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Management of Non-alcoholic Fatty Liver Disease in Adults: An update

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1. Abstract

Non-Alcoholic Fatty Liver Disease (NAFLD) is an extensive term which covers a spectrum of conditions that are characterized by evidence of hepatic steatosis on imaging or histology (macro-vesicular steatosis), and absence of secondary causes of hepatic steatosis such as significant alcohol consumption, chronic use of medications that can cause hepatic steatosis or hereditary disorders. This review article gives a comprehensive and updated review on the management of Non-alcoholic fatty liver disease in the light of latest standard guidelines.

2. Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is characterised by excessive hepatic fat accumulation, associated with Insulin Resistance (IR), and defined by the presence of steatosis in >5% of hepatocytes according to histological analysis or by a proton density fat fraction (PDFF, providing a rough estimation of the volume fraction of fatty material in the liver) >5.6% assessed by proton Magnetic Resonance Spectroscopy (1H-MRS) or quantitative fat/water selective magnetic resonance imaging (MRI) [1]. NAFLD refers to the presence of hepatic steatosis in absence of any secondary cause for hepatic fat accumulation like significant alcohol consumption, chronic use of medications that can cause hepatic steatosis or hereditary disorders. NAFLD may progress to cirrhosis and is likely an important cause of cryptogenic cirrhosis [2-5]. Non-alcoholic fatty liver disease is most often diagnosed incidentally or when it presents with complications. Around 20 to 30% pf population in western countries is affected with NAFLD [6].

NAFLD can develop through multiple stages, including simple steatosis, steatohepatitis, fibrosis, cirrhosis, and eventually hepatocellular cancer. When the only histological result is steatosis, the illness has a benign course and is referred to as a silent liver disease. Non-alcoholic steatohepatitis is defined as hepatic damage along with inflammation (with or without fibrosis) (NASH) [6-7]. This paper will review the management of non-alcoholic fatty liver disease.

2.1. Management of Non-alcoholic Fatty Liver disease

NAFLD management principles have been defined in a number of clinical guidelines or position papers endorsed by either scientific bodies or expert panels [1, 12, 23]. All of these documents agree that lifestyle changes are still the most effective way to manage NAFLD and should be used in all patients. According to the data, one of the nutrition types to be advised is the Mediterranean diet, which is connected with caloric restriction aimed at achieving a 7–10 percent drop of basal body weight [24]. Following measures are recommended for all patients with NAFLD.

1. Alcohol abstinence: excessive alcohol consumption is associated with disease progression [8]. Compared to abstainers, individuals with light-to-moderate alcohol consumption (70-210 g/week) had a higher risk of diabetes in a recent study focusing on NAFLD patients. As a result, patients with NASH or significant liver fibrosis should be counselled not to drink alcohol and in particular avoid heavy alcohol use (ie, >14 drinks per week or >4 drinks on a given day for men and >7 drinks per week or >3 drinks on a given day for women). In patients without substantial hepatic fibrosis, however, based on new evidence, just light alcohol use (10 g/day) may be authorised, as long as they are closely monitored. This recommendation is based on the fact that no study has shown that light alcohol use causes considerable harm, whereas several studies have shown significant benefits [9].

2. Modify risk factors for Cardiovascular Disease (CVD): Patients with NAFLD are at an increased risk of cardiovascular dis-

ease and frequently have numerous risk factors (eg, hypertension, hyperlipidemia). NAFLD has a greater prevalence and incidence of CVD than matched controls, which is due to the association between NAFLD and Metabolic syndrome components [10, 11]. CVD is a more common cause of death than liver disease in NAFLD (11). The routine evaluation of cardiovascular disease and its risk factors is imperative in patients with NAFLD, since cardiovascular events are additional risk factors of morbidity and mortality [12, 13]. NAFLD is a risk factor for atherosclerosis, hence assessing and treating dyslipidemia, when needed, should be a therapeutic goal for these patients [12, 14]. It's important to emphasize that statins can be used safely in these people, and that not taking them can lead to more harm [12, 15]. NASH is also linked to arterial hypertension [16]. As a result, in the initial evaluation of patients with arterial hypertension, the degree of liver illness should be considered [12].

3. Weight loss: Weight loss is the primary treatment for NAFLD patients. It is advised for all patients with NAFLD who are overweight (BMI >25 kg/m) or obese (BMI >30 kg/m) to lose weight since weight loss can improve liver biochemical testing, liver histology, serum insulin levels, and quality of life in individuals with NAFLD [17-19] EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease recommends a structured programmes targeted at lifestyle changes such as a nutritious diet and regular physical activity and suggests a goal of 7-10% weight loss for overweight/obese NAFLD patients. Energy restriction and the avoidance of NAFLD-promoting components (processed foods and foods and beverages high in added fructose) should be part of dietary guidelines. It also recommends three to five sessions of 150-200 minutes of moderate-intensity aerobic physical activity per week for NAFLD patients [1]. The low-carbohydrate diet, low-fat diet, Dietary Approaches to Stop Hypertension (DASH) diet, and the Mediterranean diet are the four most frequent dietary patterns [20]. Patients with NAFLD have been shown to benefit from increased physical activity in terms of survival [21, 22]. Longer duration of physical activity (measured by accelerometers) was linked to a lower risk of all-cause mortality during an average follow-up of nearly 11 years in a longitudinal study of 2793 people with NAFLD (adjusted hazard ratio [aHR] 0.46, 95 percent confidence interval [CI] 0.28-0.75) [22].

4. Medications: For the treatment of patients with NASH, pharmacologic treatments have been investigated. Most trials, however, have been too short to determine an influence on crucial patient-centred clinical outcomes (e.g., decompensated cirrhosis), and instead report on surrogate outcomes, such as serum aminotransferase levels or histologic findings, with often contradictory results [25]. The treatment of NAFLD should include the treatment of both the liver disease and the metabolic comorbidities such as obesity, hyperlipidemia, insulin resistance, and T2DM. Because people with NAFLD who do not have steatohepatitis or any fibrosis have a good prognosis for their liver [23]. Drug therapy should be considered for both progressing NASH (bridging fibrosis and cirrhosis) and early-stage NASH with a high risk of fibrosis advancement (age >50 years; diabetes, MetS, elevated ALT, or active NASH with high necro inflammatory activity). Currently, no medicine has been studied in phase III trials and has been approved by regulatory organisations for NASH. As a result, no specific therapy can be strongly advised, and any medication treatment would be considered off-label [1].

3. Insulin Sensitisers

3.1. Metformin: Metformin's histopathological efficacy in NASH is not well established [1, 23, 26-28]. Metformin has a limited effect on liver fat because it is unable to restore serum adiponectin levels in the short term [29]. Some preclinical findings suggest that metformin has an anti-tumorigenic effect on liver cancer, although evidence of lower HCC rates in humans is restricted to retrospective studies and insufficient for evidence-based recommendations [1]. According to two published meta-analyses [30-31], metformin therapy did not improve liver histology in patients with NAFLD and NASH. AASLD and European practice guidelines do not recommend metformin for the treatment of NASH in adults.

3.2. Pioglitazone: Pioglitazone belongs to the thiazolidinedione class of antidiabetic drugs and is a peroxisome proliferator-activated receptor (PPAR)γ agonists with insulin-sensitising efficacy. pioglitazone improves insulin sensitivity and decreases free fatty acid delivery to the liver [32]. Thiazolidinediones' potential to reverse adipose tissue malfunction and IR in obesity and T2DM has prompted RCTs to investigate their relevance in NASH [33]. Cusi et al. treated 101 patients with biopsy-proven NASH who had either prediabetes (n = 49) or T2DM (n = 52) for 18 months with a hypocaloric diet (a 500-kcal/day deficit from weight-maintaining caloric intake) and pioglitazone (45 mg/day) or placebo, followed by an 18-month open-label phase with pioglitazone medication [34]. The primary result was a 2-point reduction in the NAS (in two different histological categories) without fibrosis worsening. Steatosis, inflammation, and ballooning all improved significantly following treatment, with 58 percent of patients in the pioglitazone group meeting the primary endpoint (reduction of ≥ 2 NAS points) after 18 months. Patients with proven NASH at baseline showed considerably more benefit, with 67 percent attaining the primary endpoint (P 0.001 vs. placebo for each). Over the course of 18 months, there was evidence of a reduction in fibrosis advancement in patients treated with pioglitazone compared to those treated with placebo (12% vs. 28 %) (P = 0.039). Metabolic and histological improvements continued over 36 months of therapy [34]. In the Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Non-alcoholic Steatohepatitis (PIVENS) trial, a large, multicentre RCT in nondiabetic patients with NASH, 247 patients were randomised to pioglitazone (30 mg/day), vitamin E (800 IU/day), or placebo for 24 months. The primary outcome was a 2-point improvement in NAS with at least 1-point improvement in hepatocellular ballooning and 1-point improvement in either the lobular inflammation or steatosis

score, but no change in the fibrosis score. In the placebo group, 19% achieved this, compared to 34 percent in the pioglitazone group (P= 0.04 vs. placebo) and 43 percent in the vitamin E group (P =0.001 vs. placebo). A P value of 0.025 was considered significant a priori because this trial had two principal comparisons (pioglitazone vs. placebo and vitamin E vs. placebo). As a result, despite the fact that pioglitazone had histological advantages, this trial determined that it did not fulfil the primary goal [35]. However, resolution of NASH, a critical secondary endpoint, was accomplished in a significantly higher percentage of pioglitazone-treated patients than in placebo-treated individuals (47 percent vs. 21 percent; P 0.001). Vitamin E and pioglitazone were well tolerated, and no other side effects were seen [35]. In 74 patients with NASH, Aithal et al. conducted a 12-month RCT with either pioglitazone 30 mg/day or placebo. Hepatocellular damage was reduced by 32 percent vs. 10% and fibrosis was reduced by 29 percent vs. 20% (p = 0.05), respectively, when pioglitazone was compared to placebo. Although steatosis did not improve considerably when compared to placebo, hepatocellular damage and fibrosis were dramatically reduced [36].

AASLD guidance states that in individuals with and without T2DM who have biopsy-proven NASH, pioglitazone improves liver histology. Therefore, it may be used to treat these patients. Risks and benefits should be discussed with each patient before starting therapy. Until further data support its safety and efficacy, pioglitazone should not be used to treat NAFLD without biopsy-proven NASH [23].

4. Glucagon-Like Peptide-1 Analogues

Liraglutide-An end-of-treatment biopsy was conducted in 23 patients in the liraglutide arm and 22 patients in the placebo arm of a recent study that included 52 patients with NASH who were randomly allocated to receive liraglutide or placebo for 48 weeks. NASH was resolved in nine of the liraglutide-treated patients (39%) and two of the placebo-treated individuals (9%). (RR 4.3; 95 percent CI 1.0-17). In terms of fibrosis progression, those who took liraglutide had a lower risk of fibrosis advancement (9 versus 36 percent; RR 0.2; 95 percent CI 0.1-1.0) [37].

Semaglutide-After 72 weeks, Semaglutide (0.4 mg once daily) resulted in better rates of histologic remission of NASH than placebo in a phase 2 study involving 320 patients with biopsy-proven NASH and liver fibrosis of stage F1, F2, or F3 (59 versus 17 percent; OR 6.87, 95 percent CI 2.60-17.63) [38]. AASLD guidance statement considers GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH as premature [23].

4.1. Vitamin E

Oxidative stress is thought to be a critical factor in hepatic damage and disease development in people with NASH. Vitamin E is an antioxidant that has been studied as a NASH therapy [39, 40]. Vitamin E use is linked to a reduction in aminotransferases in NASH patients, and studies with histological endpoints show that vitamin E improves steatosis, inflammation, and ballooning, as well as the resolution of steatohepatitis, in a proportion of nondiabetic adults with NASH. Vitamin E had no effect on hepatic fibrosis [23]. The pure form of rrr α-tocopherol was orally administered at a dosage of 800 IU/day for 96 weeks in the PIVENS clinical trial [35]. The main endpoint was met in a considerably higher percentage of vitamin E-treated participants than in placebo-treated participants (42 % vs. 19 %; P< 0.001, number needed to treat = 4.4). The Treatment of Non-alcoholic Fatty Liver Disease in Children trial (TONIC), which compared vitamin E (800 IU/day) or metformin (500 mg twice-daily) to placebo in children with biopsy-proven NAFLD, found that children treated with vitamin E had significantly more NASH resolution than children treated with placebo (58 percent vs. 28 percent; P = 0.006) [41]. Vitamin E has been shown to provide substantial histological advantages in patients with NASH in two recent meta-analyses [42, 43].

There are still questions regarding vitamin E's long-term safety. A meta-analysis found that dosages of >800 IU/day were linked to an elevated risk of all-cause death. However, this meta-analysis has been questioned since some trials with low mortality were eliminated, and common characteristics such as smoking, as well as simultaneous vitamin A and other medication administration, were not taken into account [23, 44]. A major meta-analysis of 57 trials and 246,371 patients followed for one to ten years found no link between vitamin E supplementation and all-cause death [45]. Vitamin E at a dose of 400 IU/day was unexpectedly and unexplainably linked to a modest increase in the risk of prostate cancer (absolute increase of 1.6 per 1,000 person-years of vitamin E use) in a large RCT published in 2011 [46], and this risk may be influenced by baseline selenium levels or genetic variants associated with vitamin metabolism [23].

5. Bariatric Surgery

Bariatric surgery is an option for lowering weight and metabolic problems in individuals who have not responded to lifestyle modifications or medication, with long-term outcomes that are stable [1, 23]. At one year after bariatric surgery, 189 patients with biopsy-proven NASH received a follow-up liver biopsy. In 85 percent of cases, NASH was resolved [47]. Although the long-term advantages of bariatric surgery are uncertain, a 10-year post-bariatric follow-up research found that hepatic steatosis, inflammation, and fibrosis all improved [48]. Weight reduction that lasts is tough to attain and much more difficult to maintain. In most individuals, bariatric surgery improves or eliminates concomitant illness, as well as long-term survival and mortality from cardiovascular disease and cancer, the two leading causes of death in people with NAFLD [23].

6. Ursodeoxycholic Acid, Omega-3 Fatty Acids

Ursodeoxycholic acid (UDCA) has been studied in multiple Randomised Controlled Trials (RCTs) at various dosages and for up to two years, although it only showed some biochemical but no histological changes [49-51]. UDCA had no histological effect over placebo in individuals with NASH, according to a single large, multicenter

RCT [52]. Omega-3 fatty acids have been shown to be beneficial in people with NAFLD in studies [53, 54]. Treatment with omega-3 fatty acids was linked to improvements in hepatic steatosis and aspartate aminotransferase levels in a meta-analysis of nine trials with 355 participants [54]. However, two recent trials have found that omega-3 fatty acids do not provide a convincing therapeutic advantage in individuals with NAFLD or NASH [53, 55].

6.1. Obeticholic Acid

Obeticholic Acid (OCA) is the NASH medicine that is the farthest advanced in the research pipeline. It's a synthetic version of chenodeoxycholic acid that's a strong farnesoid X receptor activator (FXR). OCA is FDA authorised for the treatment of Primary Biliary Cholangitis (PBC) and is often used as a second-line medication. In the phase 2b FLINT study, OCA was first tested in individuals with non-cirrhotic NASH. Patients were given either OCA 25 mg or placebo every day for 72 weeks and had matched liver biopsies. NASH resolution occurred in 22% of OCA-treated individuals versus 13% of placebo-treated patients. Thirty-five percent of OCA patients improved their fibrosis, compared to 19 percent of placebo patients. However, there was an increase in serum LDL cholesterol and a higher incidence of pruritus in the OCA group [56]. Following that, OCA was evaluated in a comparable cohort of NASH patients with fibrosis in the phase 3 REGENERATE experiment. In the intent to treat group, OCA 25 mg resulted in statistically significant improvements in fibrosis in 23.1 percent of treated patients vs. 11.9 percent of placebo patients, according to an 18-month interim study. The endpoint for NASH resolution was not fulfilled [57]. The FDA accepted a new medication application for fast approval of OCA in November 2019 [58]. The FDA, however, issued a Complete Response Letter (CRL) on June 29, 2020, stating that the value of OCA was still unknown, that the possible hazards outweighed the benefits, and that further effectiveness and safety data were needed. Nevertheless, experts agreed Intercept's new analysis gives OCA a clean slate in NASH. Intercept's efficacy analysis with study samples from a total of 1,700 REGENERATE patients, including an additional 500 patients who were not a part of the interim analysis. These additional patients had yet to reach the 18-month data time point when the interim analysis was done. A presubmission meeting with the FDA is expected the first half of 2022. (Intercept NASH drug faces uphill battle if approved by FDA (clinicaltrialsarena.com)). OCA is also currently being studied in compensated cirrhotic populations in the phase 3 REVERSE trial (NCT03439254) which is a randomized, double-blind, placebo-controlled, multicenter trial. It is evaluating the safety and efficacy of OCA in NASH patients with compensated cirrhosis. The top line data from phase 3 REVERSE trial is also expected in first quarter of 2022. (Intercept Pharmaceuticals Provides Update on Phase 3 REVERSE Trial in Compensated Cirrhosis Due to NASH - Intercept Pharmaceuticals, Inc.) Though approval of this medicine will be welcomed for this much needed treatment, the adverse effect profile may be prohibitive, and it will almost certainly need to be used in conjunction with other treatments in the future.

7. Conclusion and Recommendations:

- American Association for the Study of Liver Diseases practice guideline and 2016 EASL–EASD–EASO Clinical Practice Guideline suggest a combination of a hypocaloric diet (daily reduction by 500-1,000 kcal) to induce a weight loss of 500–1000 g/week and moderate-intensity exercise that is likely to provide the best likelihood of sustaining weight loss over time. Weight loss of at least 3%-5% of body weight appears necessary to improve steatosis, but a greater weight loss (7%-10%) is needed to improve the majority of the histopathological features of NASH, including fibrosis. Alcohol consumption below the risk of threshold (30 g in men and 20 g in women) is recommended.
- No guideline recommends the use of metformin for the management of NAFLD in adults.
- As Pioglitazone improves liver histology in patients with and without T2DM with biopsy-proven NASH. Guidelines therefore recommend it to be used to treat these patients.
- It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH according to AASLD practice guideline.
- Guidelines recommend the use of Vitamin E (rrr α-tocopherol) administered at a daily dose of 800 IU/day to treat NAFLD in non-diabetic adults with biopsy proven NASH, as it improves liver histology in these patients. However, it is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.
- AASLD suggests Foregut bariatric surgery to be considered in otherwise eligible obese individuals with NAFLD or NASH. However, guidelines consider it premature as an established option to specifically treat NASH
- UCDA is not recommended for the treatment of NAFLD or NASH. Omega-3 fatty acids should not be used as a specific treatment of NAFLD or NASH, but they may be considered to treat hypertriglyceridemia in patients with NAFLD.
- Guidelines suggest consideration of aggressive modification of CVD risk factors in all patients with NAFLD, as patients with NAFLD are at high risk for cardiovascular morbidity and mortality.
- Patients with NAFLD or NASH are not at higher risk for serious liver injury from statins. Thus, statins can be used to treat dyslipidemia in patients with NAFLD and NASH. While statins may be used in patients with NASH cirrhosis, they should be avoided in patients with decompensated cirrhosis.

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