Nonalcoholic Fatty Liver Disease Management

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Nonalcoholic fatty liver disease (NAFLD) is a rising epidemic worldwide, involving more than a quarter of the world's population. A sedentary lifestyle and consuming a Western diet have led to substantial challenges in managing NAFLD patients. With no curative pharmaceutical therapies, lifestyle modifications, including dietary changes and exercise, that ultimately lead to weight loss remain the only effective therapy for NAFLD.

non-alcoholic fatty liver disease | Mediterranean diet | lifestyle change | weight loss

1. NAFLD Background

Under normal circumstances, only a tiny amount of fat deposits are stored in the hepatocytes [1]. Deposition of excessive fat inside the liver, also known as fatty liver, can occur for many reasons, including excessive alcohol consumption, viral infections, medications, and sometimes other medical conditions such as inflammatory bowel disease [2][3]. However, when the fatty liver is a consequence of over-nutrition and insulin resistance (IR), the condition is called nonalcoholic fatty liver disease (NAFLD) [4]. NAFLD is diagnosed when there is evidence, either by imaging or histology, that over 5% of hepatocytes are filled with fat in the absence of any history of excessive alcohol use or any other secondary causes of fatty liver [2]. NAFLD is the most common liver disorder worldwide. A systematic review of prevalence reports from around the world estimated its global prevalence as 25.2% (95%CI: 22.1%–28.7%) [5].

NAFLD comprises a spectrum of liver histopathology ranging from the presence of a benign fatty liver, referred to as nonalcoholic fatty liver (NAFL), to fatty liver superimposed by inflammation, hepatocyte death, and fibrosis, also known as nonalcoholic steatohepatitis (NASH), and ultimately to cirrhosis [2]. NASH, unlike NAFL, is a pathological diagnosis needing a liver biopsy and is defined as the presence of NAFL complicated by inflammation and hepatocyte injury (e.g., ballooned hepatocytes or Mallory hyaline), with or without fibrosis [2]. A meta-analysis has identified the prevalence of NASH to be 59.1% (47.6–69.7) among biopsied NAFLD patients and 6.7% (2.2%, 18.7%) among patients biopsied for reasons other than NAFLD [5]. NASH is the second most common indication for liver transplants in the United States behind hepatitis C [6]. The global prevalence of NASH is estimated to be between 3% and 6% [7], while NASH cirrhosis is estimated to be 0.18% [8]. The overall annual fibrosis progression rate from a baseline stage of no fibrosis (i.e., F0) in patients with NASH is estimated to be 0.09 stage (95% CI, 0.06–0.12), with 40.8% of patients showing fibrosis progression [5]. Aside from cirrhosis and the detrimental complications associated with it, NAFLD and NASH are concerning diagnoses due to the increased prevalence of hepatocellular carcinoma (HCC), especially with NASH [9][10]. The annual incidence of HCC in NAFLD patients is

estimated to be 0.44 per 1000 person-years, whereas in patients with NASH, this incidence rate increases to 5.29 per 1000 person-years [5].

1.1. NAFLD and metabolic syndrome

NAFLD is considered a component or hepatic manifestation of metabolic syndrome (MetS) [4]. MetS is a cluster of metabolic abnormalities resulting from IR and is often identified in obese and sedentary patients [11][12]. MetS is diagnosed when central obesity in addition to any two of the following components are present in an individual: High blood triglyceride (TG) levels, low high-density lipoprotein (HDL) cholesterol levels, hypertension, increased fasting blood glucose, or established type 2 diabetes mellitus (T2DM) [13]. In Western countries, the prevalence of MetS is estimated to affect 20% of the adult population [14], and an increased prevalence of NAFLD has been reported in patients with MetS. For example, a meta-analysis of 80 studies from 20 countries in individuals with T2DM (n = 49,419) demonstrated a prevalence of NAFLD of 55.5% (47.3%–63.7%) [15]. Similarly, MetS or T2DM is present in as high as 85% of NAFLD patients [16]. Hypertension is also more common among NAFLD patients than in the control non-NAFLD group (OR = 1.24, 95% CI: 1.14–1.36) [17]. Since the components of MetS are all risk factors for cardiovascular morbidity and mortality, cardiac-related comorbidity and death are increased in patients with NAFLD. Of major concern, cardiovascular disease is the main cause of mortality in patients with NAFLD [2], significantly surpassing liver-related mortality among NAFLD patients (48% vs. 7%, respectively) [18]. Notably, only 0.1% of all deaths in the general population are liver-related [18]. Although obesity and MetS are the major risk factors for NAFLD, up to 30% of NAFLD patients are neither obese nor have any MetS components [19]. Lean NAFLD cases highlight a role for genetic susceptibility in the pathogenesis of NAFLD [19].

1.2. Pathogenesis of NAFLD and NASH

The pathophysiological hallmark of NAFLD is IR [20]. IR leads to elevated portal and circulating free fatty acids (FAs), which results in increased hepatic uptake. When increased hepatic FA input (uptake and biosynthesis) overcomes hepatic clearance by beta-oxidation or by secretion as very-low-density lipoprotein (VLDL), FAs accumulate within hepatocytes as TGs [21][22][23]. These TGs are secreted into the bloodstream in the form of VLDL to be transferred to adipose tissues. Under conditions where hepatocytes cannot fully secrete all TGs as VLDL, the TGs are stored as cytosolic lipid droplets within hepatocytes as lipid vesicles isolated from the cytoplasm by a phospholipid monolayer [24].

The source of FA input to the liver is through either dietary fat intake, in the form of chylomicrons, or plasma-free FA pool (also known as circulating non-esterified FAs (NEFAs), which are released from adipose tissue) [21]. Additionally, the hepatic uptake of excess dietary carbohydrates can also be used as a substrate for FA biosynthesis and is another important source for FA input to the liver [22]. The relative contribution of each source of FA is different between fed and fasting states. Donnelly *et al.* (2005) showed that in the fasting state, the contributions of peripheral NEFAs, FA biosynthesis, and dietary fats to hepatic fat content were 59% (45.1%–74.3%), 26.1% (12.7%–37%), and 14.9% (4.3%–28%), respectively [22]. Therefore, NEFA originating from visceral adipose tissue may be the primary lipid source for increased hepatic fat content in NAFLD, followed by de novo

biosynthesis and diet. Free FAs (FFAs) may be oxidized for routine use; however, in NAFLD, increased FFA oxidation causes oxidative stress that uncouples mitochondrial oxidation and phosphorylation and generates reactive oxygen species (ROS) [23]. Mitochondria have several defense mechanisms against toxic by-products, such as ROS (e.g., antioxidants, glutathione, catalase, etc.); if these defense mechanisms are overcome, organelle damage may occur [25]. Mitochondrial damage might result in decreased lipid oxidation or even cell death, which in turn can lead to inflammation, production of cytokines, recruitment of inflammatory cells, generation of fibrosis, and progression to NASH [23].

1.3. Risk Factors for NAFLD

While there are several non-modifiable risk factors for NAFLD, include age, sex, genetic background, ethnicity, and family history of T2DM, fatty liver, or premature cardiovascular disease [26], the important modifiable risk factors for NAFLD include obesity, over-nutrition, dietary composition, and inactivity. Obesity, especially central obesity, is possibly the most important modifiable risk factor for NAFLD and results from over-nutrition and inactivity [26]. Most patients with NAFLD are either obese or overweight. The overall prevalence of obesity among NAFLD patients worldwide is estimated at 51.3%, and 81.8% of NASH patients are obese [5]. Results from 12,454 adult participants in the Third National Health and Nutrition Examination Survey (NHANES) describe the prevalence of NAFLD in various body mass index (BMI) categories: 7.5% in normal-weight men (BMI of 18.5–24.9), 38.6% in obesity class 1 (BMI of 30.0–34.9), and 56.6% in obesity class 2 (BMI 35 or above) [27]. Similar trends have also been reported for women with NAFLD. Prevalence of NAFLD was 6.7% in women with a normal BMI compared to 24.7% in women with a BMI of 30.0 to 34.9, and 44.3% in those with a BMI of 35 and above [27]. Central obesity, measured through waist circumference (≥ 102 cm for men and ≥ 88 cm for women), is an independent risk factor for both NAFLD and MetS [28]. A widely accepted hypothesis is that visceral adipocytes are detrimental to the liver as they release more FAs, pro-inflammatory cytokines, and adipokines than peripheral adipose tissue pools [4].

Modern societies spend increasingly more time being sedentary and less time engaged in physical activity due to environments that minimize activity and require prolonged sitting times at work, home, and transportation [29]. Sedentary behavior is defined as low-energy expenditure in a sitting or reclining position during waking hours. It has been linked to chronic low-grade inflammation and contributes to obesity [30]. High sitting times (e.g., >8 h/day) compared to low sitting times (e.g., < 4 h/d) almost double the risk of developing T2DM and increase the incidence and mortality risk associated with cancer and CVD by 10% to 20% [31]. The association between sedentary lifestyle and obesity, MetS, and T2DM has been supported by epidemiological research [30][32][33]. Low levels of moderate-intensity physical activity and high amounts of sedentary time are associated with IR, T2DM [34], and NAFLD [35][36].

The relationship between diet and the development of NAFLD is complex and extends beyond total energy intake. Certainly, over-nutrition results in obesity by altering the energy balance. However, dietary patterns may have an independent effect on NAFLD apart from energy density. A "Western" style diet is a well-recognized diet pattern associated with MetS and NAFLD [37][38][39]. This pattern is generally hypercaloric; it consists of high intakes of animal products high in saturated fat, refined sugars, and grains; sugar-containing soft drinks; and high intakes of processed food high in trans-fats and low in fiber and phytochemicals [40]. The high glycemic index associated with

the Western dietary pattern results in a rapid increase in insulin and postprandial serum glucose levels and contributes to the induction of liver lipogenesis and VLDL secretion, resulting in obesity [40][41]. Besides the Western dietary pattern, the consumption of restaurant-based fast-foods is another example of an energy-dense, low-nutrient-rich diet [42]. In a clinical trial in Sweden, 18 healthy volunteers were given at least two fast-food-based meals a day to double the regular caloric intake, in combination with adopting a sedentary lifestyle for four weeks. They then were compared to a control group [41]. The results showed an average 6.4-kg weight gain, a significant rise in serum alanine aminotransferase (ALT) levels, and an increase in average intrahepatic TG (IHTG) levels from 1.1% to 2.8% compared to controls [41]. Of note, eating patterns have also been associated with NAFLD. A prospective study of 2254 NAFLD-free subjects over three years found that individuals who habitually eat before bedtime had double the risk of developing NAFLD [43]. Hyper-caloric snacking between meals increases liver fat while consuming the same snacks with meals does not cause liver fat accumulation [44].

2. NAFLD Management Overview

NAFLD management has focused on reducing IR, limiting oxidative stress, and modifying underlying risk factors [45][46]. Lifestyle modification remains the most effective treatment for NAFLD and NASH and is achieved through dietary changes and physical activity. Nevertheless, there are several challenges to achieving these outcomes [47][48][49][50]. Aggressive weight loss can aggravate liver inflammation in subjects with NAFLD if it reaches a rate greater than 1.6 kg per week [51]. Furthermore, weight loss maintenance is challenging, limiting long-term results. This weight gain is attributed to the challenges of maintaining a hypocaloric diet in an environment of overabundance and easy access to high-energy, palatable food options.

Consequently, it is essential to define which dietary components are most likely to induce NAFLD, allowing for the targeted increase in the availability of resources and programs to assist patients with long-term weight loss maintenance and achieving success. In NAFLD patients with more advanced liver disease stages and those with high genetic risk or T2DM, pharmacological treatment might be necessary to intensify lifestyle interventions. However, for the time being, there is no approved drug for the treatment of NAFLD.

2.1. Lifestyle Modification in NAFLD

Weight loss in NAFLD is effective in improving liver disease severity. A recent meta-analysis has evaluated the effect of weight loss on NAFLD-related biomarkers from 22 clinical trials (2588 combined subjects) using various interventions, including behavioral weight loss programs (15 studies), pharmacological (6 studies), and surgical procedures (1 research) [52]. Results were compared to a lower-intensity weight loss intervention. In patients with NAFLD, weight loss (median –3.61 kg) achieved within the 6-month program was associated with significant improvements in ALT levels, liver steatosis, histologic NAFLD activity score, liver stiffness, and the disappearance of NASH. However, there was no significant effect on liver fibrosis score [52].

Most studies relating to the association of weight loss with NAFLD have focused exclusively on NASH, possibly due to the importance of NASH in developing adverse clinical outcomes, such as cirrhosis. For example, a

randomized controlled trial by Wong *et al.* (2013) in a group of 154 NAFLD patients compared the effect of a dietitian-led lifestyle modification program for 12 months linked to a standard care protocol that included physician follow-up on remission of NAFLD. Remission was defined as a reduction in IHTG content to less than 5%. Findings indicated that a 10% weight reduction leads to remission of NAFLD in 97% of the patients, compared to only 13% in patients who lost less than 3% body weight [53]. Another study examining the effect of the drug orlistat in patients with NASH found that at least a 5% weight reduction was required to improve the NASH activity score (NAS), liver fat content, and insulin sensitivity compared to those who did not lose weight [54]. Vilar-Gomez and colleagues studied the effect of a 52-week weight loss program in 293 patients on histological features of NASH [55]. They compared before and after liver biopsy results and demonstrated that the degree of weight loss was independently associated with improvements in all NASH-related histological parameters. In their study, 90% of patients who lost ≥ 10% of body weight had a resolution of NASH, and 45% had liver fibrosis regression; however, only 10% of study participants achieved a 10% weight loss [55]. The beneficial effects of weight loss on NASH-related liver parameters were still significant even with a 5% to 10% weight loss, and 30% of participants achieved this degree of weight loss [55].

2.2. The Effect of Exercise on NAFLD

Physical activity has numerous beneficial effects on MetS. Increasing physical activity reduces IHTG content and markers of hepatocellular injury in patients with NAFLD, independent of weight loss [56]. A systematic review and meta-analysis from 17 studies on the impact of structured exercise training, and associated weight loss, on IHTGs in individuals with NAFLD, showed that exercise reduced IHTG levels independent of significant weight change. However, the benefits achieved were substantially more significant when weight loss occurred [57]. The guidelines from the European Associations for the Study of the Liver (EASL), Diabetes (EASD), and Obesity (EASO) recommend 150 to 200 min/week of moderate-intensity aerobic physical activity for NAFLD patients, in three to five sessions [58]. Moderate-intensity physical activity requires a moderate effort and noticeably accelerates the heart rate and breathing without being out of breath [59]. Examples include brisk walking, dancing, sports activities, resistance training, and household activities that increase the heart rate [59]. Vigorous activities, for comparison, get the heart pounding and make breathing very fast. Examples include bicycling up a hill, fast swimming, and exercise classes [59].

Since most clinical trials in NAFLD have focused on the effects of a combined physical activity and therapeutic diet approach in NAFLD, studies focusing on physical activity alone are less common. In a physical activity-only systematic review of 28 randomized clinical trials in a combined total of 1644 participants, increased physical activity was associated with a significant reduction in liver fat content and serum aminotransferase levels, a significant decrease in BMI, and improved peripheral insulin sensitivity [60]. The effect of physical activity on hepatic liver fat content was more prominent in young patients and patients with a higher baseline body mass index [60]. In line with these findings, a clinical trial by van der Heijden [61] also showed that a 12-week controlled moderate-intensity physical activity program without weight loss resulted in a significant decrease in hepatic fat content and visceral fat content. However, IR decreased only in obese adolescents and not in lean adolescents. Considering the difficulty obese patients have in losing weight on a hypocaloric diet and the independent benefits of physical

activity, setting realistic goals for increasing moderate-intensity activity provides another option for patients with NAFLD.

Regarding the optimal type of physical activity training (aerobic vs. resistance), a systematic review and meta-analysis of 12 randomized clinical trials (13 aerobic and 4 resistance exercise protocols) showed that both aerobic and resistance exercise improve hepatic steatosis [62] and also significantly improve NAFLD [56].

2.3. The Effect of Diet on NAFLD

Long-term adoption of a low-calorie diet is associated with decreased liver fat and improved cardiovascular risk [63]. Reducing caloric intake by at least 30% (or approximately 750 to 1000 kcal/day) improved IR and fatty liver. However, as discussed previously, the sustainability of such hypocaloric diets is low. The multifactorial origin of NAFLD and NASH has led to management strategies that incorporate dietary interventions to tackle the multiple hits occurring during the onset and evolution of this disease. For example, dietary patterns that reduce the intake of high glycemic index foods, increase dietary fiber and resistant starch, reduce saturated fat, and promote monounsaturated FA (MUFA) and polyunsaturated FA (PUFA) intake may have a positive effect on gut microbiota composition and function, intestinal barrier function, and IHTG accumulation.

Dietary patterns that leverage the above-described principles may reduce NASH development, possibly even in the absence of weight loss. The four most common dietary patterns include the low-carbohydrate diet, the low-fat diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and the Mediterranean (MD) diet.

Low-carbohydrate diets are diets in which less than 40% of calories are from carbohydrates [64]. NAFLD patients receiving low-carbohydrate diets had a significant weight loss only in the short term (6 months) than those consuming a conventional high-carbohydrate/low-fat diet. Still, at one year, no difference in weight loss was observed [64]. Subjects on low-carbohydrate diets show improvements in biochemical parameters of MetS in comparison with those on high-carbohydrate diets. However, adherence rates to low-carbohydrate diets in the long term are poor [65].

The low-fat diet limits fat intake to 30%, with 50% of calories coming from carbohydrates and 20% from protein, and includes a restricted intake of trans-fat, saturated fat, and cholesterol (no more than 300 mg/day) [66][67]. Low-fat diets are intended to reduce conditions such as heart disease and obesity [68]. In NAFLD, the comparison of low-fat and low-carbohydrate diets has demonstrated inconclusive results. For example, when prescribed to overweight people, both diets are equally effective for weight loss [69]. In contrast, one study in patients with NAFLD in Korea showed greater efficacy for a low-carbohydrate diet in reducing total energy intake and hepatic fat content [70]. The authors explained their findings based on low-fat energy consumption as part of the habitual diet, with less than 20% of calories from fat [70]. It is important to note that low-fat diets generally do not distinguish between the type of dietary fat consumed. Whether saturated, monounsaturated, or polyunsaturated, all fats are treated similarly, although the biological effects likely differ.

The DASH diet was first introduced to manage hypertension and focused on lowering energy-dense food items and decreasing total fat, saturated fat, and cholesterol. This dietary pattern is low in added sugars, sugar-sweetened beverages, and red and processed meats and is enriched in vegetables, fruits, low-fat dairy products, whole grains, poultry, fish, and nuts [66]. It is rich in potassium, magnesium, calcium, and protein, and fiber [66]. The DASH dietary pattern is associated with a reduced risk of cardiovascular disease [71]. In a randomized controlled clinical trial including 60 overweight or obese adults with NAFLD diagnosed by ultrasonography, adherence to the DASH diet for eight weeks, compared to a contemporary control diet, was significantly more effective in reducing weight and improving liver enzymes, markers of IR, serum TGs, and VLDL levels [72]. A cross-sectional study in 3051 subjects between the ages of 40 and 75 showed that adherence to the DASH diet was independently associated with a significantly lower prevalence of NAFLD [73]. The DASH diet has been demonstrated to improve blood pressure and hyperlipidemia, translating to protective effects in NAFLD [74]. Nevertheless, despite the benefits of the DASH diet for T2DM and cardiovascular disease [71], the evidence for its efficacy in NAFLD is limited.

The MD diet has been recommended for NAFLD treatment by various clinical practice guidelines [75]. It has the most significant evidence to prevent and manage MetS and its components, particularly T2DM and CVD [76]. In the MD diet, high consumption of extra-virgin olive oil, vegetables (especially root and green varieties), fruits (fresh in particular), whole grains (cereals, bread, rice, or pasta), legumes, nuts (walnuts, hazelnuts, or almonds), and moderate consumption of fish (especially fatty fish rich in omega-3 FAs), low-fat dairy products, and red wine is recommended over the consumption of red and processed meat, processed and high-sugar food, refined carbohydrates and high-fat milk products [66]. The MD diet has a higher fat content (about 40% of total calories), is low in saturated fat (less than 10% of total calories), high in MUFA and omega-3 PUFA, with a decreased omega-6 PUFA content, and high in fiber (25 and 35 g/day for women and men, respectively) [66]. Substantial evidence supports the benefits of the MD diet in controlling body weight, fasting plasma glucose, serum TG, and blood pressure [71]. Recently, Kaliora *et al.* studied the effect of the MD diet on clinical, biochemical, and inflammatory profiles in patients with simple NAFLD. Untreated NAFLD patients with no significant fibrosis (n = 44) underwent a 24-week diet intervention after nutritional counseling to increase adherence to the MD diet. Commitment to the diet was associated with significant improvements in liver imaging, liver fibrosis score, blood pressure, fasting glucose, hemoglobin A1C, and several other biomarkers compared with pre-intervention values [77]. In another study, 278 participants with abdominal obesity/dyslipidemia were randomly assigned to either a low fat (LF) or Mediterranean/low-carbohydrate (MD/LC + 28 g walnuts/day) diet for 18-months [78]. The MD/LC diet induced a more significant reduction in hepatic fat content than the LF diet, which reached statistical significance after 18 months (–4.2% vs. –3.8%, p = 0.04). Interestingly, the advantageous effect of the MD/LC diet in reducing hepatic fat content compared to that obtained with the LF diet was significant in both patients without NAFLD (hepatic fat content ≤5%, p = 0.04) and in NAFLD patients (hepatic fat content >5%, p = 0.014). Compared to the LF diet, the MD/LC diet induced a more significant increase in HDL and a greater decrease in blood pressure, triglycerides, and triglyceride/HDL ratio [78].

2.4. Surgical and Pharmacological Treatment of NAFLD

Bariatric surgery has been used to control obesity and consequently treat NAFLD. Significant improvement in the prevalence and severity of fatty liver occurs following bariatric surgery, although its benefits and safety in patients with NASH have yet to be established [79].

Since IR has been implicated in the pathogenesis of NAFLD, insulin-sensitizing agents have been investigated, with most studies examining the use of metformin and pioglitazone. Metformin is a biguanide drug that works through different mechanisms to lower blood glucose levels, including reducing postprandial and fasting glucose levels and inhibiting hepatic and renal gluconeogenesis [80]. In contrast, pioglitazone is a thiazolidinedione that inhibits hepatic gluconeogenesis and enhances glucose uptake in muscles and adipose tissue by activating peroxisome proliferator-activated receptor gamma (PPARγ) [45]. A systematic review and meta-analysis on these two medications' efficacy in NASH patients demonstrated that metformin (*n* = 81 patients) did not significantly improve liver histology scores for steatosis, ballooning, or fibrosis. At the same time, it significantly worsened lobular inflammation [81]. On the other hand, pioglitazone improved steatosis and lobular inflammation but did not improve fibrosis [81]. Considering the recognized role of inflammation and oxidative stress in the pathogenesis of NASH, vitamin E, an antioxidant, has been studied as a treatment option in NASH. Although the results indicated that while a daily dose of 800 to 1000 IU did not improve fibrosis, it significantly improved histologic scores, lobular inflammation, and ballooning in non-diabetic adults with biopsy-proven NASH [81]. However, additional data is required to show that vitamin E is beneficial in other groups of NAFLD patients [63]. While many new drugs are being investigated in NASH clinical trials, these pharmacological treatments are currently limited to patients with biopsy-proven NASH in the context of clinical trials [2].

3. Conclusion

NAFLD is considered the hepatic manifestation of MetS and is a rising epidemic worldwide. It will be the leading cause of cirrhosis, HCC, and liver transplant within the next decade. Since currently there are no curative medical therapies available, lifestyle modifications, including dietary changes and exercise, aimed at weight loss remain the only effective therapy for NAFLD. With the evaluation of multiple diets, including the low-carbohydrate, the low-fat, the DASH, and the MD diets, it seems that NAFLD patients have shown better outcomes with a modified diet, such as the MD diet, where patients are encouraged to increase the consumption of fruits and vegetables, whole grains, and olive oil. Such dietary recommendations would be accompanied by three to five sessions of 30-45 min of moderate-intensity activity in a week.

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