Chapter

Effectiveness of Lifestyle Interventions for Nonalcoholic Fatty Liver Disease Treatment

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Abstract

The prevalence of nonalcoholic fatty liver disease (NAFLD), which affects around 25% of the world's population, has been rapidly rising along with the rate of obesity in the world. NAFLD is now the leading indicator for liver transplantation in developed countries. NAFLD is a spectrum of diseases ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), which can progress to advanced fibrosis and cirrhosis, eventually culminating in hepatocellular carcinoma. NAFLD management continues to pose challenges for patients, physicians, and healthcare systems because there is presently no approved effective pharmacotherapy. The current standard of care emphasizes intensive lifestyle interventions that include calorie restriction, increased physical activity, and weight loss. Several studies have demonstrated that weight loss of 5% or more of body weight can put NAFLD into remission. However, strict compliance and long-term effort have been an issue for many NAFLD patients precisely because of the difficulty of maintaining a sustained weight reduction. This chapter discusses the evidence supporting lifestyle intervention's effectiveness in improving NAFLD and the barriers that hinder the implementation of lifestyle adjustments and behavior changes. Finally, a few tips to help overcome these barriers are briefly discussed.

Keywords: NAFLD, steatosis, lifestyle intervention, diet, exercise

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by the buildup of lipids in the hepatocytes, as evidenced by radiologic or histologic examination. NAFLD occurs without a coexisting etiology of chronic liver diseases, such as medications, alcoholism, or viral hepatitis. The spectrum of NAFLD encompasses two subtypes: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NAFL is marked by simple mild steatosis, described as an excessive buildup of hepatic triglycerides, typically above 5% of the liver's weight. Steatosis is generally a "benign" condition, and it does not cause liver damage but can pave the way for NASH to develop if not reversed. NASH is more aggressive and develops when steatosis combines with lobular and portal inflammation and liver cell damage in the form of hepatocyte ballooning [1]. The inflammation and liver damage of NASH can cause fibrosis,

or scarring, of the liver and may lead to cirrhosis, in which the liver is scarred and permanently damaged [2]. In some cases, cirrhosis can develop into hepatocellular carcinoma [3] (**Figure 1**). Clinically, it is essential to distinguish between NAFL and NASH, as most NAFLD patients have steatosis without necroinflammation or fibrosis and do not require medical therapy.

NAFLD affects about 25% of the global population [4] and up to 30% in certain regions like the Middle East and South America [5]. NASH has emerged as the Western world's fastest-growing liver transplant indication [6]. The exact etiology of NAFLD remains elusive. However, it is accepted that obesity, type 2 diabetes (T2D), dyslipidemia, and insulin resistance (IR) are its primary causes [7]. The global prevalence of NAFLD among patients with T2D is ~55.5% [8]. Conversely, NAFLD is associated with an increased risk of developing T2D [9]. It is worth noting that NAFLD can also affect lean individuals, who account for 10–15% of all NAFLD cases [10].

The pathophysiology of NAFLD is complex and implicates increased de novo fatty acid synthesis in hepatocytes and lipid retention resulting from reduced hepatocyte apolipoprotein production and β-oxidation [11]. Epidemiological, familial, and twin studies have also provided evidence for an element of heritability of NAFLD [11–13].

An increased emphasis is being placed on discovering novel medicines to prevent, treat, or cure NAFLD due to the disease's skyrocketing incidence and the resulting medical and financial burden. Notwithstanding all efforts, no NAFLD

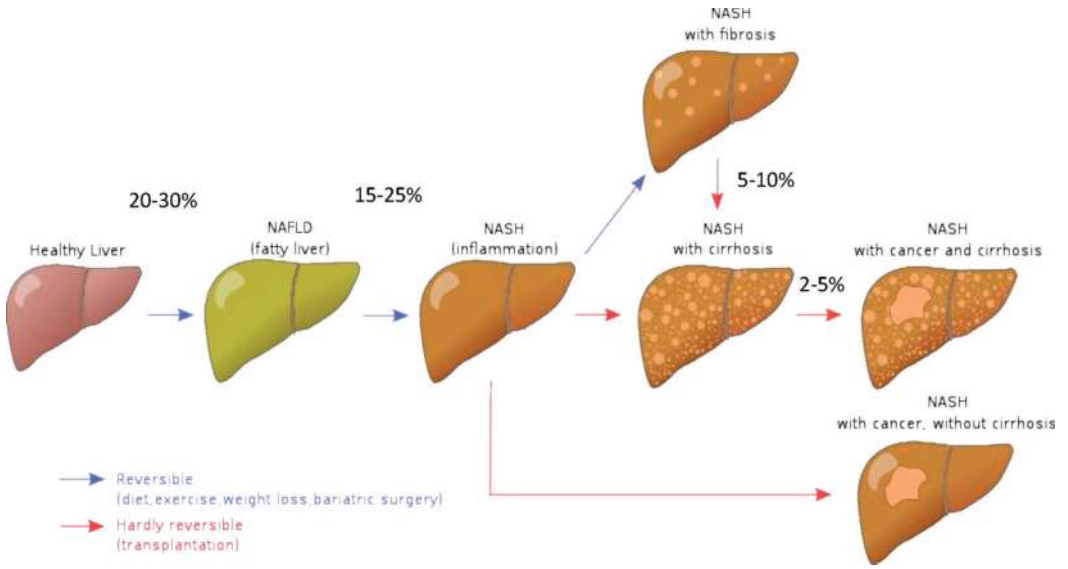

Figure 1.
The spectrum of NAFLD progression and estimated prevalence of the disease stages (adapted from https://commons.wikimedia.org/wiki/File:NAFLD_liver_progression.svg). NAFLD encompasses four stages: 1) simple steatosis (or NAFL), where fat accumulates in the hepatocytes without inflammation, ballooning, or fibrosis. Steatosis affects 20–30% of the world's population. 2) nonalcoholic steatohepatitis (NASH), where there is massive steatosis with indications of hepatocyte injury, i.e. inflammation, ballooning degeneration with or without fibrosis. Some 15–25% of steatotic patients progress to NASH. 3) within 10–20 years, some 5–10% of NASH patients may progress to liver cirrhosis, an end-stage liver disease in which most of the hepatocytes are replaced by collagen. 4) cirrhosis eventually progresses to hepatocarcinoma (HCC), where the liver is unable to regenerate and repair (liver failure), and transplantation is required. HCC affects 2–5% of cirrhotic patients. Factors that cause simple steatosis include calorie-dense Western diets, obesity, T2D, and insulin resistance. Inflammation and hepatocyte apoptosis are factors that contribute to the development of NASH. Liver fibrosis is a transitional phase of NASH that results in the development of liver cirrhosis. Steatosis and NASH/fibrosis could be reversed with lifestyle adjustments, while cirrhosis and HCC are hardly reversible.

pharmacotherapy has yet been approved [5]. At best, physicians can prescribe various medicines to manage the disorders associated with the condition, including hypertension, hypercholesterolemia, T2D, and obesity. Nowadays, weight loss remains the cornerstone treatment for NAFLD. Several randomized controlled trials (RCTs) have shown that ≥5% weight loss improved steatosis, while ≥7% weight loss improved the NAFLD activity score (NAS) [14]. Dietary interventions showed that energy restriction was crucial to improvement in liver fat and transaminase levels. Intensive lifestyle interventions (ILIs) have shown significant success in NAFLD [15]. In the sections below, the limitations of the current NAFLD treatments and the results obtained with ILI-based clinical trials will be discussed.

2. Limitations of current NAFLD treatments

NAFLD is one of the medical requirements with the greatest unmet potential for pharmacotherapeutic treatments, despite being the most common cause of chronic liver disease globally. NAFLD patients frequently have metabolic comorbidities such as obesity, hyperlipidemia, IR, and T2D [16]. Therefore, the management of NAFLD should consist of treating liver disease as well as these comorbidities. Some of the treatments that have been tried so far include dietary supplements, including polyunsaturated fatty acids (PUFAs), vitamins, and resveratrol, and drugs, including metformin, thiazolidinedione, incretin analogs, glifozines, statins, ACC, FAS, and DGAT1/2 inhibitors, obeticholic acid, SARTANS (telmisartan, valsartan, and losartan), and finally the more invasive bariatric surgery.

Supplementation with polyunsaturated fatty acids (PUFAs) was examined in the management of NAFLD, considering the promising outcomes gained by using a Mediterranean diet (MD) high in PUFAs. A meta-analysis of nine studies involving 355 participants looked at the effect of omega-3 or fish oil supplementation on NAFLD and found that, despite being extremely heterogeneous, some results showed that supplemented patients had significantly lower fatty liver [17]. n-3 PUFA supplementation dramatically reduced liver fat compared to placebo, and it also improved levels of triglycerides, total cholesterol, high-density lipoprotein, and BMI, according to a new meta-analysis comprising up to 22 RCTs and 1366 participants [18]. However, alanine transaminase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transferase (GTT) levels were not significantly improved [18]. Higher blood levels of total n-6 PUFA and linoleic acid were linked to lower probabilities of developing NAFLD in middle-aged and older Finnish people, according to a recent study [19]. The exact mechanism of ω-3 PUFAs' beneficial effect on NAFLD is not fully understood. However, it might result from the combination of their transcriptional repression activity on acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN), and L-pyruvate kinase, critical hepatic glycolysis, and de novo lipogenesis enzymes [20], as well as their prominent antioxidant, regenerative, and antitumor properties [21]. Despite these promising results, there is a need for well-designed RCTs which quantify the magnitude of the effect of PUFAs supplementation on liver fat as well as the quantities required to achieve a significant effect on liver fat content and improve liver enzyme levels.

Diet and exercise-related lifestyle decisions made by an individual have a major impact on NAFLD. Accordingly, research has highlighted the significance of calorie restriction and macronutrient composition in influencing illness outcomes. However, the liver is also crucial in micronutrient metabolism, and dysregulation of

this metabolism may contribute to NAFLD development. Recent studies have highlighted the relation between dietary vitamins and fat accumulation in the liver [22]. A growing number of studies have linked vitamins, notably vitamin E, to NAFLD, and vitamin supplementation has been suggested as a possible therapeutic strategy in treating NAFLD [23]. Changes in the serum levels of vitamin D, vitamin B_{12}, and folate have demonstrated a high link with the severity of NAFLD, and the antioxidant activities of vitamins C and E have been credited with reducing hepatocyte injury. Several biochemical alterations in NAFLD, including the lipotoxic hepatic environment, the altered immune system, the unwarranted inflammation, the oxidative stress, the epigenetic modifications, and the gut dysbiosis, correlate to derangement in vitamins [24]. More carefully planned studies on the human population are still required to establish vitamins' effectiveness and safety as therapeutic agents, despite the attractive prospective choices to improve NAFLD management with vitamins. In fact, high doses of vitamin E were shown to be toxic and could increase the risk of cardiovascular mortality [25].

Resveratrol is a polyphenol in berries, including grapes, blueberries, and blackberries [26], and was suggested as a potential treatment option for managing NAFLD given its anti-inflammatory and antioxidant properties, as well as calorie restriction-like effects [27]. By reducing lipogenesis and inflammation, resveratrol reduces hepatic steatosis in high-fat-fed mice [28]. For treating NAFLD in humans, a 12-week supplementation of 500 mg of resveratrol and lifestyle modification was superior to lifestyle modification alone [29]. This effect was attributed partially to the attenuation of inflammatory markers and hepatocellular apoptosis. However, the number of participants was small (n = 50 for both arms), and studies with larger cohorts are warranted for validation.

Presently, neither the FDA nor the EMA (European Medicines Agency) has approved a medication for the treatment of NAFLD. Consequently, the agencies concur that any drug provided for therapeutic purposes for NAFLD is regarded as an off-label treatment, and that this therapeutic strategy is addressed with the patient while considering the risk/benefit ratio [30]. Some of the drugs considered relevant for NAFLD treatment are presented in **Table 1**. It is beyond this chapter's scope to discuss each drug's mechanisms of action, but the reader can find ample information in the literature, such as in [101–103].

3. Lifestyle modification in NAFLD treatment

It is commonly accepted that lifestyle variables, such as an excessive intake of calorie-dense foods and a sedentary lifestyle, are directly related to the pathophysiology of NAFLD, even though the involvement of genetic predisposition in the development of the disease cannot be eliminated. This link is demonstrated by the parallelism between the occurrence of NAFLD and obesity worldwide. Intensive lifestyle interventions, such as dietary changes and regular physical activity that led to significant weight loss, have been the mainstays of NAFLD management and treatment thus far. When successful, lifestyle modifications are far more effective at lowering fibrosis and necroinflammatory alterations in NASH than medications currently being trialed. Therefore, lifestyle modification is considered the main clinical recommendation and the initial step in managing NAFLD. The research supporting the use of lifestyle modification to treat NAFLD/NASH patients' hepatic steatosis and liver histology is examined in this section. Since long-lasting lifestyle changes and

Drug action	Medication	Action on NAFLD/NASH	Limitations	References
Anti-diabetic drugs	Metformin	• Decrease in hepatic and peripheral insulin resistance • ↓Hepatic neoglucogenesis • ↓De novo lipogenesis • ↑FA oxidation	Gastrointestinal side effects including acidosis lactic acid and hepatotoxicity	[31–42]
	Thiazolidinedione	• PPAR-γ agonists • ↑ Adiponectin • ↑ β-Oxidation • ↓ Lipogenesis • ↑ Adipogenesis	Myocardial infarction + bladder cancer: drugs withdrawn from sale in France	[43–52]
	Incretin analog	• GLP-1 (liraglutide) analogs • Resolution of steatosis without the aggravation of fibrosis in NASH patients. • Improved insulin sensitivity, weight loss, and decreased DNL • OPP-IV inhibitors (sitagliptin) • Correlation between DPP-IV level and NAFLD'NASH stage • Improvement of liver function	• Lack of data and need for further studies • Little effect on =NAFLD and NASH despite improvement in liver function	[32, 33, 53–63]
SGLT2 Inhibitors	Glifozines	• Urinary glucose excretion: • Weight loss • Improvement of liver function • Improvement of liver fibrosis	• Urinary side effects include urosepsis, urogenital infections, and pyelonephritis	[49, 64–67]
Hyperlipidemia drugs	Statines	• Hepatic cholesterol synthesis via inhibition of HMGCoA reductase: improvement of hepatic fibrosis and steatosis	• Mixed results hepatotoxic potential	[68–71]
	Ezetimibe	• ↑Insulin sensitivity, • ↓Steatosis, cholesterol levels, and ALT levels	• No effects on fibrosis and hepatic inflammation	[72–74]

Drug action	Medication	Action on NAFLD/NASH	Limitations	References
Regulators of hepatic lipid metabolism	ACC inhibitors	• ↓DNL and hepatic steatosis • ↑β-Oxidation of FAs	• First-generation inhibitors associated with hypertriglyceridemia • Second-generation inhibitors: partial 5 days of DNL without reactive hypertriglyceridemia (study in progress)	[75–82]
Regulators of hepatic lipid metabolism FXR agonists	FAS inhibitors	• DNL inhibition. Effective in NAFLD and NASH	PHASE I	[48, 83–85]
	DGAT1/2 Inhibitors	• ↓DNL and hepatic steatosis • ↑β-Oxidation of FAs	• Efficacy controversial-on fibrosis DGAT1:gastrointestinal toxicity	[76, 86–88]
	OBETICHOLIC ACID	• Anti-inflammatory • Anti-fibrotic	• Atherogenic potential and pruritus	[89–97]
Antihypertensive drugs	SARTANS (telmisartan, valsartan, losartan)	• Losartan: 5 days hepatic fibrosis + necroinflammation • Valsartan: IR improvement + fibrosis • Telmisartan: IR improvement + fibrosis +↓ circulating FAs levels + steatosis	• Further studies are needed	[52, 98–100]

Table 1.
A non-exhaustive table of studies that tried different potential pharmaceuticals for the treatment of NAFLD/NASH.

weight loss are challenging to achieve [104] and unfortunately, altering one's lifestyle alone does not always succeed, the different hurdles to adopting these changes are highlighted, along with strategies to overcome them.

A number of RCTs have demonstrated that altering one's lifestyle aids individuals with NAFLD in shedding pounds, lowering liver fat content, and raising their NAFLD activity score, which is a combination of steatosis, inflammation, and hepatic ballooning and is determined by liver biopsy. In a very recent meta-analysis of 30 RTCs involving 3280 participants with proven NAFLD, Fernandez et al., [104] found that combined exercise and diet intervention leads to significant reductions in ALT, AST, and HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) than diet or exercise alone. Also, Peterson and coworkers [105] reported a reversal of intrahepatic lipid in eight obese subjects following a 12-week moderately hypocaloric, very-low-fat (3%) diet (~1200 kcal/day) that led to a weight loss of only ~8 kg. Furthermore, in an RCT examining the effects of weight loss on clinical parameters of NASH, Promrat et al., [106] employed a 48-week ILI that combined diet, exercise, and behavior change, and targeting 7 to 10% weight loss, on 31 overweight/obese adults with biopsy-proven NASH. The patients were randomized in a 2:1 ratio to receive ILI or structured education (control). The change in NASH histological activity score (NAS) was the primary outcome (NAS ranges between 0 and 8) and is used to grade NAFLD: NAS $\geq$ 5 indicates NASH, and NAS $\leq$ 3 indicates no NASH [106]. In contrast to the control group, which lost 0.2% of weight after 48 weeks, patients allocated to ILI lost an average of 9.3% of their body weight. A significant correlation was observed between percent weight reduction and improvement in NAS ($r = 0.497$, $P = 0.007$). When compared to the control group (4.9 to 3.9), NAS dramatically improved in the ILI (from 4.4 to 2.0;$P = 0.05$). Compared to those who lost less than 7%, the patients who achieved the study weight loss goal significantly improved steatosis, lobular inflammation, ballooning injury, and NAS.

In an RCT undertaken by Katsagoni and coworkers in Greece [107], 63 ultrasonography-proven obese NAFLD patients with high ALT and/or GGT levels received 6 months of Mediterranean lifestyle intervention consisting of a Mediterranean diet (MD) along with guidance to increase physical activity and improve sleep habits. Compared to control patients, who received only written information for a healthy lifestyle, the Mediterranean lifestyle intervention patients showed a significant 50% reduction of ALT levels and liver stiffness after adjusting for % weight loss and baseline values. An RCT has looked at the impact of the green Mediterranean diet (GMD), which further restricts red and processed meat while enhancing green vegetables and polyphenols, on NAFLD as measured by intrahepatic fat (IHF) reduction. [108]. In this 18-month study, 294 participants with abdominal obesity/dyslipidemia were divided into three weight-loss groups: healthy dietary guidelines (HDGs), MD, and green-MD, all of which included physical activity. NAFLD prevalence declined significantly to 54.8%, 47.9%, and 31.5% in HDG, MD, and GMD groups, respectively ($p = 0.012$ between groups). Even while the two MD groups experienced similar modest weight reduction, it is interesting to note that the GMD group experienced over twice as much intrahepatic fat (IHF) % loss (−38.9% proportionately) as compared to the MD and HDG groups.

In a very recent parallel, multicenter RCT, George and coworkers [109] looked at the impact of a Mediterranean diet (MD) on hepatic and metabolic outcomes in NAFLD. The 42 participants were randomized (1:1 ratio) to MD or low-fat diet (LFD) for 12 weeks. The results revealed that intrahepatic lipids and insulin resistance (measured by HOMA-IR) improved significantly within the LFD group but not within

the MD group. The visceral fat was reduced significantly in both groups. It is worth noting that this RCT did not involve any physical activity, which could have improved the results. Results from a recent [110] 52-week phase IV double-blind parallel RCT comparing the effects of lifestyle and dietary intervention plus Ezetimibe to lifestyle versus dietary intervention alone (placebo) on the progression and complications of NASH revealed that Ezetimibe administered in addition to lifestyle and dietary modification failed to significantly improve the histology of NASH beyond what is achieved with lifestyle and dietary modification alone.

In a 2-year RCT, Marin-Alejandro and colleagues examined the results of two customized dietary approaches in NAFLD patients [111]. The 98 participants were divided into two groups at random: the test group received the Fatty Liver in Obesity (FLiO) diet and the control group received the American Heart Association (AHA) diet. The AHA diet is based on AHA recommendations for eating habits and lifestyle changes, and it aims to reduce body weight by at least 3–5% and as much as 10% to reduce liver disease-related necrotizing inflammation. The FLiO diet is a Mediterranean diet that has the same targets as the AHA diet and is based on a quantitively and qualitatively good distribution of macronutrients, meal frequency, dietary behavior, antioxidant capacity, and lifestyle advice. The FLiO group outperformed the AHA group at the end of the study in terms of ALT, liver stiffness, and Fatty Liver Index, among other outcomes. However, weight loss percentage attenuates these differences when the analyses were adjusted. These results demonstrate that both approaches are viable substitutes for managing NAFLD. The FLiO method, however, might offer more long-lasting advantages in terms of metabolic and hepatic characteristics. Because of the limited space, only a few RTCs that reported the positive effect of lifestyle adjustments on NAFLD are reported above. **Table 2** shows some more similar RTCs conducted in the last 2 years.

4. Barriers and facilitators to implementing a lifestyle change for NAFLD

According to the evidence outlined in the previous section, NAFLD therapy based on intensive lifestyle intervention that combines diet and exercise can be successful. However, there are numerous obstacles to the clinical implementation of lifestyle intervention. For instance, the majority, if not all, intensive lifestyle therapies designed to improve NAFLD/NASH necessitate a weight loss of at least 5% of body weight. However, weight loss is notoriously difficult to achieve and even more challenging to maintain [119]. Without weight loss maintenance, the effect of ILI will, at best, be temporary. In a prospective observational cohort study, Jimenez and coworkers [110] evaluated the influence of weight regain on the NAFLD, assessed utilizing a fibrosis score 3 years post Roux-en-Y-gastric bypass surgery. They observed that of the 90 patients examined, 35.6% had obesity recurrence and that the fibrosis score in this group was significantly higher than in the group that had no weight regain. Similar to this, Nakanishi et al., [120] recently showed that among male participants who had been diagnosed with NAFLD and had entered remission, weight gain of 1.5 kg or more and a lack of exercise were related with NAFLD recurrence. The findings of these two studies strongly indicate that maintaining a weight loss is necessary to maintain NAFLD remission.

Additionally, the success of implementing ILI for NAFLD management requires the care to be best provided by multidisciplinary teams incorporating physicians who are experts in the management of NAFLD and its comorbidities, nutritionists,

Study	Design	Number of patients	Objective	Outcome
George ES et al., [112]	Parallel multicenter RTC	42 NAFLD patients	Assess the effect of MD or LFD for 12 weeks on IHL	LFD improved IHL and insulin resistance. Significant improvements in visceral fat were seen within both groups
Montemayor S et al., [113]	Cross-sectional study	155 Ow/Ob NAFLD patients with MetS	To evaluate the impact of a tailored hypocaloric diet and increased physical exercise on IHL and NAFLD progression	Subjects with NAFLD and MetS had reduced intrahepatic fat content and liver stiffness in response to diet and exercise
Noto D et al., [114]	Double-blind RCT	40 patients with ascertained NASH	Compare Lifestyle adjustment versus ezetimibe + lifestyle	Ezetimibe + lifestyle modification is not superior in improving NAHS than lifestyle modification alone
Mascaro CM et al., [115]	Prospective cohort analysis of data obtained between baseline and 6-year parallel-group randomized trial	155 NAFLD patients with MetS	Compare the effect of 6-month CD versus MD-high meal frequency or MD + physical activity on fitness status	Lifestyle 6-month intervention with diet and regular PA improved functional fitness in patients with NAFLD and MetS
Meir AY et al., [108]	Eighteen-month randomized clinical trial	294 participants with abdominal obesity/dyslipidemia	Analyze the impact of a green-MD diet, which is low in red and processed meat and high in green vegetables and polyphenols, on NAFLD as shown by loss of IHL.	Green-MD can double IHL loss and reduce NAFLD in half compared to healthy dietary guidelines or regular MD
Jovanovic GK et al., [116]	RCT	81 obese participants	After a 6-month follow-up, assess the impact of an anti-inflammatory diet with lower energy intake on the liver health in younger persons with obesity.	The anti-inflammatory diet induced a significant improvement of liver parameters in younger adults with obesity
Marin-Alejandre BA et al., [111]	RCT	98 NAFLD patients	Evaluate the long-term effects AHA and FLiO diets on weight loss, and metabolic and hepatic outcomes in overweight/obese subjects with NAFLD	The AHA and FLiO diets were able to improve body weight and body composition, as well as the metabolic and hepatic status of participants with overweight/obesity and NAFLD within a 2-year follow-up

Study	Design	Number of patients	Objective	Outcome
Franco I et al., [117]	RCT	144 patients with moderate or severe NAFLD	Estimate the effect of two different PA programs, a low (LGIMD), and their combined effect on the NAFLD score	LGIMD + aerobic activity program was the most efficient in reducing NAFLD score when compared to CD, LGIMD, aerobic activity, aerobic activity + resistance training, and LGIMD+ aerobic activity + resistance training
Ristic-Medic D et al., [118]	RCT	24 NAFLD patients	Analyze the impact of MD and LFD on patients with NAFLD's fatty acid profiles, cardiometabolic indicators, and liver condition.	Given that it improves fatty liver and decreases saturated and increases monounsaturated and n-3 polyunsaturated fatty acid status in NAFLD patients, the MD may contribute to disease treatment even more than the LFD.

Table 2.
Some of the RTCs undertaken between 2020 and the present to assess the lifestyle modifications on NAFLD. LFD: Low-fat diet; MD: Mediterranean diet; IHL: Intrahepatic lipids; ow/Ob: Overweight/obese; CD: Conventional diet; AHA: American Heart Association; FLiO: Fatty liver in obesity; PA: Physical activity; LGIMD: Glycemic index Mediterranean diet.

educators, physical exercise coaches, as well as the patients' families. It also requires discipline, monitoring for complications, and regular laboratory assessments. The goal should be to foster an environment that promotes maintaining healthy body weight and body composition as a way of life. Another barrier to implementing ILI for NAFLD management is the lack of training necessary to deliver it among the health providers. In fact, a study by Avery et al., [121] has found a significant gap between recommendations and how clinical treatment is provided in reality. Healthcare professionals acknowledged a lack of knowledge and tools on how to successfully target lifestyle behavior change to control NAFLD over the long term and the necessity for a collaborative approach across disciplines to avoid miscommunicating with patients. Patients also supported this conclusion by reporting a severe shortage of information and support at the time of diagnosis and moving forward.

Patients must comprehend their disease to be convinced to adopt successful, long-lasting lifestyle adjustments. Impactful changes in their lifestyle habits will be hindered by their lack of knowledge of their condition and their failure to recognize the relationship between their current lifestyle choices and their disease, NAFLD, in this case. Patients must comprehend that if they make and sustain effective lifestyle adjustment, NAFLD/NASH may be curable [121].

Finally, it is important to remember that a variety of factors, including gender and reproductive status, genetics, the richness of the gut microbiota, endocrine and metabolic condition, and physical activity, may contribute to the variability of

NAFLD. Therefore, the individual patient should consider all these factors to implement an individualized lifestyle adjustment. A one-size-fits-all lifestyle adjustments plan may not be adequate for all NAFLD patients. The impact of considering NAFLD heterogeneity on the development of targeted therapies for NAFLD is crucial for the success of the intervention [120].

A variety of lifestyle adjustment strategies and behavior change counseling techniques are available for usage, some with a more robust evidence base than others for addressing each stage in the process. These methods are intended to aid healthcare professionals and doctors in guiding patients toward making informed decisions about their actions and inspiring them to take ownership of their health. For instance, using motivational interviewing techniques during consultations can help patients feel more empowered to make their own health-related decisions. Some of the practical tips to support patients to make lifestyle changes include but not limited to 1) dispelling any myths, such as the idea that alcohol is the cause of NAFLD, by describing what NAFLD is and how it may be reversed with lifestyle changes; 2) explain the link between the body weight changes and the energy balance concept; 3) set a weight loss target that is realistic, personalized, quantifiable, attainable, and relevant; 4) encourage the use of self-monitoring tools, such as routine weighing, tracking calorie consumption by keeping a daily log, wearing activity trackers, understanding nutritional labels and choosing healthier options, acquiring knowledge of how to buy for, prepare, and serve meals; 5) utilize the proper interventions, such as regular meal patterns, fewer snacking, and portion control; 6) motivate patients to join local gyms, weight management programs, and walking groups; there is evidence that diet and physical activity interventions delivered in groups are effective in promoting clinically meaningful weight loss [122].

5. Conclusion

In the absence of an approved pharmacotherapy for NAFLD, ILIs remain the cornerstone for treating the condition. Strong evidence indicates that a sustained weight loss of 5% or more of the body weight can lead to NAFLD remission in a sizable proportion of patients. From the several RTCs listed in this study, lifestyle changes based on Mediterranean diets and exercise appear to be the most successful for improving NAFLD in a significant number of patients. Additionally, considering patient heterogeneity with regard to their reaction to ILIs, i.e. creating individualized ILI, may enhance the success of the intervention in NAFLD patient subgroups. In certain resistive patients, subtle changes in the composition of the meals or in exercise intensity may be more beneficial. As the number of NAFLD patients keeps increasing, health providers must have the ability and capacity within healthcare settings to motivate and support patients to make long-lasting lifestyle behavior adjustments. More emphasis should be placed on engaging patients in a discussion about their choices concerning their care. To better tackle NAFLD, healthcare providers should set up multidisciplinary teams with different expertise, i.e. hepatology, diabetology, cardiology, obesity, nutrition, and physical education.

Implementing effective lifestyle interventions for NAFLD patients is crucial not only because of the significant disease prevalence worldwide but also because excess liver fat is a separate risk factor for the onset of cardiovascular disease and T2D [123].

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Conflict of interest

The author declares no conflict of interest.

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