Non-alcoholic fatty liver disease: current treatment in 2021

Authors: Avik Majumdar[1,2], Jef Verbeek[3,4], Emmanuel A. Tsochatzis[5,6]

1.   AW Morrow Gastroenterology and Liver Centre, Australian National Liver Transplant Unit, Royal Prince Alfred Hospital, Sydney, Australia
2.   Central Clinical School, The University of Sydney, Australia
3.   Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium
4.   Laboratory of Hepatology, Department of Chronic Diseases and Metabolism (CHROMETA), KU Leuven, Leuven, Belgium
5.   UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, UK
6.   Sheila Sherlock Liver Centre, Royal Free Hospital, London, UK

Corresponding Author:
Prof Emmanuel A. Tsochatzis
Royal Free Hospital
Pond St, Hampstead
London NW32QG
United Kingdom
Email: e.tsochatzis@ucl.ac.uk
Tel: +44 2074332784

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AM – manuscript preparation, study concept
JV – critical review
EAT – manuscript preparation and critical review, study concept

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease and has an estimated global prevalence of 25%. NAFLD is found in up to 80% of people with obesity and over 60% of patients with diabetes. Cardiovascular disease is the main cause of mortality, followed by extra-hepatic cancers and then liver-specific complications of cirrhosis and hepatocellular carcinoma. Lifestyle modification remains the primary intervention in NAFLD. Weight loss achieved through dietary modification and exercise can lead to histologic improvement and reversal of metabolic complications. Current drug therapy is limited to pioglitazone and vitamin E, however, several agents are currently under phase III development. This review summarises the current treatment options in NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined by the presence of more than 5% liver steatosis in the absence of excess alcohol consumption or other co-existent causes of hepatic steatogenesis. NAFLD is sub-classified into simple steatosis without hepatocellular damage (NAFL, non-alcoholic fatty liver) or non-alcoholic steatohepatitis (NASH). NASH is characterised by histologic evidence of hepatocellular injury and inflammation with or without fibrosis[1]. Advanced liver fibrosis is the most consistent histologic predictor of clinical outcomes in patients with NAFLD[2-4]. Obesity and other metabolic complications are inextricably linked, with NAFLD found in up to 80% of people with obesity and over 60% of those with diabetes[5, 6]. Recently, the term Metabolic Associated Fatty Liver Disease (MAFLD) has been proposed to replace NAFLD with the aim of more accurate pathophysiological characterisation, but is not yet universally accepted[7-9].

NAFLD is now the most common cause of chronic liver disease, with an estimated global prevalence of 25%[10]. The prevalence of NASH is less clear due to the requirement of liver biopsy for diagnosis. However, it is estimated to range between 1.5% and 6.5% in the general population and approximately 25% in those with NAFLD[11, 12]. NAFLD incidence varies from 28 per 1000 person-years in Western populations to 52 per 1000 person-years in Asia[10, 13]. In line with the global obesity epidemic, both the prevalence and incidence of NAFLD are both rising. Moreover, NAFLD is the fastest rising indication for liver transplantation (LT) according to transplant registry data from the US[14], Europe[15] and Australia and New Zealand[16]. Indeed, a recent US study has confirmed that NAFLD is now the leading indication for LT in females and is only second to alcohol related liver disease in males[17]. NAFLD is projected to become the leading indication overall for LT in the US within the next decade[18].

Cardiovascular disease is the main cause of mortality in NAFLD, followed by extra-hepatic cancers and then the liver-specific complications of cirrhosis and hepatocellular carcinoma (HCC), which occur in the context of NASH[19-21]. Indeed, NAFLD is independently associated with additional cardiovascular risk beyond that of traditional risk factors[22, 23] and it is estimated that the risk of cancer is approximately 1.9 times that of the general population[24]. Potential pathophysiological mechanisms

for this increased risk include contributions of the diseased liver to increased endothelial dysfunction, structural alterations of the arterial wall, increased oxidative stress, alterations in the lipid profile, low grade systemic inflammation and alterations in angiogenesis and haemostasis. The complications of cirrhosis or HCC are thought to develop in less than 10% of NAFLD patients, however the burden of disease is significant due to the high prevalence of disease[3]. In light of this, the recognition of the current and projected impacts of NAFLD has catalysed the development of potential therapeutic agents, however none have yet achieved US FDA (Food and Drug Administration) or EMA (European Medicines Agency) approval. This review summarises the current treatment options for NAFLD, including post LT.

Lifestyle modification

Lifestyle modification remains the main first-line intervention in NAFLD and should be recommended to all patients (Table 1). Weight loss through dietary modification and exercise can reverse NAFLD disease progression by reducing hepatic steatosis and NASH[25]. Moreover, weight loss reduces the risk of developing cardiovascular disease and diabetes mellitus[26, 27]. The amount of weight loss also impacts outcomes. A 5% or more reduction of total body weight (TBW) results in a reduction in liver fat, a 7% or more TBW reduction may resolve NASH and 10% TBW reduction may result in stabilisation or regression of liver fibrosis[25, 28, 29]. Based on these data, consensus guidelines have recommended a weight loss target of 5-10% of TBW[11, 30]. A recent analysis of two randomised control trials (RCTs) in NAFLD found that for every kilogram of weight lost, the odds of fibrosis regression increased by 5%[31]. However, the impact of lifestyle modification on clinical outcomes in NAFLD such as death, decompensation, cirrhosis or HCC is unclear according a Cochrane Collaboration meta-analysis of 59 RCTs[32], predominantly due to the short duration of follow-up in the included studies (2 to 24 months).

A recent American Gastroenterological Association (AGA) Clinical Practice Update recommends that four guiding principles should be followed for effective and safe weight loss; assessment, intensive weight-loss intervention, weight stabilisation and prevention of weight regain. Interventions should centre around a reduced calorie diet, exercise, medications and bariatric surgery (or endoscopy), with the latter two reserved for patients with severe obesity, diabetes mellitus or evidence of significant

liver fibrosis[29]. Although the direct additive effects of diet and exercise in NAFLD are not well quantified, combination regimens are suggested to be more effective[33].

Diet

The optimal diet for patients with NAFLD is one that is easily followed in the context of individual eating preferences, with the goal of sustained adherence. Hypocaloric diets can lead to a reduction in liver steatosis and insulin resistance. Moreover, the improvements in steatosis can persist for up to two years after weight loss, even in the context of weight regain[27]. Weight loss is often clinically apparent once calorie intake is reduced by 500-1000 kcal/day from baseline, ideally with a total target intake of approximately 1200 kcal/day for women and 1500 kcal/day for men[11, 29, 30, 34]. The role of very low-calorie diets (eg 800 kcal/day) is not well established in NAFLD, nor is the utility of intermittent fasting or meal replacement schedules. Similarly, the ideal macronutrient composition in diets for NAFLD is not known. Refined sugar intake, particularly fructose in the form of corn syrup and other sweeteners, is associated with the development and severity of NAFLD and should be minimised[35-37]. The consumption of processed and/or red meats has also been linked to insulin resistance and NAFLD[38]. Although several types of diets may be of benefit in NAFLD, the Mediterranean Diet (MD) is the best studied. The MD is largely plant-based, rich in monounsaturated and omega-3 fats, with low levels of dairy and red or processed meat consumption. Randomised control trials have demonstrated that adoption of a MD reduces cardiovascular events as well as hepatic steatosis[39-42]. Additionally, data from one RCT has demonstrated that adherence to the MD is better than an alternative low-fat diet[42].

Population studies have suggested a benefit of coffee consumption in NAFLD, HCC development and other chronic liver disease, presumable due to antioxidant effects[43-45]. However, there are no clinical trial data on coffee drinking and hence coffee cannot be specifically recommended as a therapeutic intervention, but it should not be actively avoided. The influence of alcohol consumption on NAFLD progression is not well quantified from cross-sectional epidemiological studies, however, a recent prospective study of over 8000 patients demonstrated that 10-19g of alcohol per day increased the risk of advanced liver disease, while >30g per day was associated with increased mortality[46]. Alcohol consumption should be avoided in all patients with cirrhosis or

HCC[47]. However, in people with simple steatosis, it remains unclear what level of alcohol consumption is considered safe.

Exercise

Exercise has the predominant impact of reducing hepatic steatosis in NAFLD, which is an effect that appears independent of the degree of weight loss[48]. Liver fat content decreases by improving peripheral insulin sensitivity, reducing de novo hepatic lipogenesis, decreasing lipolysis of adipocytes and, decreasing hepatic free fatty acid delivery[48, 49]. The type of exercise may influence the rate of steatosis reduction, with resistance training suggested to have a slower rate of reduction compared to aerobic exercise. However, all types of exercise (high intensity interval training, aerobic, resistance/strength training) appear to have a beneficial effect in NAFLD[48]. The AGA Clinical Practice Update recommends a target of 75-150 minutes per week of vigorous intensity (>6 metabolic equivalents) aerobic exercise or 150-300 minutes of moderate intensity aerobic exercise (3-6 metabolic equivalents) per week for patients with NAFLD, with resistance training suggested as an adjunct rather than a replacement[29]. These recommendations are similar to consensus NAFLD guidelines from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD)[11, 30].

Bariatric surgery

Bariatric surgery may be considered in the event that lifestyle modification does not achieve the weight loss target of 5-10% of TBW in patients with a body mass index of 40 or greater (or ≥35 and obesity related comorbidities). Indeed, bariatric surgery can achieve durable weight loss of up to 15-25% in appropriately selected candidates[50]. The risks and benefits of surgery must be balanced against an often multimorbid patient group. Sleeve gastrectomy and Roux-en-Y gastric bypass are the preferred procedures. Bariatric surgery has been shown to improve liver histology in terms of NASH and fibrosis as well improve associated metabolic complications of NAFLD and be cost-effective[50, 51]. Potential surgical candidates should be assessed for the presence of cirrhosis and portal hypertension in addition to the standard perioperative assessment of cardiorespiratory factors. Bariatric surgery is not contraindicated in patients with compensated cirrhosis in the absence of portal hypertension. Portal

hypertension or poor baseline liver function, however, are associated with poor outcomes and alternative treatment should be sought[52]. If LT is being considered in patients with advanced liver disease or HCC, concomitant sleeve gastrectomy has been performed with good results, or alternatively, bariatric surgery can be performed 6-12 months after successful LT[53, 54]. Endoscopic bariatric procedures have been explored but NAFLD-specific outcomes, both short and long-term are yet to be comprehensively described.

Pharmacological approach

No approved pharmacotherapy currently exists for the specific treatment of NAFLD. However, several agents targeting diverse mechanisms of disease have been investigated or are currently under investigation in clinical trials. Metabolic comorbidities such as type 2 diabetes (T2DM) and cardiovascular risk factors should be optimally managed with drug therapy as necessary, even if these medications have no specific benefit in NAFLD *per se*, as in the case of statin therapy for dyslipidaemia.

Current pharmacotherapy

PPAR (peroxisome proliferative-activated receptor)-gamma is a nuclear receptor that is mainly expressed in adipose tissue and is involved in the modulation of insulin sensitivity, which is the proposed mechanism of therapeutic agonists in NAFLD. Current EASL and AASLD guidelines suggest that the PPAR -gamma agonist pioglitazone can be considered in patients with biopsy confirmed NASH with or without T2DM[11, 30]. However, the use of pioglitazone for non-diabetic indications may constitute off-label use in many jurisdictions. Pioglitazone at doses of 30-45mg has been shown to improve histologic inflammation and/or fibrosis compared to placebo in several moderate-sized RCTs[55-57]. The PIVENS trial examined pioglitazone 30mg or Vitamin E compared to placebo over 96 weeks and did not find an improvement in NASH, but did demonstrate improvements in lobular inflammation, steatosis and liver biochemistry[57]. In an RCT of 101 pre-diabetic or diabetic patients, pioglitazone 45mg over 36 months was found to resolve NASH in 51% and reduced NASH without worsening fibrosis in 58%, compared to 19% and 17% in the placebo group, respectively (p<0.001 for both comparisons)[56]. These findings were confirmed for both diabetic and non-diabetic patients in a meta-analysis of 392 patients from 5 RCTs, which showed that pioglitazone resolved NASH (odds ratio [OR] 3.51, 95% CI 1.76-

7.01) and improved advanced fibrosis (OR 4.53, CI 1.52-13.52)[58]. Pioglitazone also has additional cardiovascular benefits, which is of particularly importance given that cardiovascular mortality is the primary cause of death in NAFLD[59, 60]. However, weight gain remains a major concern with RCTs reporting up to 4% of TBW, in addition to an increased risk of non-osteoporotic fracture, fluid retention and higher incidence of heart failure in susceptible patients. Furthermore, the long-term effects on mortality and progression to cirrhosis or liver cancer are not yet known.

Vitamin E is thought to be effective in NAFLD primarily due to its antioxidant effect and purported impact on lipid and glucose metabolism in animal models[61]. The use of vitamin E at a dose of 800 U/day is also supported by consensus guidelines in non-diabetic and non-cirrhotic patients with biopsy proven NASH[11, 30]. This is largely based on the PIVENS trial, which found that vitamin E reduced serum liver biochemistry and histologic features of NASH, but not fibrosis, compared to placebo[57]. A recent phase II RCT of patients with T2DM and NASH that randomised patients to 18 months of vitamin E, vitamin E combined with pioglitazone or placebo found that only the combination regimen reached the primary endpoint (reduction of inflammation as measured by NAFLD activity score by 2 points or greater and no worsening of fibrosis)[62]. Neither intervention had any effect on fibrosis. The long-term impacts of vitamin E are not established and the potential adverse effects must be considered before use, including the risk of bleeding[63]. A perceived increase in all-cause mortality due to vitamin E is not supported by the most recent meta-analysis on the topic[64].

Ultimately, the overall quality of evidence for the above therapies appears limited with no phase III studies. A recent Cochrane Collaboration meta-analysis of 41 RCTs of medical interventions in NAFLD up to 2016 found that there was no benefit of any treatment[65]. Moreover, the included studies were assessed to be of low quality due to small sample size, limited follow-up and the reliance on histological surrogates rather than defined clinical endpoints[65]. The authors concluded that clinical endpoints such as mortality or the development of HCC should be used in future trials. However, the FDA decision to approve two histological endpoints (resolution of NASH without fibrosis worsening; improvement of fibrosis of one stage or more without worsening NASH) in an effort to accelerate drug development may confound future trial design.
Emerging pharmacotherapy

The agents currently undergoing phase III trials and are in late stages of drug development are listed in Table 2, with earlier data summarised for these agents below. Cenicriviroc and elafibranor have been recently abandoned after interim analyses demonstrated no benefit compared to placebo in phase III trials. Several drugs are in phase II development either alone or in combination[66]. There are separate registration trials for non-cirrhotic and cirrhotic patients.

Obeticholic acid (OCA), a Farnesoid X receptor (FXR) agonist, is furthest along the drug development pipeline. The initial phase IIb trial of OCA 25mg was terminated after an interim analysis at week 24 of 72, which demonstrated reduction in NAFLD activity score of 2 points or more without worsening fibrosis in the OCA group compared to placebo (relative risk 1.9, 95% CI 1.3 to 2.8; p=0.0002)[67]. A planned interim analysis at 18 months in the phase III REGENERATE trial has suggested that fibrosis improvement occurred in 23% of patients taking OCA 25mg compared to 12% in the placebo group[68].

Resmetirom is a selective agonist of thyroid hormone receptor beta (THR-β), which is involved in liver-specific lipid metabolic pathways and is associated with reduced levels in patients with NAFLD. According to phase IIb data, higher rates of NASH resolution were seen compared to placebo (27.4% versus 6.5%, p=0.02), however fibrosis did not differ between group after 12 weeks[69].

Aramchol inhibits stearoyl coenzyme A desaturase which results in lipid lowering by increasing fatty acid oxidation. Aramchol was found in Phase II data to reduce liver fat concentration on magnetic resonance spectroscopy compared to placebo at doses of 100mg to 300mg daily[70].

Semaglutide is a glucagon-like peptide-1 (GLP-1) agonist that is commonly used in T2DM treatment with the known benefit of weight loss. A phase III obesity trial reported that semaglutide at a dose of 2.4mg (weekly subcutaneous injection) for 68 weeks resulted in a mean reduction in TBW of 14.9% compared to 2.4% in the placebo group[71]. Phase II data in NAFLD patients with F2-F3 fibrosis examined doses between

0.1mg and 0.4mg and found that the endpoint of NASH resolution without fibrosis worsening was achieved in all dosage groups with response ranging from 36% to 59%, compared to 17% in the placebo group[72].

NAFLD after liver transplantation

NAFLD may manifest post LT as either de novo an/or recurrent disease with identified risk factors including weight gain, diabetes, hyperlipidaemia, hypertension and possibly female sex[73-76]. High-dose corticosteroid induction immunosuppression regimens are associated with increased liver steatosis and metabolic syndrome complications post-LT[77]. Steroid-free or steroid-minimisation immunosuppression protocols may be considered[75, 78]. The specific impact of other immunosuppressants such as calcineurin inhibitors on NAFLD and NASH have not been well-studied, as opposed to other metabolic complications[75, 79]. Management of NAFLD post-LT is similar to the pre-LT setting and should focus on active weight loss in obese individuals, weight gain prevention, management of pre-existing metabolic syndrome complications and individualised cardiovascular screening. Minimisation of immunosuppression to prevent metabolic complications should also be considered[75]. Other preventative interventions or specific management (including bariatric surgery) that are of benefit after LT require further investigation[54, 80].

Conclusions

The rapid rise of NAFLD over the past two decades has established it as the most common liver disease. Despite a concomitant evolution of the understanding of the disease process and possible therapeutic targets, lifestyle modification remains the most important intervention. Bariatric surgery is an effective option but only in highly selected individuals in whom lifestyle interventions fail. The currently available pharmacotherapeutic options of pioglitazone and vitamin E do not have a strong evidence base but can be considered according to phase II studies and consensus guidelines. However, several promising drugs are in development and are being investigated in phase III trials. Although the available armamentarium against NAFLD in 2021 is relatively unchanged compared to recent years, new therapeutic options are on the horizon.

Table 1: Summary of lifestyle modification in NAFLD

Modification	Target	Comments
Weight Loss	5-10% of total body weight	• 5% weight loss reduces steatosis • 7% or more loss may resolve NASH • 10% loss may reduce fibrosis • Odds of fibrosis regression is 5% per kilogram of weight lost
Diet	500-1000 kcal/day reduction from baseline	• Aim for 1200 kcal/day total for women, or 1500 kcal/day for men • Avoid fructose and refined sugars • Reduce red/processed meat content • Effect of macronutrient content on NAFLD is not known • Mediterranean diet recommended • Unclear evidence for intermittent fasting or meal replacement diets
Coffee	No restrictions	• No clinical trial data to support benefit for NAFLD • Benefit of coffee has been suggested in epidemiological studies
Alcohol	• Abstinence in patients with cirrhosis or HCC • Limit alcohol in non-cirrhotic NAFLD	• 10-19g/day may increase risk of advanced liver disease • >30g/day associated with increased mortality
Exercise	• 75-150 of mins vigorous intensity exercise per week (>6 metabolic equivalents) • 150-300 mins of moderate intensity per week (3-6 metabolic equivalents)	• Aerobic exercise is preferred • High intensity interval training and resistance training may be less effective

Table 2: Summary of current phase III trials in NAFLD

Drug (dose)	Trial	Primary Endpoint	Patient Population	Study Size (n)	Interim Analysis	Trial Duration
Obeticholic Acid (10mg, 25mg)	REGENERATE (NCT02548351)	≥1 stage fibrosis improvement without NASH worsening or NASH resolution without worsening of fibrosis	Non-cirrhotic NASH F2/F3 fibrosis	2480	18 months	7 years
Resmetirom (80mg, 100mg)	MAESTRO-NASH (NCT03900429)	NASH resolution	Non-cirrhotic NASH F2/F3 fibrosis	2000	After first 900 patients recruited	54 months
Aramchol (300mg BD)	ARMOR (NCT04104321)	≥1 stage fibrosis improvement without NASH worsening or NASH resolution without worsening of fibrosis	Non-cirrhotic NASH F2/F3	2000	52 weeks	5 years
Semaglutide	(NCT04822181)	≥1 stage fibrosis improvement without NASH worsening or NASH resolution without worsening of fibrosis	Non-cirrhotic NASH F2/F3	1200	72 weeks	5 years

Abbreviations; NASH; non-alcoholic fatty liver disease

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