of hepatic triglycerides generated from de novo lipogenesis is five times higher (26%) in patients with NAFLD than in healthy people (5%) because of insulin resistance in patients with NAFLD.[36] Given that *de novo* lipogenesis mostly results from the metabolism of

Table 3. National Lipid Association Nutrition and Lifestyle Task Force classification of low carbohydrate, very low carbohydrate ketogenic, and very low-calorie diets[29]

Nomenclature	Ketogenic	Total calories per day	% Macronutrients in total calories per day		
			CHO	Protein	Fat
VLCHF/KD	Yes	>1,000	<10 (<20–50 g/day)	Around 10 (1.2–1.5 g/kg/day)	70–80
Low CHO	No	>1,000	10–25 (38–97 g/day)	10–30	25–45
Very low-calorie diet	Yes/No varies	<800	Varies	Varies	Varies
Classic KD	Yes	Varies	3	7	90

CHO, carbohydrate; KD, ketogenic diet; VLCHF, very low CHO.

circulating glucose, this physiological perspective could explain the promising role of ketogenic diet exposure in NAFLD management.

Nutritional ketosis, ketone bodies, generated in response to carbohydrate restriction could further facilitate weight loss by promoting satiety leading to reduction of total energy intake.[37] In addition, growing evidence has shown beneficial effects of ketone bodies in the inhibition of obesity-induced inflammation and oxidative stress and might play a role in modulating NAFLD pathophysiology. In particular, Youm *et al*.[38] reported that β-hydroxybutyrate (BHB) reduced NLRP3 inflammasome-mediated interleukin (IL)-1β and IL18 production in human monocytes together with an attenuation of IL1β secretion a in mouse model, a key inflammatory cytokine related to obesity and insulin resistance. Activation of NLRP3 inflammasome also had a central role in liver inflammation and fibrosis in a mouse model.[39] BHB is a ligand for hydroxycarboxylic acid receptor-2 (HCA_2), which is highly expressed in immune cells such as macrophages and monocytes, and has been shown to have anti-inflammatory properties in atherosclerosis, obesity, and cancer.[40] BHB is an epigenetic modifier by inhibiting histone deacetylase, resulting in histone acetylation, and expression of oxidative stress resistance gene.[41]

Evidence of ketogenic diet exposure effects on NAFLD outcomes

The study that initially reported beneficial effects of VLCKD was published in 2007.[11] Tendler *et al*.[11] placed five patients with biopsy-proven NAFLD on a restricted diet of <20 g/day of carbohydrates for 6 months without total calorie restriction. At the end of the study period, the patients had an average weight reduction of 10.9%. On follow-up liver biopsy, a significant reduction in the degree of hepatic steatosis was observed, with a trend towards improvement in liver fibrosis (p=0.07). Table 1 summarizes the studies of VLCKD and effects on the outcomes of patients with NAFLD. The majority of studies on VLCKD had a single arm with a limited number of patients and involved caloric restriction below 1,200 kcal/day, resulting in significant weight loss and hepatic steatosis improvement. It is difficult to determine whether the reduction in hepatic fat content was caused by the VLCKD pattern or weight loss in general. Nonetheless, Mardinoglu *et al*.[12] conducted a single arm interventional study in which 10 Nordic patients with NAFLD were instructed to consume <30 g/day of carbohydrates, without total energy restriction. The average energy intake was 3,115 kcal/day). They observed a significant reduction in hepatic fat content of 43.8% despite a minimal weight loss of 1.8%. Another recent report from Wolver *et al*.[13] demonstrated interesting outcomes of VLCKD for 6-months. with significant improvement of both liver steatosis and liver fibrosis. However, this was a preliminary result of the study and presented in a conference abstract only, and no data regarding total calories per day were mentioned. The final results of that study are eagerly awaited.

A randomized controlled trial (RCT) by Kirk *et al*.,[14] observed a similar degree of weight loss in patients in VLCKD and low-calorie control diet. The intrahepatic triglyceride content decreased significantly from baseline but was not different in the two groups at the end of the study. More recently, Holmer *et al*.[15] conducted an RCT in patients with NAFLD who received a standard of care (SoC) or VLCKD for 12 weeks. Patients in the VLCKD arm experienced a significantly greater weight loss and intrahepatic fat content reduction, despite a smaller reduction in daily total energy intake. However, the benefit in terms of liver fibrosis was not demonstrated.

Previously, the largest RCT with a long-term follow-up duration was conducted by Gepner *et al*.[16] in 278 patients, with 139 on a VLCKD with 40 g/day of carbohydrates for 2 months and was gradually increased to 70 g/day for a total of 18 months with a Mediterranean-style diet (Med/LC). The control group included 139 patients on a low-fat diet for the 18 month period. The reduction in liver fat content was significantly greater in the Med/LC group than in the low-fat diet group. Unfortunately, liver fibrosis, the important surrogate marker of long-term outcomes in patients with NAFLD, was not reported. In addition, VLCKD exposure lasted only for the first 2 months of the total study period; hence, it was impossible to conclude whether the greater reduction in hepatic fat content was caused by the VLCKD or resulted from the beneficial effect of the Mediterranean-style diet.

Overall, based on the current evidence of VLCKD effects in patients with NAFLD, a significant reduction in intrahepatic fat content was observed in patients exposed to VLCKD. However, it is important to keep in mind that most data came from a combination of VLCKD with calorie restriction (hypocaloric diet). And the control arms in comparative studies, when the diets were hypo-energetic, the intrahepatic fat content was reduced as well. Without hypocaloric diet, the beneficial effect of VLCKD is yet to be defined. Furthermore, based on available data on isocaloric diet effects compared between patients exposed to low-fat, high-carbohydrate diets and in those exposed to high-fat, low-carbohydrate (above the VLCKD level) diets, intrahepatic fat content tended to be lower in patients exposed to low-fat diets than in those exposed to low-carbohydrate diets.[42]

Safety concerns

Ketogenic diets require an extreme avoidance of carbohydrate foods to generate nutritional ketosis. Carbohydrates are a good source of vitamins, minerals, and bioactive compounds such as polyphenols, and thus long-term exposure to a ketogenic diet can result in micronutrient inadequacy or deficiency if the diet is not appropriately guided. Reduction in thiamine, folate, calcium, magnesium, iron, iodine, and fiber intake have been reported after ketogenic or low-carbohydrate diets.[43] Moreover, case reports have highlighted occurrences of Wernicke's encephalopathy, cardiac beriberi, and optic neuropathy in patients with low carbohydrate intake.[44,45]

As mentioned earlier, there is less emphasis on types of fat and protein consumed, which could contribute to different metabolic responses. The ketogenic diet is usually high in saturated fats, which increases LDL cholesterol levels and insulin resistance,[46,47] thereby potentially augmenting the risk of atherosclerotic cardiovascular diseases.[48,49] A longitudinal cohort study also showed that a high intake of animal fat and protein, in place of carbohydrates, is associated with high risk of mortality and type 2 diabetes.[50–52] Several recent case reports have highlighted the occurrence of ketoacidosis in people following ketogenic diets,[53–56] lactating women,[57,58] and patients with type 2 diabetes using SGLT-2 inhibitors reportedly have a higher risk of ketoacidosis.[59] Exacerbating panic and anxiety disorders in a woman on a ketogenic diet has been reported, probably resulting from diet-induced reductions brain serotonin and plasma tryptophan.[60]

Apart from possible adverse events of VLCKD in general, some had been reported in the studies of patients with NAFLD. Most of the studies did not report the adverse effects following VLCKD, however, muscle cramping had been reported in one patient in a study by Tendler *et al.*,[11] in

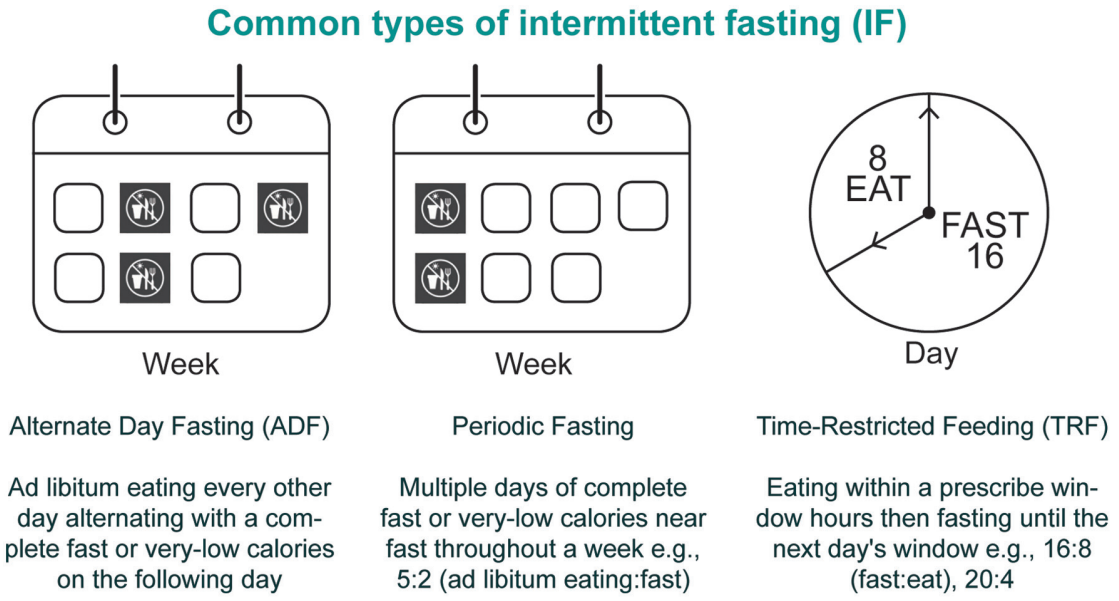

Fig. 2. Common types of intermittent fasting (IF).

and six of 25 patients in Holmer *et al*.[15] experienced either dyspepsia, nausea, headache, or vertigo, and felt that the diet was difficult to implement, which led to diet discontinuation in five patients. In addition, a case series reported that two cirrhotic patients tolerated VLCKD well for weight reduction for 28–30 weeks before liver transplantation without significant adverse effects.[61] Nonetheless, elevation of total bilirubin was observed at the end of the VLCKD period in both patients, and elevations in serum alanine transaminase (ALT) and creatinine were observed in one patient. In our opinion, more data are needed to confirm the safety of VLCKD in patients with cirrhosis.

IF

Rationale

IF refers to a period of voluntary abstinence from food and/or drink for caloric restriction, or no caloric intake over a specified period of time.[62] There are three types of IF, alternate-day fasting (ADF), periodic fasting, and time-restricted fasting (TRF).[63] The most well-known periodic fasting schedule is 5:2, which means having a regular diet for 5 days a week and fasting or near fasting for 2 days a week. The most well-known TRF schedule is 16:8, which means fasting for 16 h and eating for 8 h a day (Fig. 2). IF has gained attention as an effective strategy for weight loss in people with NAFLD, given that weight loss is the mainstay of NAFLD management for fat content and fibrosis extent reduction.[63] Generally, people following IF have approximately 10% or 300 kcal less energy intake than people taking normal diets or in non-fasting periods (Table 2). In addition, several health benefits of IF have been reported, including improvements in insulin resistance, inflammation, blood pressure, and blood cholesterol levels.[64] Extensive studies in rodents and non-human primates have demonstrated that the molecular mechanisms whereby dietary restriction promotes health and longevity primarily involve inhibition of mammalian target of rapamycin signaling, insulin/insulin-like growth factor signaling, growth hormone signaling, and autophagy pathways.[64]

Evidence of IF effects on NAFLD outcomes

In contrast to VLCKD, IF or a time-restricted diet effects just have been recently studied in patients with NAFLD. Figure 2 depicts the common types of IF,[63,65] and Table 2 summarizes studies of the effect of IF on NAFLD outcomes. Ramadan is a holy month for Muslims and fasting is one of Islam's Five Pillars. Healthy adults are expected to practice Ramadan fasting (RF). Muslims who observe RF refrain from eating or drinking from dawn to sunset every day for 1 month.[17] Several studies have evaluated the effects of RF in NAFLD patients.[17,66–68] However, there was only one observational study evaluated the effects of RF on liver fat outcomes.[17] The study included 83 patients in Iran and demonstrated that those who fasted during Ramadan had greater weight loss and improvement in hepatic steatosis grade on ultrasound than those who did not fast. Improvements in liver enzymes and cholesterol levels were also observed in the RF group. Moreover, daily caloric intake appeared to be lower in patients who fasted.

Four RCTs investigating the effect of IF on the outcomes of patients with NAFLD who underwent different methods of fasting have been published. One was an abstract and three were published manuscripts. Two of the RCTs had conflicting results of the impact of ADF on patient outcomes. Cai *et al*.[18] randomly assigned patients to an ADF with a 25% caloric intake on fasting days or a control group for 12 weeks. Patients in ADF group had a lower daily energy intake, end-of-study weight, and total body fat mass. Nevertheless, the degree of liver fibrosis measured by transient elastography, was not improved and was comparable to that in the control group. Johari *et al*.,[19] whose study was published in the same year, reported greater weight loss, greater reduction in hepatic steatosis grade, and improved liver fibrosis measured by shear wave elastography in patients with modified ADF with 70% caloric intake during fasting days, compared with patients who consumed their usual diet for a duration of 8 weeks. Cai *et al*.[18] compared the outcomes of TRF using the 8:16 h method with SoC outcomes. Intriguingly, the TRF group had a greater weight loss than the SoC group even though the daily caloric intake appeared to be a little higher in the TRF group. The study showed no change in the extent of liver fibrosis, but the patients had a high degree

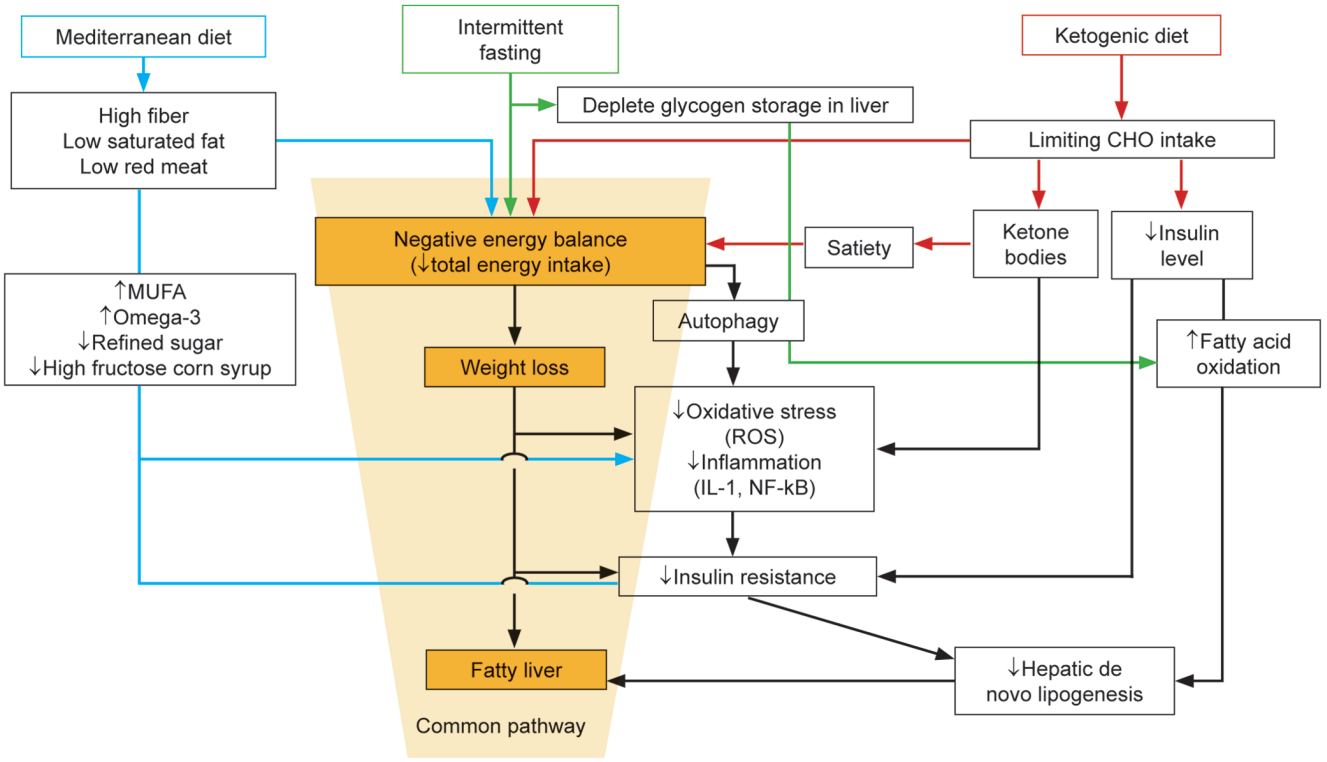

Fig. 3. Proposed mechanistic pathways of Mediterranean diet, ketogenic diet and intermittent fasting for NAFLD. NAFLD, nonalcoholic fatty liver disease.

of fibrosis, with a mean liver stiffness >18 kPa, which is comparable to stage 4 fibrosis or cirrhosis, in both groups. Hodge *et al*.[20] conducted an RCT using TRF as IF. Patients in IF arm had a significant reduction in both liver steatosis and liver fibrosis measured by liver stiffness. The same results were not observed in patients in the control group despite similar degrees of body mass index (BMI) reduction.[20] A recent RCT by Holmer *et al*.[15] evaluated and compared the effects of IF and SoC on patient outcome. The IF group used the 5:2 dietary approach with a caloric restriction of 500 cal/day in women and 600 kcal/day in men for two non-consecutive days per week. Patients in the IF group had a greater reduction in daily caloric intake, lost more weight, and had a greater reduction in hepatic steatosis than those in the SoC group. Moreover, an improvement in hepatic fibrosis measured by transient elastography was observed in both groups. Notably, liver stiffness improvement was numerically higher in the IF than in the SoC group (1.8 vs. 1.5 kPa). In spite of the better liver-related outcomes reported in both observational RF studies and RCTs compared with controls, it is unclear whether the improved outcomes resulted from IF or weight loss. Notwithstanding, IF may be a viable alternative for patients who are unable to maintain weight control by daily caloric restriction.

Safety concerns

IF is simple and relatively safe for most people, with fewer safety concerns compared with a ketogenic diet. Possible concerns related to IF include hypoglycemia in patients with diabetes receiving insulin therapy or insulinogenic drugs and hypotension in patients taking antihypertensive medications. In addition, in patients with liver cirrhosis undergoing IF, overnight fasting can mimic 72 h starvation, resulting in malnutrition and increased complications. IF can also aggravate starvation effects, thereby causing negative outcomes. In the clinical trials of IF in patients with NAFLD, most studies reported that no significant adverse events were observed. Holmer *et al*.[15] reported only one hypoglycemic and one presyncope episode in a patient participated in the study.

There is also a concern that IF could trigger binge eating, i.e. overeating after food is made available, as IF requires a shift in regular mealtimes. Although one study showed no relationship between IF and pathologic eating patterns in people with no history of eating disorders,[65] two studies in individuals with eating disorders showed an increase in food intake following 6 h and 14 h fasts.[69,70] A longitudinal study also reported that self-reported fasting was a predictor of eating pathologies and recurrent binge eating.[71]

Comparisons of Mediterranean Diet, Ketogenic Diet, and IF on Liver Outcomes in Patients with NAFLD

Although there was no head-to-head comparison evaluate liver fat and liver fibrosis outcomes of the three dietary patterns, there are some overlaps on proposed mechanistic pathways in the Mediterranean diet, VLKCD, and IF (Fig. 3). Briefly, all dietary patterns are associated with lower total energy intake and negative energy balance that leads to weight loss. Apart from negative energy balance, the Mediterranean diet is characterized by low saturated fat and refined sugar and high omega-3 and mono-unsaturated fatty acid intake, which has a theoretical benefit on reduction of oxidative stress and improvement of insulin resistance.[72] VLKCDs limit carbohydrate intake that results in persistently low insulin level, and fatty acid oxidation is promoted, which leads to a reduction of *de novo* hepatic lipogenesis.[34,35]

Table 4. Key findings and concepts of Mediterranean diet, ketogenic diet, and IF on liver outcomes in patients with NAFLD

Dietary patterns	Mediterranean diet	Ketogenic diet	Intermittent fasting
Characteristics	High intake of plant-based food and fish, olive oil, limited consumption of refined sugar and processed food, red meat, moderate consumption of yogurt and wine[63]	Limits carbohydrate intake to <20–50 g/day or <10% of total energy intake, regardless of total daily energy	Voluntary abstinence from foods and/or drinks for caloric restriction in a specific period, or no caloric intake over a specified period of time
Concept	Healthy dietary pattern, low in saturated fat, high in polyunsaturated fat. High fiber and low refined sugar	Limiting carbohydrate intake results in relatively low blood glucose levels and thus reduces hepatic de novo lipogenesis	Less energy intake than people taking usual diets. And possible reduce insulin resistance, inflammation, and enhance autophagy
Fatty liver outcomes	Significant reduction in liver fat compared with their respective control groups in the literature. Improvement in liver fibrosis measured by liver stiffness had been observed	Significant reduction in liver fat compared with their respective control groups in the literature. Inconclusive results on liver fibrosis improvement	Significant reduction in liver fat compared with their respective control groups in the literature. Improvement in liver fibrosis measured by liver stiffness had been observed
Follow-up time in the literature	Longitudinal data available up to 18 months	Most are short term data no longer than 3 months except Tendler *et al*.[11] and Wolver *et al*.[13]	To date, all are short term data no longer than 3 months
Concerns	Availability. Palatability. Affordability	Risk of micronutrients deficiency. Might induced ketoacidosis. Might experience an adverse event of gastrointestinal disturbance. Patients might shift to consume high saturated fat and long-term cardiovascular risk is uncertain	Might not be suitable in patients with cirrhosis. Hypoglycemia in patients with diabetes should be aware

Lastly, for IF, prolonged fasting of more than 12 h also leads to hepatic glycogen depletion and augmented hepatic lipolysis, that would reduce hepatic steatosis.[72]

The key concepts and evidence of the effects of dietary pattern on liver outcomes in patients with NAFLD are summarized in Table 4.[11,13,63] The Mediterranean diet is associated with the lowest possible adverse effects and long-term liver-related benefits.[16,73–75] Ketogenic diets and IF also have scientific rationales and clinical results of improving liver outcomes in patients with NAFLD, but some concerns and long-term results are uncertain.

Summary

In the light of an increasing global burden of NAFLD, lifestyle intervention is the mainstay of NAFLD management, as effective therapeutic medications have not been established. Although the Mediterranean diet is recommended by many guidelines, it is not easily accessible for many patients. Ketogenic diets and IF have recently become dietary patterns of general interest. The pros and the cons of both dietary patterns are summarized in Table 4. With some plausible mechanisms underlying a reduction in intrahepatic fat content, it remains inconclusive whether the abovementioned outcomes resulted from the dietary pattern itself or from a hypocaloric intake after exposure to the dietary pattern. In our opinion, ketogenic diets and IF appear acceptable in patients without significant comorbidities. Both ketogenic diets and IF should not be routinely recommended in all patients with NAFLD, but can be considered as alternative therapeutic options in patients who do not achieve targeted weight loss by conventional lifestyle intervention recommendations. They may have some additional benefits in patients who can tolerate and adhere to the dietary patterns, such as reduction in liver fat, and to a lesser extent, reduction in liver fibrosis. Nonetheless, there are concerns of possible adverse events following exposure to the dietary patterns, which should be considered.

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Conflict of interest

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Author contributions

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