Review

Fasting, Nutrition and Weight Loss: An Approach to Refine Non-Alcoholic Fatty Liver Disease

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Summary Non-alcoholic fatty liver disease (NAFLD) is considered as one of the most common causes of chronic liver disease. It includes a group of conditions associated with fat deposition in liver cells. Also, NAFLD is strongly associated with obesity and insulin resistance (IR). Until now, there is no pharmacological treatment validated for this disease. Fasting, nutritional intervention, and weight loss can be considered the first line in treating hepatic steatosis. This review is based on the scientific evidence showing the results of these interventions in the past years. The results include fasting and nutritional support for NAFLD treatment in humans. In clinical trials and cohort studies, an increase in hepatic fat content was correlated with a weight loss of at least 7% and a diet resembling the Mediterranean diet (MD) improving hepatic biomarkers and histological regression of NAFLD. Fasting is a dietary approach known to improve the lipid profile in healthy and obese populations by decreasing overall cholesterol, triglycerides, LDL, and increasing HDL. Bariatric surgery helps improve liver fat content in patients with serious health problems due to overweight.

Key Words fasting, non-alcoholic fatty liver disease (NAFLD), nutrition, obesity, weight loss

Non-alcoholic fatty liver disease (NAFLD), also known as metabolic dysfunction-related fatty liver disease, is an increased fat accumulation in the liver, exceeding 5% without any cause such as drinking alcohol, viral infection or any other liver disease etiology (1–3). It ranges from relatively benign hepatic steatosis to more severe non-alcoholic steatohepatitis (NASH), hepatic fibrosis, cirrhosis, liver failure, liver cancer, or even cardiovascular disease (4–8). It affects about 25% of the world's population and is the world's most widespread liver disease (9) with the prevalence of 24%, 25% and 30% in European, Italian and American citizens, respectively (10, 11), while the prevalence in Asia area ranges from 15% to 40% (12).

This disease is increasing among obese people and those with other metabolic syndromes (MetS) (13–16), with a prevalence of up to 80% in obese patients against only 16% in normal build people without any metabolic risk factor. Fatty liver disease correlates with body mass index (BMI), but it is more closely related to visceral fatness (17, 18). In addition, it is estimated that 25 to 75% of diabetic patients, according to the studies, have steatosis (19, 20). Almost three-quarters of older people with diabetes or obesity are believed to have NASH, with progressive fibrosis (14).

Considering that no known pharmacological treat-

ment has been validated till date as per the studies (21, 22), diet modification and weight loss have been put forward as the first line of action undertaken for NAFLD management. The studies have shown that a healthy diet and weight loss in the early stages of NAFLD could be sufficient to control disease progression (23, 24). The fasting regimen has been rising in popularity over the past decade as a treatment (25, 26). Thus, this review discusses the pathophysiology and nutritional implications including the benefits of fasting and nutritional support itself for the NAFLD treatment, as per the scientific results conducted in the past years.

Pathophysiology and Nutritional Implications

Hepatic steatosis is defined as intrahepatic fat of at least 5% of liver weight (27). The theory results from an increase in the flow of free fatty acids (FFA) in the liver (food intake, excessive fat storage, decreased mitochondrial beta-oxidation, decreased synthesis and secretion of lipoproteins) (28, 29). An excess of dietary fat or fatty acid (FA) originating from adipose tissue and exceeding the possibilities of catabolism by mitochondrial beta-oxidation or secretion of lipoproteins can lead to hepatic triglyceride development (30). Indeed, overtaking mitochondrial beta-oxidation catabolic capacities or lipoproteins' formation can contribute to this hepatic accumulation of triglycerides (31).

In obese subjects and diabetic patients, obesity may lead to insulin resistance (IR) and MetS (32). IR would

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Fig. 1. Pathogenesis of steatohepatitis. FFA: free fatty acids, and VLDL: very low-density lipoproteins.

cause an increase in the flow of FA reaching the liver due to an increase in mass adipose tissue and a decrease in the antilipolytic effect of insulin. Export of FA in the form of VLDL is diminished and apolipoprotein B-100 is less synthesized due to the combined action of IR and TNF- α secreted by the adipose tissue. An excess of de novo synthesis of hepatic triglycerides can also explain steatosis (Fig. 1).

The progression to steatohepatitis would be linked to lipid peroxidation, oxidative stress, endotoxins and cytokines (especially TNF- α) through hepatic cytotoxicity via different mechanisms (33, 34). Several studies show that a diet rich in saturated fatty acids and a lesser extent in polyunsaturated fatty acids (PUFA) from the omega-3 families quickly results in IR in the liver, muscle and adipose tissue (35–37). In humans, IR is most often associated with an increase in saturated membrane FA's contribution, especially with a long chain and a decrease in FA of the omega-3 families (38).

Cortez-Pinto et al., in their study showed that the patients with NASH had higher consumption of saturated fatty acids and cholesterol than the control subjects, leading to an excess of FFA and plasma triglycerides. The diet of patients with NASH was low in carbohydrates and fiber, high in fat and the ratio of omega-6/omega-3 was also higher (39).

A study from the Rotterdam highlighted animal proteins' role in NASH development in overweight or obese subjects. This study included 3,400 adults, with a mean age of 71, including 70% overweight or obese. NASH

was diagnosed by ultrasound examination in about 35% of patients. A high-protein diet, especially protein-based animals, was associated with NASH (odds ratio, OR: 1.50; 95% CI=1.17–1.92). On the other hand, food rich in fruits and vegetables was protective (40). However, this result remains doubtful because most studies on the subject show a low-carbohydrate diet (25 to 45% of the energy intake daily) improving liver fat content (41).

In general, hepatic steatosis is an accumulation of triglycerides in the liver due to an increase in FFA flow to the liver by increasing food intake or decreased mitochondrial beta-oxidation lipoproteins. The hepatic steatosis in the IR and MetS resulted from increased adipose tissue mass and reduced insulin's antilipolytic effect. Steatohepatitis progression will be associated with lipid peroxidation, oxidative stress, endotoxins and cytokines by hepatic cytotoxicity via different methods.

Nutritional Strategy in the Treatment of the NAFLD

Fasting

Fasting is defined as a voluntary refrainment of some or all caloric foods and beverages for spiritual, therapeutic, or political reasons (42). Intermittent fasting (IF) regimes for a period lasting between 12–16 h for 3 wk (43). IF is a short time of feeding originating in religious and spiritual traditions (44). The holy month of Ramadan, which is a time when millions of Muslims abstain from food and water consumption from sunrise

(Sahur) to sunset (Iftar), lasts from 8–18 h according to the season and latitude. It's correlated with sleep schedule changes, physical activity, eating habits, and food intake quality, leading to metabolism changes (45, 46). Other forms of IF are also studied, such as alternating day fasting (ADF), whose basic principle includes an alternating day of regular food intake with a full day of fasting (47). This fasting form does not need water consumption limits because it doesn't have a religious connection (48, 49).

Previous studies have shown that 4–12 wk of ADF administration can effectively decrease body weight and visceral fat mass (50–52). The beneficial findings for blood lipids (decrease in LDL cholesterol and triglycerides, increase in size particle of LDL) have been reported in addition to these favorable effects of ADF and Ramadan Fasting (RF) on body composition (53–56).

In a randomized controlled trial, 271 NAFLD patients were randomized to the ADF group, time-restricted feeding group, or the control group and subjected to the respective diet for 12 wk. This study confirms that the ADF diet for NAFLD patients is healthy and tolerable and resulted in decreased bodyweight, fatty mass, and overall cholesterol and triglycerides. Besides, time-restricted feeding resulted in substantially lower BMI and cost-effective intervention in obese and NAFLD patients. The overall reduction of NAFLD patients' weight was 6.1% after 4 wk of dietary intervention and an additional 5.4% after 12 wk. The ADF also benefits NAFLD patients since fat mass reduction was observed without improving fat-free mass (55).

Meta-analysis has shown that Ramadan's mean weight loss is 1.34 kg and that most weight has been recovered a couple of weeks after Ramadan (57). RF has shown a certain impact on the circulation of several biochemical markers correlated with vascular and metabolic disorders as a significant weight and body composition reductions (i.e., fat mass expressed as a percentage of weight (%) or absolute mass (kg), and fat-free mass (kg)) and significantly decreased ($p < 0.05$) in apoprotein B, lipoprotein (a) and LDL-C/HDL-C ratio, while total cholesterol, TG, LDL-C, HDL-C and fasting blood glucose did not change during Ramadan (58, 59). Visceral adiposity index (VAI) has proven to be an indicator of insulin sensitivity and has a good association with visceral adiposity. Increased VAI was related to cardiometabolic risk (60). Concerning NAFLD, VAI was confirmed as an accurate predictor for progressive liver histology more than other authenticated non-invasive scores (61).

In a recent study, 83 NAFLD (57 male and 26 female) patients were admitted during Ramadan, 42 fasting and 41 non-fasting patients from June 18 to July 17 in 2015 to assess the impact of RF on liver function; the Atherogenic Plasma Index (AIP) and VAI. This study found that the fasting group's liver enzyme concentrations were greater than the control group ($p = 0.05$ and $p = 0.03$ for SGPT and SGOT, respectively). Also, the total cholesterol, TG, and LDL were significantly reduced

compared with before Ramadan values. The anthropometric parameters including weight, BMI, hip circumference, waist circumference, and waist-hip ratio showed significant differences in the RF group but not in another group. By the end of Ramadan, the mean values of VAI decreased and there was a significant improvement in the severity of NAFLD among the fasting groups ($p = 0.02$) (62).

In Islam; the pregnant or breastfeeding women who believe fasting for long hours will harm them or their babies (63), the elderly who cannot tolerate fasting, the sick who believe fasting will aggravate their condition, and patients with chronic medical condition such as diabetes are freed from performing this religious obligation (64, 65).

Regarding the risks and contraindications of fasting during Ramadan in NAFLD-related disease, in patients with diabetes, there isn't enough evidences to correlate RF to an increased or decreased risk of cardiovascular events. However, there were some indications that stroke risk might be increased (66). Diabetic individuals experience had a higher rate of hypoglycemia during RF (67, 68), and dehydration (69). On the other hand, several previous studies have found an increase in blood glucose levels during Ramadan (45, 70, 71), but other studies revealed that RF had no elevation on blood glucose levels (72–74). Also, according to recent research, the risk of diabetic ketoacidosis does not rise during RF (75).

Overall, different fasting forms are cost-effective and are beneficial in reducing BMI and improving lipid profiles. VAI has proved to be a precise marker for indicating progressive liver histopathology and IF has improved NAFLD by reducing VAI mean values.

Dietary support

Low-restrictive personalized diets seem to be the most suitable in subjects with NAFLD. It showed that compliance is better with this type of diet compared to more severe and restrictive diets. Indeed, very low dietary prescriptions calories (800 or 1,000 kcal per day) or a little less restrictive (providing 1,200 to 1,500 kcal) can cause worsening of some liver damage. Some studies have shown that sudden weight loss can lead to worsening hepatic histological lesions. In a series of 41 morbidly obese subjects, weight loss obtained from a low-calorie diet resulted in significant improvement in fatty liver disease ($p < 0.001$), but inflammation or periportal fibrosis appeared in 24% of subjects emphasizing the risk imposed by a substantial restriction (76).

Several studies have enunciated on the role of PUFA in NAFLD evolution. PUFA would improve the NAFLD parameters via several mechanisms by reducing lipogenesis and inflammation mediators, such as IL-6 and TNF- α (77), would decrease liver fat content (78) and improve liver biochemical test and IR (79). However, there was significant heterogeneity between studies.

The patient with NAFLD should be encouraged to increase fiber intake by increasing the amount of fruits, vegetables, and whole grains and legumes in their diet (80). Research on the impacts of diets high in fiber and

proteins in NAFLD is starting to be published; a prospective observational cohort investigated the association of a low-calorie diet rich in fiber and protein and the elastographic tests of liver fat content in 60 patients with hepatic steatosis (81). The results showed a significant reduction in hepatic fat content measured after 14 d of follow-up; a decrease in gamma-glutamyl transferase (GGT) and plasma lipids were also reported.

New evidence has accumulated in recent years suggesting that the Mediterranean diet (MD), rich in monoacid and PUFA, and aromatic compounds like polyphenols, might benefit NAFLD patients (82, 83).

A clinical trial was conducted to detect dietary differences in intestinal permeability in NAFLD patients with the Mediterranean or low-fat diet. Twelve patients underwent a 48-wk crossover diet for dietary therapy: 16-wk Mediterranean, 16-wk free wash-out diet and 16-wk low-fat diet. The validated method of urinary excretion of chromium-51 ethylene diamine tetraacetate (51Cr-EDTA) excretion testing was used to assess intestinal permeability at the beginning and end of each dietary period. Excretion of 51Cr-EDTA is a strong predictor of intestinal mucosal severity to detect the alteration of intestinal permeability caused by diet in patients following an MD or low-fat diet with NAFLD. The finding after 16 wk of a Mediterranean diet, there was a significant reduction in the mean of waist circumference (-7.9 ± 4.9 cm, $p=0.001$), body weight (-5.3 ± 4.1 kg, $p=0.003$), and transaminase levels (SGPT -28.3 ± 11.9 IU/L, $p=0.0001$; SGOT -6.4 ± 56.3 IU/L, $p=0.01$). These advantages were sustained after 16 wk of washout and 16 wk of the low-fat diet, with no further improvements. Fourteen of 20 patients had intestinal permeability alteration at baseline (mean percentage retention of 51Cr-EDTA=5.4%), but no significant changes in intestinal permeability were observed at the end of the 16 wk of the low-fat or Mediterranean diet (84).

Increased cardiovascular risk in MetS patients and NAFLD has been associated with elevated fasting remnant cholesterol (REM-C) levels NAFLD (85). The objective of secondary analysis of the MEDIDIET study was to estimate the impact of various diets on the level of REM-C in MetS patients and the relation between NAFLD and REM-C. To measure the NAFLD score at baseline, 237 patients with MetS who received liver ultrasound were studied at 3- and 6-mo follow-up. The MD, low glycemic index diet (LGID) or low glycemic index Mediterranean diet (LGIMD) is assigned randomly to the subjects. Study findings: REM-C levels in subjects with moderate or severe NAFLD were higher than in subjects with mild or absent NAFLD. After 3 and 6 mo, the three diets (MD, LGID and LGIMD) had a clear impact on decreasing the levels of REM-C. This effect was more significant among LGIMD in adherent subjects as opposed to the control group. Subjects with severe NAFLD have experienced a substantial rise in REM-C levels after 3 mo and a decline after 6 mo (85).

In a prospective study, fifty Caucasian patients were arbitrarily split into three categories (Groups A–C). The

customized moderately hypocaloric MD was recommended for all patients in the A and B groups. In addition to the diet, Group B routinely obtained an antioxidant supplement for 6 mo. Group C had no medication of any kind. The study found that anthropometric parameters, lipid profile, and decreased hepatic fat accumulation and liver stiffness were improved by the MD alone (Group A) or in combination with the antioxidant complex (Group B), compared to the patients with no any medications (Group C). Moreover, the patients in Group B, whose diet included antioxidants, exhibited not only a substantial increase in insulin sensitivity, but also a considerable improvement in glucose tolerance. When compared to Group A patients, there was a more consistent drop in anthropometric indices. These findings established that the MD can enhance anthropometric measurements and lipid profile, as well as reduce hepatic fat buildup and stiffness. Furthermore, combining this dietary plan with antioxidant supplements may help to improve insulin sensitivity metrics. These findings suggest that antioxidant supplementation might be used as a coadjuvant treatment in NAFLD (11).

A randomized controlled trial of 56 NAFLD patients found a gap in the evidence about the influence of diets on hepatic steatosis. Patients were randomly assigned to one of two dietary intervention groups: low fat (LF) or moderate fat (MD). Dietary recommendations from the National Health and Medical Research Council and the American Heart Association were used to create the LF diet. The LF diet's target macronutrient energy contributions were 50% carbohydrates, 30% fat (with 10% of energy as saturated fat), and 20% protein. The MD was created by studying actual foods used in traditional Cretan meals and making changes to allow for standardization protein with the LF diet. The energy contributions from carbohydrates, fat, and protein were 40, 35–40, and 20% respectively. Related physical activity was assessed at the beginning and end of the study, and patients were advised to sustain the same usual physical activity during the test. Both MD and LF diets led to a similar degree of reduction (25–32%) in hepatic steatosis and resolution of NAFLD. The results demonstrated that both MD and LF diets lead to a significant improvement in hepatic steatosis and measures of liver function (86). This finding complements the clear evidence of the effectiveness of diet-induced weight loss as the primary treatment for NAFLD.

A systematic review was done to evaluate the performance of various dietary patterns on hepatic endpoints of interest, including reduction of hepatic steatosis and fibrosis, weight loss, and metabolic endpoints. A total of 317 patients with a median age of 46 and BMI of 31.5; 64.3% were male and were represented from six different populations. The effects of the MD were examined in five of the six trials, whereas the sixth study looked at modified alternate-day calorie restriction. This study found that a statistically significant reduction in hepatic steatosis was founded in 3/5 MD, one IF, one low-carbohydrate, and 1/2 low-fat diet interventions. There were considerable weight reductions on 3/5 studies using

MD, 1/2 low-fat interventions, and the one IF intervention. In two out of five trials evaluating MD, significant improvement in TG was observed. The preponderance of data favors MD-based therapies, although further randomized research is needed to evaluate NAFLD treatments' comparative efficacy (87).

In general, personalized diets are hepatic-friendly in NAFLD patients, in contrast to other ways that cause sudden weight loss, making the liver more vulnerable to severe damage. High-fiber and high-protein diet are suggested to improve hepatic-enzymes and lipid profiles. MD has beneficial outcomes in NAFLD subjects and MD consisting of PUFA with antioxidant supplements can actually reduce hepatic fats and refine IR, plasma lipids and anthropometric parameters.

Weight loss

Weight loss remains the proven therapy for NAFLD regression (4). The degree of histological change in the liver is directly proportional to the amount of weight loss. Seven percent and 9.3% of weight loss have improved histological lesions of steatosis and NASH confirmed via biopsy, respectively (88, 89). Recent research mentioned the effects of weight loss on liver disease biomarkers in patients with hepatic steatosis. Twenty-two randomized trials were analyzed ($n=2,500$ patients) to study the effect of weight loss through dietary intervention, drug therapy or bariatric surgery, alone or a combination. The interventions on weight loss were significantly associated with an improvement in liver biomarkers, GPT and improved histological criteria for steatosis and steatohepatitis measured histologically or radiologically. Statistically, there are significant histological changes in liver fibrosis (90).

To explain how NAFLD's progression or remission is correlated with weight loss and lifestyle changes, a longitudinal cohort study reviewed the health check-up data for 1,421 subjects without liver disease besides NAFLD who had received at least two health check-ups between 2009 and 2018. Finally, they proved that weight change was related to NAFLD development and NAFLD remission (91).

In summary, weight loss and the associated interventions have markedly improved liver conditions structurally, histologically and biochemically. Weight loss of more than 7% and 9.3% have resulted in improving steatosis and NASH, respectively.

Place of bariatric surgery

Bariatric surgery involves a number of operations for patients who suffer from morbid or severe obesity with BMI of >40 kg/m² or with BMI of at least 35 kg/m² with serious comorbid conditions. This type of surgery is performed by altering the levels of intestinal hormones responsible for hunger and satiety, leading to a new hormonal weight set point (92, 93).

Bariatric surgery in most patients reduced steatosis and steatohepatitis and was associated with improvement in both histologic and biochemical markers of NAFLD (94, 95), and in 30% of patients, it resolved liver fibrosis. Compared with other procedures, Roux-en-Y gastric bypass surgery (RYGB) has a larger effect

on NAFLD histology. A systematic review and meta-analysis of 21 studies ($n=2,374$) by Fakhry et al. on NAFLD's improvement by bariatric surgery provided clear evidence that the histological and biochemical manifestations of NAFLD are greatly improved by bariatric surgery. More specifically, in 30% of patients, bariatric surgery halted the progression or resolved liver fibrosis, which is superior to any other NASH procedure (96).

A prospective longitudinal study in 2014 compared the benefits of RYGB versus adjustable gastric band (AGB) on NAFLD. One thousand two hundred thirty-six obese patients were included, 681 in the RYGB and 555 in the AGB. The weight loss at 5 y was $25.5 \pm 11.8\%$ after RYGB against $21.4 \pm 12.7\%$ after AGB ($p<0.001$); all parameters of NAFLD improved after surgery ($p<0.001$) and even more significantly after RYGB (97).

In 2020, Cherla et al. published a work to study the long-term effects of RYGB and sleeve gastrectomy on NAFLD in 310 patients presented with NASH diagnosed intraoperatively by liver biopsy: 84% normalized their liver enzymes at the end of follow-up. There was no significant difference in patients' proportions with standardized values between RYGB and sleeve gastrectomy groups (84% vs. 82%, $p=0.66$) (98).

The weight loss caused by bariatric surgery is usually accompanied by enzyme improvement and even hepatic histology. However, this improvement seems to vary depending on the type of intervention and severe liver damage. Interventions bypassing the small intestine's proximal part have a more marked metabolic effect, especially on glycemic regulation, which raises the question of the importance of their hepatic effect.

Conclusion

NAFLD is the hepatic manifestation of overweight and MetS. Till date, no pharmacological methods have been established, so lifestyle modifications remain the mainstay of NAFLD treatment. Studies have highlighted regimens like fasting and nutritional intervention as the treatment of NAFLD. These methods aid in reducing liver fat content, visceral obesity and also help to improve liver biomarkers and lipid profiles which prove to be effective in the management of NAFLD. Recently, MD has gained popularity among many and has found to be promising in dealing with various causes of NAFLD; it has resulted in better steatosis outcomes even without weight loss. A weight loss goal of 10% of the initial weight or the maximum weight is realistic and sufficient to improve hepatic histological lesions. However, it remains difficult in some patients to achieve optimal weight loss with diet modifications and physical exercises. In such a scenario, bariatric surgery plays a vital role in supporting weight loss in NAFLD patients.

Future Directions

Future researchers are suggested to use quantitative caloric consumption indicators, sleep length, energy expenditure and metabolic disorder signs, and provide more diverse studies. Further studies are needed to de-

cide if the MD will potentially improve gut permeability in NAFLD patients. The beneficial effects of periodic fasting on fatty liver and glucose-lipid metabolism changes are still in their nascency, so additional experiments with a control group and follow-up for long-term adaptation are needed.

Until now, no precise data are available on the beneficial effects of Ramadan on NAFLD's severity; thus, further research is needed to be conducted before establishing any conclusion.

Additional studies on the improvement of liver functions after bariatric surgery are necessary to determine the association of steatosis and metabolic surgery in obese patients.

Authorship

Research conception and design: Xian-Yan Tang, Galal A. Al-Samhari; administrative support: Xian-Yan Tang; collection and assembly of the research materials and data: all authors; writing the manuscript: Xian-Yan Tang, Galal A. Al-Samhari, Gaber M. Al-Mushiki, Rashi Tamrakar; final approval of manuscript: All authors.

Disclosure of state of COI

The authors declare no conflict of interest.

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Ethical consideration

No known conflict of interest was associated with this publication. This manuscript was read and approved by all named authors, and there are no other persons who satisfied the criteria for authorship but are not listed. The order of authors listed in the manuscript has been approved by all the contributors. The authors have nothing to declare.

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