sciendo Acta Marisiensis - Seria Medica 2023;69(1):3-10 DOI: 10.2478/amma-2023-0001

REVIEW

Intermittent fasting for the management of NAFLD: Is there enough evidence?

Simona Cernea[1,2*], Florina Ruța[3]

1. Department M3, Internal Medicine I, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania
2. Diabetes, Nutrition and Metabolic Diseases Outpatient Unit, Emergency County Clinical Hospital, Târgu Mureș, Romania
3. Department of Community Nutrition and Food Safety, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania

The pathogenesis of the non-alcoholic fatty liver disease (NAFLD) has been described as multifactorial, with genetic and environmental factors acting synergistically and causing excessive hepatic lipid accumulation, insulin resistance, and downstream pathogenetic insults. High-calorie diets, particularly those rich in foods with high (saturated) fat and sugar content, and sugar-sweetened beverages, are among the behavioral risk factors with a crucial role in the disease pathogenesis. In addition, meal frequency and meal timing appear to be relevant factors associated with NAFLD. Current guidelines recommend a hypocaloric, preferably Mediterranean diet as the main dietary intervention approach, but various other dietary models have been evaluated in patients with NAFLD. Among these, several intermittent fasting regimens have shown promising results. Diets based on Time-Restricted Feeding and Intermittent Energy Restriction have demonstrated some improvements in body adiposity, liver enzymes, and hepatic steatosis, but most studies included a small number of subjects, were of relatively short-duration, and used surrogate markers of NAFLD. The best intermittent fasting regimen for NAFLD is not yet known, and further well-designed research that evaluates the feasibility (mainly on long-term), safety and efficacy outcomes of these dietary interventions is still needed. Our review has evaluated the up-to-date information regarding the intermittent fasting dietary intervention in NAFLD and generated some key-point messages that are relevant to physicians and dietitians involved in the care of patients with NAFLD.

Keywords: NAFLD, dietary intervention, intermittent fasting, time-restricted feeding

Received 7 December 2022 / Accepted 26 December 2022

Introduction

The non-alcoholic fatty liver disease (NAFLD) has emerged as a major cause of chronic liver disease, affecting about a quarter of the adult general population worldwide [1, 2]. Moreover, the global prevalence of NAFLD is double in patients with type 2 diabetes mellitus (T2DM) [3].

NAFLD is characterized by an excessive accretion of lipids in the liver (hepatic steatosis) affecting >5% of hepatocytes, in the absence of other secondary causes (including viral hepatitis, or alcohol intake exceeding 20 g/day for women and 30 g/day for men) [4]. The hepatic lipid accumulation is associated with insulin resistance, which is in fact a key pathogenetic mechanism in NAFLD, and with components of the metabolic syndrome (obesity, T2DM, dyslipidemia) [5]. NAFLD in fact comprises several conditions: simple steatosis (nonalcoholic fatty liver (NAFL)), nonalcoholic steatohepatitis (NASH) (without or with various grades of fibrosis, including hepatic cirrhosis), and hepatocellular carcinoma (HCC) [4, 6].

The role of diet in the pathogenesis of NAFLD

The pathogenesis of NAFLD is multifactorial, and a number of genetic/epigenetic, demographic, and environmental/lifestyle risk factors have been identified. The complex interaction between these factors is responsible for the initiation and development of the pathogenetic mechanisms of the disease. According to the "multiple-hit" theory, genetic and environmental factors act synergically and lead to excessive and dysfunctional adiposity, lipid accumulation in the liver and lipotoxicity, insulin resistance, further causing inflammation, oxidative stress, hepatocellular apoptosis and fibrosis [7, 8].

Among the lifestyle risk factors, diet/diet composition has a crutial role in NAFLD pathogenesis [9]. The excessive caloric intake appears to be a distinctive dietary feature in patients with NAFLD and experimental overfeeding studies demonstrated that hypercaloric diets promoted hepatic fat accumulation [10, 11].

Although it is more difficult to distinguish the effect of a specific macronutrient/dietary component on modulating the risk of liver steatosis, overall data seem to indicate that the intake of foods rich in fats (mainly saturated fats), sugar (mainly fructose, but also glucose) and sugar-sweetened beverages favors lipid accumulation in the liver, insulin resistance, and increases the likelihood of NAFLD [10-14]. Apparently, the negative effect of fructose on the intrahepatocellular lipids and transaminases is mainly seen in the context of hypercaloric diets [15]. Dietary carbohydrates stimulate de novo lipogenesis, increase the free fatty acid pool in the liver, and may also have pro-inflammatory effects [10, 15, 16]. The intervention studies also support the findings from the observational studies, showing greater reduction of hepatic steatosis with low-carb/sugar diets and with low-fat diets [17-23]. A meta-analysis of 11 studies showed no significant differences between low-carbohydrate diet and low-fat diet on the hepatic fat content and transaminases levels in subjects with NAFLD

* Correspondence to: Simona Cernea
E-mail: simonacernea@yahoo.com

[24]. However, the type of dietary fats is relevant since the saturated fats increase hepatic liver accumulation and insulin resistance more than polyunsaturated fats [25-29]. Studies have shown that the monounsaturated fat-enriched diets and the Mediterranean diet (based on olive oil consumption as a main source of fat, which is rich in monounsaturated fats) are associated with lower intrahepatic triglyceride content [30-32]. Moreover, diets rich in insoluble fibers and fruit fiber consumption in the context of energy restriction improve liver health (decrease liver steatosis and transaminases) [33]. The protective effects of dietary fibers might be due to direct anti-inflammatory effects and/or indirect ones (through modulation of the gut microbiome) [11]. Data on dietary protein is less consistent. There is some evidence that red meat/animal protein intake is also associated with liver steatosis, but the intervention studies showed that high protein diets reduced liver fat [34-39].

In addition to diet composition, meal frequency and meal timing appear to be other significant factors associated with hepatic steatosis/NAFLD. A randomized controlled trial (RCT) in patients with NAFLD has demonstrated that in the context of a hypercaloric diet, higher meal frequency, but not meal size, was associated with increased intrahepatic triglyceride content (mean relative increase of 45%, p=0.016), suggesting that snacking is an independent contributor to hepatic steatosis [40]. The same was shown by a Japanese community-based cross-sectional study indicating that snacking ≥2 times/day significantly increased the prevalence rate of NAFLD both in men and women (41.1% in men, and 15.3% in women) [41]. Interestingly, an Australian study has shown that a "grazing" temporal eating pattern (defined as a more frequent ingestion of minimum 50 kcal, lower probability of eating at conventional meal times, also associated with later timing of first food ingestion) was associated with a poorer diet quality and higher overall and visceral adiposity in women (OR: 1.57 [95%CI: 1.15, 2.13], and 1.73 [95%CI: 1.19, 2.50], respectively) [42]. In contrast, a preliminary report that analyzed the third National Health and Nutrition Examination Survey (NHANES III) data indicated that rather more meals per day decreased the odds of severe liver steatosis, but skipping breakfast and lunch had an opposite effect (increased the odds of liver steatosis) [43]. Thus, although evidence is still weak, it appears that circadian misalignments favor visceral adiposity and hepatic steatosis/NAFLD. Indeed, the circadian clock plays an important role in regulating major metabolism pathways and other physiologic functions in the liver, which show diurnal variations [44]. Thus, circadian disruption by improper meal timing may cause major disturbances leading to insulin resistance, increased levels of free fatty acids and triglycerides, eventually leading to NAFLD [44, 45].

The role of dietary intake is further substantiated by the fact that caloric restriction and weight loss through dietary interventions and physical exercise are the mainstay of intervention in NAFLD, recommended by current guidelines [4, 6, 46]. This is associated with amelioration of insulin resistance. A histologic reference study has demonstrated that weight loss through lifestyle intervention (low-fat hypocaloric diet and physical activity) in patients with NASH resulted in liver benefits (steatosis reduction, NASH resolution, and fibrosis regression), in direct relationship with the degree of weight loss (OR: 1.1-2.0, p<0.01) [47]. The NASH-related histologic improvements were seen with a minimum 5% weight loss, and patients that obtained ≥10% weight loss also presented regression of hepatic fibrosis [47]. Thus, the current guidelines generally recommend a hypocaloric diet for the management of NAFLD [6, 46]. The Mediterranean diet is a preferred dietary pattern in patients with NAFLD, as it is associated with improvement of liver steatosis and insulin resistance [48, 49]. However, other dietary interventions (DASH diet, low-carb diet, low-fat diet, ketogenic diet, etc.) have been investigated and seem to bring liver-specific benefits, but choosing the best dietary intervention for each NAFLD patients is still a challenging task [50]. Nutritional interventions based on time-restricted feeding/intermittent fasting are novel and potentially promising approaches for NAFLD, that deserve attention.

Intermittent fasting – regimens and mechanisms of health benefits

Fasting (i.e. restricted food intake) is an ancient practice based on cultural and religious beliefs, and has also been used for healing purposes in the past [51]. Religious fasting is practiced in Christianity, Judaism, Islam, and other religions, but it varies by dietary pattern (food selection) and fasting duration, and has been shown to bring cardiometabolic benefits (decrease in body weight, blood lipids, insulin resistance, etc.) [52].

Intermittent fasting (also known as periodic energy restriction) refers to dietary intervention strategies that restrict food intake to certain periods of time (within a day or a week) [53, 54]. The periods of fasting/energy restriction are usually followed by periods when food is used ad libitum [55]. There are several regimens of intermittent fasting, which can be broadly categorized into two major groups (table I):

- Time-Restricted Feeding (TRF), which implies a restriction of feeding during certain daily time windows, and
- Intermittent Energy Restriction (IER), which implies short periods of energy restriction alternating with normal eating/diet; this category comprises several regimens; a special form of IER is the alternate-day fasting (ADF), and its modified form; the energy restriction during the fasting time varies between 75% and 100% [56].

In addition to the main intermittent fasting regimens mentioned in table I, there are several other modified forms, including the combination of intermittent fasting

Table I. Characteristics of the intermittent fasting regimens [51-57].

	Fasting period	Eating period
Time-Restricted Feeding (TRF)		
TRF (16:8; 15:9, etc)	≥14 h; no energy intake is allowed;	usually ≤10 h; early TRF regimen is preferred (eating between 8:00 am and 2:00 pm or up to 5:00 pm, depending on the regimen); ad libitum feeding;
B2 regimen	14-16 h; no energy intake is allowed;	2 main meals per day: breakfast (06:00-10:00 a.m.) and lunch (12:00-04:00 p.m.); no dinner; ad libitum feeding;
Ramadan (during the Islamic holy month)	dawn to sunset; no energy intake (including drinking) is allowed;	sunset to dawn; ad libitum feeding;
Intermittent Energy Restriction (IER)		
Alternate-day fasting	every other day (24 h); no energy intake is allowed;	alternate day to fasting day; ad libitum feeding;
Alternate day-modified fasting	20 h, every other day; up to 25% of daily energy intake (mid-day meal);	alternate day to fasting day; ad libitum feeding;
5:2 (twice weekly fasting)	2 days (24 h) a week (usually non-consecutive); up to 25% of daily energy intake or ~500 kcal/day;	5 days a week; ad libitum feeding;
Modified periodic fasting	5 consecutive days; a very-low-caloric diet (up to 25% of daily energy intake);	at least 10 days following the fasting period; ad libitum feeding;

and caloric restriction (i.e. one day of fasting and six days of caloric restriction) [58].

Intermittent fasting has proven to bring cardiovascular benefits (reductions in systolic and diastolic blood pressure, body weight, and ectopic fat depositions, improvements in blood lipids, insulin sensitivity and inflammatory markers) [53, 57]. However, there is no clear superiority of the intermittent fasting regimens compared to the continuous caloric restrictions, suggesting that in fact the reduction of energy intake (energy deficit) might be the main reason for the observed health benefits, although some data also support the weight-loss independent effects of intermittent fasting on cardiometabolic parameters [57].

There are several proposed mechanisms for the effects of intermittent fasting on health. During fasting, a switch in substrate utilization occurs (from carbohydrate to fat, and ketone body production and oxidation) [59]. Glucose is the main energy fuel for most cells, and during fasting, insulin levels drops, and glucose is released through glycogen breakdown from liver depots [55]. In addition, there is a breakdown of triglycerides and free fatty acids release from the adipose tissue, which undergo β-oxidation in the liver [55]. In prolonged fasting periods, free fatty acids are metabolized into ketone bodies, which are an alternative energy substrate for extrahepatic tissues (i.e. brain and heart) [55]. Therefore, during (intermittent) fasting a ketogenic state is induced, as evidenced by the elevation of blood ketone levels [60, 61]. Thus, a switch from fat storage to utilization occurs, promoting weight loss (intermittent metabolic switching/"keto-adaptation") [53, 55]. Ketone bodies also promote the activation of the cellular stress responses under fasting conditions, which result in removal of damaged organelles and proteins, improve mitochondrial function, and promote cellular repair mechanisms [51, 52, 55]. The nutritional ketosis induced by the intermittent fasting regimens determines the keto-adaptation which is linked to many health benefits [55].

A second hypothesis (proposed mechanisms) is reduction of the oxidative stress, induced by a decrease of energy intake and free radicals production, and possibly by activation of redox-sensitive transcription factors (shift of redox status) [63].

Thirdly, intermittent fasting might directly influence the gut microbiota composition, which is also involved in metabolic signaling and bile acid metabolism [56, 64, 65].

Finally, the circadian rhythm theory might well explain the beneficial effects associated with some intermittent fasting regimens (mainly TRF) [53]. When properly timed, it allows the resynchronization between the body's circadian rhythm and the time of fasting-feeding [53, 66]. The circadian rhythm allows the expression of clock-controlled genes that regulate many molecules involved in metabolic functions, and there is evidence supporting a strong relationship between circadian clock and metabolism [65]. In fact, circadian rhythm disruption (i.e. in case of shift workers, jet leg, etc.) is associated with various metabolic diseases (obesity, impaired glucose tolerance/diabetes, etc.) [67-70]. Animal data indicate that intermittent fasting (TRF regimens) can restore the oscillation of metabolic regulators (such as AMPK, mTOR, CREB, etc) and their target gene expression [67, 71]. Moreover, the feeding/fasting rhythms and diet may modulate the cyclic fluctuations of the gut microbiome, which influence the secondary metabolite production, involved in the maintenance of the peripheral circadian rhythm [72].

Nevertheless, the exact mechanisms through which the various intermittent fasting regimens are associated with health benefits are not fully deciphered, and probably many factors (i.e. diet composition, time of fasting, duration of interventions) influence the results.

Intermittent fasting for the management of NAFLD

NAFLD is a complex disease associated with a variety of metabolic disturbances, and dietary intervention and weight loss are at the core of its management. As mentioned, various dietary interventions have been evaluated in patients with NAFLD, some (i.e., the Mediterranean

diet) proving clear benefits [73]. Recently, various intermittent fasting regimens have been evaluated with regards to liver-related outcomes in NAFLD.

We review here the up-to-date main findings from the clinical studies in patients with NAFLD (table II). We have search PubMed without language restrictions since database inception to December 2022 using the terms: "NAFLD" or "non-alcoholic fatty liver disease" and "intermittent fasting" and subsequently, "time-restricted feeding" or "Ramadan fasting" or "alternate-day fasting" or "in-

Table II. The effects of different intermittent fasting regimens on anthropometric and liver-related outcomes in patients with NAFLD

Reference/ study type	Dietary intervention	Patients	Main findings
Time-Restricted Feeding (TRF)			
Kord-Varkaneh H. et al[76]/RCT	TRF (16 h fasting/8 h feeding) plus low-sugar diet vs control, for 12 weeks	45 NAFLD patients (22 intervention, 23 control)	In intervention group after versus baseline: Body weight ↓(83.75 to 80.54 kg; p<0.001) BMI ↓(29.13 to 28.02 kg/m^2; p<0.0001) Body fat ↓(26.69 to 24.22 kg; p=0.001) Waist ↓(104.59 to 101.91; p=0.042) Change in intervention group versus control group: ALT ↓(34.04 to 21.22 U/l) vs ↓(30.34 to 28.04 U/l); p=0.003 AST ↓ (26.31 to 20.5o U/l) vs (23.68 to 23.77 U/l); p=0.031 TG ↓(201.50 to 133.27 mg/dl) vs ↑(187.6 to 199.56 mg/dl); p<0.001 TC ↓(190.04 to 157.8 mg/dl) vs ↑(172.21 to 180.72 mg/dl); p<0.001 LDLc ↓(104.63 to 84.04 mg/dl) vs ↑(93.73 to 97.45 mg/dl); p=0.017 CK-18 ↓(1.35 to 1.16 ng/ml) vs ↑(1.32 to 1.85 ng/ml); p<0.001 Fibrosis score ↓(6.33 to 5.15 kPa) vs ↓(5.82 to 5.46 kPa); p=0.024 CAP ↓(322.90 to 270.90 dB/m) vs (311.52 to 306.00 dB/m); p<0.001
Hodge A. et al[77] (abstract only)/randomized pilot study	TRF (16 h fasting from 8 pm to 12 pm next day /8 h feeding) vs standard of care (SoC), for 12 weeks	28 NAFLD patients (17 TRF, 15 SoC)	Weight ↓(81.9 to 79.8 kg; p=0.0024) (TRF) and ↓(82.3 to 81 kg; p=0.0066) (SoC) BMI ↓(29 to 28 kg/m^2; p=0.002) (TRF) and ↓(30 to 29 kg/m^2; p=0.006) (SoC) Total body fat mass ↓(29 to 28 kg; p=0.0001) (TRF) and ↓(31 to 29 kg; p=0.0031) (SoC) Liver stiffness (Fibroscan®) ↓(7.33 to 5.84 kPa; p=0.0088) (TRF) and (6.32 to 6.09 kPa; p=0.7305) (SoC) CAP ↓(287 to 263 dB/m; p=0.012) (TRF) and (268 to 268 dB/m; p=0.981) (SoC)
Badran H. et al[78] /interventional multicenter study	Ramadan fasting (16 hours), for 22-29 days	98 NAFLD patients (diagnosed based on US)	Before vs after fasting: Weight ↓(97.44 to 96.69 kg; p≤0.01) BMI ↓(37.03 to 36.74 kg/m^2; p≤0.01) HbA1c ↓(6.1 to 5.9%; p≤0.01) HOMA-IR ↓(2.13 to 1.96; p≤0.01) TC ↓(241.1 to 218.48 mg/dl; p≤0.01) TG ↓(171.01 to 157.49 md/dl; p≤0.01) HDLc ↑(45.3 to 48.5 md/dl; p≤0.01) ALT ↓(36.5 to 32.7 U/l; p≤0.01) AST ↓(38.5 to 32.8 U/l; p≤0.01) GGT ↓(41.1 to 37.1 U/l; p=0.047) FIB-4 ↓(1.48 to 1.33; p≤0.01) APRI ↓(0.61 to 0.52; p≤0.01)
Rahimi H. et al[79] /prospective study	Ramadan fasting and low-fat low-calory diet	60 NAFLD patients (34 fasting, 26 not fasting=control)	Before vs after fasting (versus control): Body weight (-0.80 kg) (fasting) and (-0.89 kg) (control); p=0.936 BMI (-0.26 kg/m^2) (fasting) and (-0.36 kg/m^2) (control); p=0.749 ALT ↑(+7.38 U/l) (fasting) and ↓(-0.12 U/l) (control) p=0.002
Arabi SM. et al[80] /prospective observational study	Ramadan fasting (between 13 h and 35 min and 14 h and 42 min), for 27.3 days	50 NAFLD patients (diagnosed based on US)	Before vs after fasting: BMI (29.5 to 29.0 kg/m^2; p=0.07) (M) and (34.15 to 33.4 kg/m^2; p=0.09) (F) TC ↑(190.60 to 220.72 mg/dl; p=0.001) (M) and ↑(199.95 to 229.1 mg/dl; p=0.001) (F) HDLc (42.72 to 45.27 mg/dl; p=0.22) (M) and ↑(46.52 to 53.91 mg/dl; p=0.04) (F) Fasting BG ↑(85.5 to 133.56 mg/dl; p<0.001) (M) and ↑(100.0 to 120.23 mg/dl; p<0.001) (F) ALT ↓(18.0 to 13.0; p<0.001) (M) and ↓(14.0 to 11.0; p=0.001) (F)
Aliasghari F. et al[81]/ observational study	Ramadan fasting	83 NAFLD patients (42 fasting, 41 not fasting=control)	Fasting vs control group (change before to after): Weight ↓(-2.14 vs -0.08 kg; p<0.001) BMI ↓(-0.80 vs -0.02 kg/m^2; p<0.001) Waist ↓(-0.95 vs -0.036 cm; p<0.001) Fasting BG ↓(94.02 to 92.4 mg/dl; p<0.001) (fasting) vs (94.75 to 94.46 mg/dl; p=0.05) (control) HOMA-IR ↓(3.49 to 3.48; p=0.011) (fasting) vs (3.78 to 3.81; p=NS) (control)
Mari A. et al[82] /retrospective case-control study	Ramadan fasting	155 NAFLD patients (diagnosed by US) (74 fasting, 81 not fasting=control)	Fasting group (before vs after interventions): BMI ↓(36.7 to 34.5 kg/m^2; p<0.005) HbA1c ↓(5.89 to 5.28%; p<0.005) HOMA-IR ↓(2.92 to 2.15; p<0.005) AST ↓(44.2 to 34.23 U/l; p<0.005) ALT ↓(51.43 to 39.23 U/l; p<0.005) GGT ↓(52.3 to 43.25 U/l; p<0.005) NFS ↓(0.45 to 0.23; p<0.005) BARD ↓(2.3 to 1.6; p<0.005) No significant changes in control group

(Continued on p. 7)

(Continued from p. 6)

Reference/ study type	Dietary intervention	Patients	Main findings
Ebrahimi S. et al[83] /observational study	Ramadan fasting	83 NAFLD patients (42 fasting, 41 not fasting=control)	Fasting vs control group (change end vs before intervention): Weight ↓(-2.14 vs -0.08 kg; p<0.001) BMI ↓(-0.80 vs -0.02 kg/m²; p<0.001) Body fat ↓(-0.68 vs -0.29%; p=0.003) TC ↓(-13.71 vs -7.80 mg/dl; p=0.016) AST ↓(-4.66 vs -2.36 U/l; p=0.031) ALT ↓(-3.43 vs +2.58 U/l; p=0.046) Severity of US hepatic steatosis between groups (p=0.024)
Intermittent Energy Restriction (IER)			
Cai H. et al[84] /RCT	Alternate-day fasting (ADF) vs TRF (16:8) vs control, for 12 weeks	264 NAFLD patients (90 vs 95 vs 79)	Body weight ↓(-4.04 kg) (ADF) vs (-3.25 kg) (TRF) vs (-1.85 kg) (control) (p<0.001 vs control) Fat mass ↓(-3.48 kg) (ADF) vs (-2.62 kg) (TRF) vs (-1.05 kg) (control) (p<0.001 vs control) TG ↓(-0.64 mmol/l) (ADF) vs (-0.58 mmol/l) (TRF) vs (-0.25 mmol/l) (control) (p<0.001 vs control)
Ezpeleta M. et al[85] (abstract only) /randomized study	Modified ADF (600 kcal on fast day) vs exercise vs combination vs control (usual diet), for 12 weeks	NAFLD patients (n = 48)	Body weight ↓(-5.3 %; p<0.05) (ADF) and (-4.9 %; p<0.05) (combination) and (-1.9 %; p=NS) (exercise) vs (-0.3 %) (control) ALT ↓(-29 %; p<0.05) (combination) and (-9 %; p=NS) (ADF) and (1%; p=NS) (exercise) vs (17%) (control) No change in liver fat
Johari MI. et al[86] /RCT	Alternate-day modified fasting (ADMF) (70% calory restriction on fasting day; 2 meals at 2 pm and 8 pm) vs control, for 8 weeks	43 NAFLD patients (33 ADMF vs 10 control)	Body weight ↓(80.80 to 78.79 kg; p=0.003); MD=3.06; p=0.01 BMI ↓(31.73 to 30.95 kg/m²; p=0.003) (ADMF); MD=1.08; p=0.02 ALT ↓(84.33 to 59.17 U/l; p=0.001) (ADMF); MD=18.6; p=0.02 AST ↓(51.40 to 42.77 U/l; p=0.004) (ADMF) Fasting BG ↓(6.62 to 5.87 mmol/l; p=0.006) (ADMF) Liver steatosis grade ↓(1.93 to 1.43; p=0.001) (ADMF); MD=0.38; p=0.01 SWE ↓(5.87 to 5.01 kPa; p=0.001) (ADMF); MD= 0.74; p=0.01
Holmer M. et al[87] /RCT	5:2 diet vs low-carb high-fat diet (LCHF) vs standard of care (SoC), for 12 weeks	74 NAFLD patients (1:1:1 ratio)	Change from baseline to end of treatment: Body weight ↓(-7.4 kg) (5:2 diet) vs (-7.3 kg) (LCHF) (-2.5 kg) vs (SoC) (p<0.0001 for all) HOMA-IR ↓(-3.2; p<0.001) vs ↓(-2.9; p=0.006) (LCHF) vs (–2.4; p=0.097) (SoC) ALT ↓(-17.6 U/l; p<0.001) (5:2 diet) vs ↓(-17.6 U/l; p=0.013) (LCHF) vs ↓(-11.8 U/l; p=0.006) (SoC) CAP ↓(–63.8 dB/m; p<0.001) (5:2 diet) vs ↓(-61.9 dB/m; p<0.001) (LCHF) vs (–20.2 dB/m; p=0.118) (SoC) Elastography ↓(-1.8 kPa; p<0.001) (5:2 diet) vs (-0.3 kPa; p=0.522) (LCHF) vs ↓(-1.5 kPa; p= 0.005) (SoC)
Kord Varkaneh H. et al[88]/RCT	5:2 diet vs control (usual diet), for 12 weeks	44 NAFLD patients (21 IF vs 23 control)	In the intervention group after versus baseline: Body weight ↓(86.65 to 82.94 kg; p<0.001) BMI ↓(30.42 to 29.13 kg/m²; p<0.001) Waist ↓(103.52 to 100.52 cm; p=0.001) Fat mass ↓(26.64 to 23.85 kg; p=0.039) ALT ↓(41.42 to 28.38 U/l; p=0.043) AST ↓(34.19 to 25.95 U/l; p=0.013) TG ↑(171.23 to 128.04 mg/dl; p<0.001) CK-18 ↓(1.32 to 1.19 ng/ml; p<0.001) Fibrosis score (Fibroscan®) ↓(6.97 to 5.58 kPa; p=0.009) CAP ↓(313.09 to 289.95 dB/m; p<0.001), For ALT, ASL, TG, CK-18, Fibrosis score and CAP, p<0.05 versus the change in control group after adjustment for variables

RCT= randomized controlled trial; TRF=Time-Restricted Feeding; NAFLD=non-alcoholic fatty liver disease; BMI=body mass index; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyl transferase; HDLc=high density lipoprotein cholesterol; LDLc=low density lipoprotein cholesterol; TG=triglyceride; TC=total cholesterol; HOMA-IR= Homeostatic Model Assessment for Insulin Resistance; NFS=NAFLD Fibrosis Score; ADF=alternate-day fasting; APRI=aspartate aminotransferase/platelet ratio; FIB-4=Fibrosis-4; CAP=controlled attenuation parameter; MD=mean difference; SWE=shear wave elastography; SoC=standard of care; CK-18=Cytokeratin-18; M=males; F=females; BG=blood glucose; LCHF=low-carb high-fat diet

termittent energy restriction", by selecting "meta-analysis", "clinical trial", "observational study" and "randomized clinical trial". Duplicate articles were removed and the data were summarized descriptively.

There are several studies that have evaluated the effects of TRF regimens, and most have in fact been focused on Ramadan fasting. The meta-analysis by Faris M. et al. has recently evaluated the effect of Ramadan diurnal intermittent fasting (RDIF) on liver function tests in healthy individuals (n=20 studies, 601 adults) and has shown that RDIF was associated with small but significant reductions in aspartate aminotransferase (AST) (standardized mean difference (SMD): -0.257 [95%CI: -0.381, -0.133]), alanine aminotransferase (ALT) (SMD: -0.105 [95%CI: -0.282, 0.07]), gamma glutamyl transpeptidase (GGT) (-0.533 [95%CI: -0.842, -0.224]), and may confer a short-term protection against NAFLD [74]. Although not performed in patients with NAFLD (but T2DM patients), the study by Kahleova H et al. demonstrated that a hypocaloric B2 regimen (comprising two larger meals a day: breakfast and lunch) decreased the hepatic fat content to a slightly greater extent than a hypocaloric A6 (comprising 6 smaller meals) (-0.04% [95%CI: -0.041, -0.035] vs -0.03% [95%CI: -0.033, -0.027]; p=0.009) [75]. Although no similar study has been performed in patients with NAFLD so far to our knowledge, this finding is worth being mentioned.

The only RCT that primarily investigated a TRF (16:8) regimen was the one performed by Kord-Varkaneh H. et al., which demonstrated benefits regarding body adiposity, liver enzymes, steatosis, with slight improvement in markers of fibrosis (table II) [76]. Another small proof-of-con-

cept study published as abstract only has also indicated reductions in body adiposity with a TRF (16:8) regimen [77]. This was also observed in the standard of care group, but with TRF there was also an improvement in liver steatosis and stiffness, as evaluated by transient elastography [77].

The other studies were in fact observational, generally small (some without a control group), and were evaluating the effect of Ramadan fasting on various anthropometric and laboratory markers [77-82]. They overall seem to indicate modest improvements in BMI, liver enzymes, and markers of steatosis (although not all findings were in concordance) (table II) [78-83]. It should be mentioned though that there is a major difference between "classic" TRF regimens and the Ramadan fasting, as the later does not synchronize the fasting period with the physiological feeding/fasting time (as the fasting is diurnal).

Various Intermittent Energy Restriction regimens were assessed in several RCTs and they were associated with a decrease in body weight and fat mass, improvements in transaminases values and markers of liver steatosis, and slight decreases in markers of liver fibrosis (although not all studies have investigated the latter two parameters) (table II) [84-88]. Nevertheless, it should be mentioned that the studies were of relatively short duration (8-12 weeks), had no histologic evaluation of NAFLD (they used surrogate markers of liver steatosis and fibrosis), and except for one study (Cai H et al,.), all the others included a relatively small number of patients.

Additional data worth mentioning here is that reported by Drinda S. et al, although the study did not specifically include NAFLD patients, but individuals with or without T2DM undergoing periodic fasting (n=697) [89]. At baseline, 37.9% of subjects had a Fatty Liver Index (FLI) ≥ 60 (indicating liver steatosis) [89]. The mean fasting duration was 8.5±4 days, and it allowed a maximum energy intake of 250 kcal/day (consisting of fruit juice/vegetable broth) during the fasting period [89]. At the end of the intervention, 49.9% of subjects lost ≥5% of body weight, the BMI was reduced by -1.51 ± 0.82 kg/m^2, and the FLI decreased significantly (-14.02 ± 11.67; p<0.0001), in correlation with number of fasting days and magnitude of BMI reduction [89].

Finally, a systematic review and meta-analysis of six studies (n=417 patients with NAFLD) that approached various intermittent fasting regimens, has reported that these dietary interventions were associated with a small but significant decrease in weight (mean difference (MD): -2.45 [95%CI:-3.98, -0.91], p≤0.00), BMI (MD: -0.50 [95%CI:-0.93, -0.07], p=0.02), ALT (MD: -10.54 [95%CI:-14.01, -7.08], p≤0.00), and AST (MD: -11.31 [95%CI:-14.30, -8.32], p≤0.00), but with no significant changes in waist circumference, blood glucose, fasting insulin and HOMA-IR, blood lipids or liver stiffness (although except for weight and BMI, all other analyses included only 2-4 studies) [90].

Potential risks associated with intermittent fasting

The safety of the intermittent fasting regimens was rather less well investigated in the NAFLD studies (some did not report any safety data, some indicated no adverse effects, and one study reported a hypoglycemic event/pre-syncope associated with intermittent fasting) [76-88]. Although apparently this dietary intervention seems safe, it should be noted that it poses risk of hypoglycemia, mainly in patients with diabetes treated with insulin and/or other glucose-lowering medications (and they should be carefully monitored during the intervention), but also other possible adverse events (malnutrition in patients with advanced liver disease/cirrhosis or older individuals, binge eating, or other psychologic adverse effects (i.e. mood swings), constipation, headache etc.) [90-91]. For some patient categories (such as pregnant or lactating mothers, older individuals, those with advanced chronic diseases, with eating behavior disorders) there is no sufficient safety data to even consider advising this intervention, and it is prudent to refrain from doing so. More short- and long-term safety data is definitely needed in patients with NAFLD, as well as other patient categories, and these should be consistently evaluated in future studies.

Conclusions

There is limited but promising evidence so far regarding the beneficial effects of an intermittent fasting intervention in patients with NAFLD. Most studies included a relatively small number of subjects, were of relatively short-duration, and used anthropometric parameters and surrogate markers of NAFLD (i.e. liver enzymes, ultrasonography). Some of the regimens (mainly Time-Restricted Feeding and Intermittent Energy Restriction) showed some improvements in body adiposity, liver enzymes, and hepatic steatosis, but the best intermittent fasting regimen for NAFLD is not yet known. Further well-designed research that evaluates the feasibility (mainly on long-term), safety and efficacy outcomes of these dietary interventions for patients with NAFLD is still needed.

Authors contribution:

SC contributed by conception of the review, research the literature, drafted the paper, and revised it critically for important intellectual content; final approval of the version to be published.

FR contributed to the design of the review paper; researched the literature, revised the paper for important intellectual content; final approval of the version to be published.

Conflict of interest

None to declare.

References

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic

assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84.
2. Younossi ZM, Marchesini G, Pinto-Cortez H, Petta S. Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: Implications for Liver Transplantation. Transplantation. 2019;103(1):22-27.
3. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, Qiu Y, Burns L, Afendy A, Nader F. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol. 2019;71(4):793-801.
4. Cernea S, Raz I. NAFLD in type 2 diabetes mellitus: Still many challenging questions. Diabetes Metab Res Rev. 2021;37(2):e3386.
5. Arrese M, Arab JP, Barrera F, Kaufmann B, Valenti L, Feldstein AE. Insights into Nonalcoholic Fatty-Liver Disease Heterogeneity. Semin Liver Dis. 2021;41(4):421-434.
6. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. Diabetologia. 2016;59(6):1121-1140.
7. Gerges SH, Wahdan SA, Elsherbiny DA, El-Demerdash E. Non-alcoholic fatty liver disease: An overview of risk factors, pathophysiological mechanisms, diagnostic procedures, and therapeutic interventions. Life Sci. 2021;271:119220
8. Peverill W, Powell LW, Skoien R. Evolving concepts in the pathogenesis of NASH: beyond steatosis and inflammation. Int J Mol Sci. 2014;15(5):8591-638.
9. Juanola O, Martínez-López S, Francés R, Gómez-Hurtado I. Non-Alcoholic Fatty Liver Disease: Metabolic, Genetic, Epigenetic and Environmental Risk Factors. Int J Environ Res Public Health. 2021;18(10):5227.
10. Wehmeyer MH, Zyriax BC, Jagemann B, et al. Nonalcoholic fatty liver disease is associated with excessive calorie intake rather than a distinctive dietary pattern. Medicine (Baltimore). 2016;95(23):e3887.
11. Hydes T, Alam U, Cuthbertson DJ. The Impact of Macronutrient Intake on Non-alcoholic Fatty Liver Disease (NAFLD): Too Much Fat, Too Much Carbohydrate, or Just Too Many Calories? Front Nutr. 2021;8:640557.
12. Vancells Lujan P, Viñas Esmel E, Sacanella Meseguer E. Overview of Non-Alcoholic Fatty Liver Disease (NAFLD) and the Role of Sugary Food Consumption and Other Dietary Components in Its Development. Nutrients. 2021;13(5):1442.
13. Wijarnpreecha K, Thongprayoon C, Edmonds PJ, Cheungpasitporn W. Associations of sugar- and artificially sweetened soda with nonalcoholic fatty liver disease: a systematic review and meta-analysis. QJM. 2016; 109(7):461-466.
14. He K, Li Y, Guo X, Zhong L, Tang S. Food groups and the likelihood of non-alcoholic fatty liver disease: a systematic review and meta-analysis. Br J Nutr. 2020;124(1):1-13.
15. Li Y, Guo L, He K, Huang C, Tang S. Consumption of sugar-sweetened beverages and fruit juice and human cancer: a systematic review and dose-response meta-analysis of observational studies. J Cancer. 2021;12(10):3077-3088.
16. Sevastianova K, Santos A, Kotronen A, et al. Effect of short-term carbohydrate overfeeding and long-term weight loss on liver fat in overweight humans. Am J Clin Nutr. 2012;96(4):727-34.
17. Basaranoglu M, Basaranoglu G, Bugianesi E. Carbohydrate intake and nonalcoholic fatty liver disease: fructose as a weapon of mass destruction. Hepatobiliary Surg Nutr. 2015;4(2):109-16.
18. Schwimmer JB, Ugalde-Nicalo P, Welsh JA, et al. Effect of a Low Free Sugar Diet vs Usual Diet on Nonalcoholic Fatty Liver Disease in Adolescent Boys: A Randomized Clinical Trial. JAMA. 2019;321(3):256-265.
19. Cohen CC, Li KW, Alazraki AL, et al. Dietary sugar restriction reduces hepatic de novo lipogenesis in adolescent boys with fatty liver disease. J Clin Invest. 2021;131(24):e150996.
20. Thomsen MN, Skytte MJ, Samkani A, et al. Dietary carbohydrate restriction augments weight loss-induced improvements in glycaemic control and liver fat in individuals with type 2 diabetes: a randomised controlled trial. Diabetologia. 2022;65(3):506-517.
21. Ristic-Medic D, Kovacic M, Takic M, et al. Calorie-Restricted Mediterranean and Low-Fat Diets Affect Fatty Acid Status in Individuals with Nonalcoholic Fatty Liver Disease. Nutrients. 2020;13(1):15.
22. Properzi C, O'Sullivan TA, Sherriff JL, et al. Ad Libitum Mediterranean and Low-Fat Diets Both Significantly Reduce Hepatic Steatosis: A Randomized Controlled Trial. Hepatology. 2018;68(5):1741-1754.
23. Utzschneider KM, Bayer-Carter JL, Arbuckle MD, Tidwell JM, Richards TL, Craft S. Beneficial effect of a weight-stable, low-fat/low-saturated fat/low-glycaemic index diet to reduce liver fat in older subjects. Br J Nutr. 2013;109(6):1096-104.
24. van Herpen NA, Schrauwen-Hinderling VB, Schaart G, Mensink RP, Schrauwen P. Three weeks on a high-fat diet increases intrahepatic lipid accumulation and decreases metabolic flexibility in healthy overweight men. J Clin Endocrinol Metab. 201;96(4):E691-5.
25. Ahn J, Jun DW, Lee HY, Moon JH. Critical appraisal for low-carbohydrate diet in nonalcoholic fatty liver disease: Review and meta-analyses. Clin Nutr. 2019; 38(5):2023-2030.
26. Yki-Järvinen H, Luukkonen PK, Hodson L, Moore JB. Dietary carbohydrates and fats in nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol. 2021;18(11):770-786.
27. Musso G, Gambino R, De Michieli F, et al. Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. Hepatology. 2003;37(4):909-16.
28. Rosqvist F, Kullberg J, Ståhlman M, et al. Overeating Saturated Fat Promotes Fatty Liver and Ceramides Compared With Polyunsaturated Fat: A Randomized Trial. J Clin Endocrinol Metab. 2019;104(12):6207-6219.
29. Bjermo H, Iggman D, Kullberg J, et al. Effects of n-6 PUFAs compared with SFAs on liver fat, lipoproteins, and inflammation in abdominal obesity: a randomized controlled trial. Am J Clin Nutr. 2012;95(5):1003-12.
30. Rosqvist F, Iggman D, Kullberg J, et al. Overfeeding polyunsaturated and saturated fat causes distinct effects on liver and visceral fat accumulation in humans. Diabetes. 2014;63(7):2356-68.
31. Bozzetto L, Prinster A, Annuzzi G, et al. Liver fat is reduced by an isoenergetic MUFA diet in a controlled randomized study in type 2 diabetic patients. Diabetes Care. 2012;35(7):1429-35.
32. Errazuriz I, Dube S, Slama M, et al. Randomized Controlled Trial of a MUFA or Fiber-Rich Diet on Hepatic Fat in Prediabetes. J Clin Endocrinol Metab. 2017;102(5):1765-1774.
33. Gepner Y, Shelef I, Komy O, et al. The beneficial effects of Mediterranean diet over low-fat diet may be mediated by decreasing hepatic fat content. J Hepatol. 2019;71(2):379-388.
34. Cantero I, Abete I, Monreal JI, Martinez JA, Zulet MA. Fruit Fiber Consumption Specifically Improves Liver Health Status in Obese Subjects under Energy Restriction. Nutrients. 2017;9(7):667.
35. Liu X, Peng Y, Chen S, Sun Q. An observational study on the association between major dietary patterns and non-alcoholic fatty liver disease in Chinese adolescents. Medicine (Baltimore). 2018;97(17):e0576.
36. Alferink LJ, Kiefte-de Jong JC, Erler NS, et al. Association of dietary macronutrient composition and non-alcoholic fatty liver disease in an ageing population: the Rotterdam Study. Gut. 2019;68(6):1088-1098.
37. Rietman A, Sluik D, Feskens EJM, Kok FJ, Mensink M. Associations between dietary factors and markers of NAFLD in a general Dutch adult population. Eur J Clin Nutr. 2018;72(1):117-123.
38. Thomsen MN, Skytte MJ, Samkani A, et al. Dietary carbohydrate restriction augments weight loss-induced improvements in glycaemic control and liver fat in individuals with type 2 diabetes: a randomised controlled trial. Diabetologia 2022;65:506-517.
39. Markova M, Pivovarova O, Hornemann S, et al. Isocaloric Diets High in Animal or Plant Protein Reduce Liver Fat and Inflammation in Individuals With Type 2 Diabetes. Gastroenterology 2017;152:571-585.e8.
40. Koopman KE, Caan MW, Nederveen AJ, et al. Hypercaloric diets with increased meal frequency, but not meal size, increase intrahepatic triglycerides: a randomized controlled trial. Hepatology. 2014;60(2):545-53.
41. Miyake T, Kumagi T, Hirooka M, et al. Significance of exercise in nonalcoholic fatty liver disease in men: a community-based large cross-sectional study. J Gastroenterol. 2015;50(2):230-7.
42. Leech RM, Timperio A, Livingstone KM, Worsley A, McNaughton SA. Temporal eating patterns: associations with nutrient intakes, diet quality, and measures of adiposity. Am J Clin Nutr. 2017;106(4):1121-1130.
43. Esteban JPG, Rein LE, Szabo A, Gawrieh S, Saeian K. Not Just What, but also When You Eat: Analyzing the Impact of Meal Timing Patterns on Non-Alcoholic Fatty Liver Disease. AASLD 2016;abstract 34. Hepatology 2016;64(Supplement 1):S17A
44. Mukherji A, Bailey SM, Staels B, Baumert TF. The circadian clock and liver function in health and disease. J Hepatol. 2019; 71(1):200-211.
45. Philip Esteban J, Dinani A. Lifestyle Interventions Beyond Diet and Exercise for Patients With Nonalcoholic Fatty Liver Disease. Gastroenterol Hepatol (N Y). 2020;16(3):119-130.
46. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-357.

47. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology. 2015;149(2):367–78. e5.
48. Kawaguchi T, Charlton M, Kawaguchi A, et al. Effects of Mediterranean Diet in Patients with Nonalcoholic Fatty Liver Disease: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Randomized Controlled Trials. Semin Liver Dis. 2021;41(3):225-234.
49. Properzi C, O'Sullivan TA, Sherriff JL, et al. Ad Libitum Mediterranean and Low-Fat Diets Both Significantly Reduce Hepatic Steatosis: A Randomized Controlled Trial. Hepatology. 2018;68(5):1741-1754.
50. Parra-Vargas M, Rodriguez-Echevarria R, Jimenez-Chillaron JC. Nutritional Approaches for the Management of Nonalcoholic Fatty Liver Disease: An Evidence-Based Review. Nutrients. 2020;12(12):3860.
51. Vasim I, Majeed CN, DeBoer MD. Intermittent Fasting and Metabolic Health. Nutrients. 2022;14(3):631.
52. Hoddy KK, Marlatt KL, Çetinkaya H, Ravussin E. Intermittent Fasting and Metabolic Health: From Religious Fast to Time-Restricted Feeding. Obesity (Silver Spring). 2020;28Suppl1(Suppl1):S29-S37.
53. Dong TA, Sandesara PB, Dhindsa DS, et al. Intermittent Fasting: A Heart Healthy Dietary Pattern? Am J Med. 2020;133(8):901-907.
54. de Cabo R, Mattson MP. Effects of Intermittent Fasting on Health, Aging, and Disease. N Engl J Med. 2019;381(26):2541-2551.
55. Duregon E, Pomatto-Watson LCDD, Bernier M, Price NL, de Cabo R. Intermittent fasting: from calories to time restriction. Geroscience. 2021;43(3):1083-1092.
56. Zang BY, He LX, Xue L. Intermittent Fasting: Potential Bridge of Obesity and Diabetes to Health? Nutrients. 2022;14(5):981.
57. Dote-Montero M, Sanchez-Delgado G, Ravussin E. Effects of Intermittent Fasting on Cardiometabolic Health: An Energy Metabolism Perspective. Nutrients. 2022;14(3):489.
58. Altay M. Evidence-based information about intermittent fasting in diabetes patients: useful or harmful? " Turk J Med Sci. 2022;52:873-879.
59. Anton SD, Moehl K, Donahoo WT, e al. Flipping the Metabolic Switch: Understanding and Applying the Health Benefits of Fasting. Obesity (Silver Spring). 2018;26(2):254-268.
60. Johnson JB, Summer W, Cutler RG, et al. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. Free Radic Biol Med. 2007;42(5):665-74.
61. Browning JD, Baxter J, Satapati S, Burgess SC. The effect of short-term fasting on liver and skeletal muscle lipid, glucose, and energy metabolism in healthy women and men. J Lipid Res. 2012;53:577–86.
62. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. N Engl J Med. 2019;381:2541–51.
63. Merry BJ. Oxidative stress and mitochondrial function with aging--the effects of calorie restriction. Aging Cell. 2004;3(1):7-12.
64. Beli E, Yan Y, Moldovan L, et al. Restructuring of the Gut Microbiome by Intermittent Fasting Prevents Retinopathy and Prolongs Survival in db/db Mice. Diabetes. 2018;67(9):1867-1879.
65. Patterson RE, Laughlin GA, LaCroix AZ, et al. Intermittent Fasting and Human Metabolic Health. J Acad Nutr Diet. 2015; 115(8):1203-12.
66. Di Francesco A, Di Germanio C, Bernier M, de Cabo R. A time to fast. Science. 2018;362(6416):770-775.
67. Serin Y, Acar Tek N. Effect of Circadian Rhythm on Metabolic Processes and the Regulation of Energy Balance. Ann Nutr Metab. 2019;74(4):322-330.
68. Koopman ADM, Rauh SP, van 't Riet E, et al. The association between social jet lag, the metabolic syndrome, and type 2 diabetes mellitus in the general population: the New Hoorn study. J Biol Rhythms. 2017;32(4):359-368
69. Roenneberg T, Allebrandt KV, Merrow M, Vetter C. Social jet lag and obesity. Curr Biol. 2012; 22(10):939-943.
70. Islam Z, Akter S, Kochi T, et al. Association of social jet lag with metabolic syndrome among Japanese working population: the Furukawa nutrition and health study. Sleep Med. 2018;51:53-58.
71. Hatori M, Vollmers C, Zarrinpar A, et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. Cell Metab. 2012;15(6):848-60.
72. Saran AR, Dave S, Zarrinpar A. Circadian Rhythms in the Pathogenesis and Treatment of Fatty Liver Disease. Gastroenterology. 2020;158(7):1948-1966.e1.
73. Angelidi AM, Papadaki A, Nolen-Doerr E, et al. The effect of dietary patterns on non-alcoholic fatty liver disease diagnosed by biopsy or magnetic resonance in adults: a systematic review of randomised controlled trials. Metabolism. 2022;129:155136.
74. Faris M, Jahrami H, Abdelrahim D, Bragazzi N, BaHammam A. The effects of Ramadan intermittent fasting on liver function in healthy adults: A systematic review, meta-analysis, and meta-regression. Diabetes Res Clin Pract. 2021;178:108951.
75. Kahleova H, Belinova L, Malinska H, et al. Eating two larger meals a day (breakfast and lunch) is more effective than six smaller meals in a reduced-energy regimen for patients with type 2 diabetes: a randomised crossover study. Diabetologia. 2014;57(8):1552-60.
76. Kord-Varkaneh H, Salehi-Sahlabadi A, Tinsley GM, Santos HO, Hekmatdoost A. Effects of time-restricted feeding (16/8) combined with a low-sugar diet on the management of non-alcoholic fatty liver disease: A randomized controlled trial. Nutrition. 2023;105:111847.
77. Hodge A, Mack A, Tuck C, Tchongue J, Holt DQ, Sievert W, et al. Non-alcoholic fatty liver disease intermittent fasting time intervention (NIFTI): fasting without calorie restriction improves hepatic transient elastography, visceral adiposity and insulin resistance compared to standard care. Abstract 894. J Gastroenterol Hepatol 2014;29:68.
78. Badran H, Elsabaawy M, Sakr A, et al. Impact of intermittent fasting on laboratory, radiological, and anthropometric parameters in NAFLD patients. Clin Exp Hepatol. 2022;8(2):118-124.
79. Rahimi H, Habibi ME, Gharavinia A, Emami M, Baghaei A, Tavakol N. Effect of Ramadan Fasting on Alanine Transferase (ALT) in Nonalcoholic Fatty Liver Disease (NAFLD). J. Nutr. Fast. Health 2017;5:107–112.
80. Arabi SM, Zarifi SH, Nematy M, Safarian M. The Effect of Ramadan Fasting on Non-Alcoholic Fatty Liver Disease (NAFLD) Patients. J. Nutr. Fast. Health 2015;3:40–74.
81. Aliasghari F, Izadi A, Gargari BP, Ebrahimi S. The Effects of Ramadan Fasting on Body Composition, Blood Pressure, Glucose Metabolism, and Markers of Inflammation in NAFLD Patients: An Observational Trial. J Am Coll Nutr. 2017;36(8):640-645.
82. Mari A, Khoury T, Baker M, Said Ahmad H, Abu Baker F, Mahamid M. The Impact of Ramadan Fasting on Fatty Liver Disease Severity: A Retrospective Case Control Study from Israel. Isr Med Assoc J. 2021;23(2):94-98.
83. Ebrahimi S, Gargari BP, Aliasghari F, Asjodi F, Izadi A. Ramadan fasting improves liver function and total cholesterol in patients with nonalcoholic fatty liver disease. Int J Vitam Nutr Res. 2020;90(1-2):95-102.
84. Cai H, Qin YL, Shi ZY, et al. Effects of alternate-day fasting on body weight and dyslipidaemia in patients with non-alcoholic fatty liver disease: a randomised controlled trial. BMC Gastroenterol. 2019;19(1):219.
85. Ezpeleta M, Gabel K, Varady K, Lin S, Cienfuegos S. Alternate-Day Fasting Combined with Endurance Exercise for the Treatment of Fatty Liver Disease. Diabetes 2022;71(Supplement1):121–OR.
86. Johari MI, Yusoff K, Haron J, et al. A Randomised Controlled Trial on the Effectiveness and Adherence of Modified Alternate-day Calorie Restriction in Improving Activity of Non-Alcoholic Fatty Liver Disease. Sci Rep. 2019;9(1):11232.
87. Holmer M, Lindqvist C, Petersson S, et al. Treatment of NAFLD with intermittent calorie restriction or low-carb high-fat diet - a randomised controlled trial. JHEP Rep. 2021;3(3):100256.
88. Kord Varkaneh H, Salehi Sahlabadi A, Găman MA, et al. Effects of the 5:2 intermittent fasting diet on non-alcoholic fatty liver disease: A randomized controlled trial. Front Nutr. 2022;9:948655.
89. Drinda S, Grundler F, Neumann T, et al. Effects of Periodic Fasting on Fatty Liver Index-A Prospective Observational Study. Nutrients. 2019;11(11):2601.
90. Sripongpun P, Churuangsuk C, Bunchorntavakul C. Current Evidence Concerning Effects of Ketogenic Diet and Intermittent Fasting in Patients with Nonalcoholic Fatty Liver. J Clin Transl Hepatol. 2022;10(4):730-739.
91. Lavallee CM, Bruno A, Ma C, Raman M. The Role of Intermittent Fasting in the Management of Nonalcoholic Fatty Liver Disease: A Narrative Review. Nutrients. 2022;14(21):4655.