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EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (K. NASIR, SECTION EDITOR)

Comprehensive Review and Updates on Holistic Approach Towards Non-Alcoholic Fatty Liver Disease Management with Cardiovascular Disease

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Abstract

Purpose of Review The global prevalence of non-alcoholic fatty liver disease (NAFLD) presents an unmet need in treating these, often asymptomatic, individuals. In this review, we summarised NAFLD management and described recent developments in non-alcoholic steatohepatitis (NASH) therapeutics that can shape the future of NAFLD.

Recent Findings A multi-disciplinary effort in promoting sustainable lifestyle measures is paramount, with the goal of either limiting energy surplus alone or in combination with targeting downstream pathways of inflammation and fibrosis. Several antidiabetic medications like PPAR-γ agonist and glucagon-like peptide receptor agonists have beneficial effects on the metabolic profile as well as NASH histology. Vitamin E has shown promise in specific groups of patients with the haptoglobin2 allele protein. Newer drugs have demonstrated promising results in NASH resolution and fibrosis improvement such as obeticholic acid, resmetirom, aramchol, efruxifermin, aldafermin and lanifibranor. Apart from discussing the results of late stage clinical trials and the possible challenges in managing these patients with limited approved therapies, we also discussed the specific management of comorbidities (diabetes, hypertension, hyperlipidaemia, cardiovascular diseases) in NAFLD patients.

Summary Treatment strategy needs to target improvements in liver-related outcomes and cardiometabolic profile.

Keywords Pharmacology · Non-alcoholic fatty liver disease · Non-alcoholic steatohepatitis · Intervention

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease with the growing prevalence mirroring the worldwide obesity pandemic [1,2]. It is diagnosed clinically by imaging or histology based on intrahepatic fat accumulation with the absence of alcohol consumption [3]. There are two distinct phenotypes — (1) non-alcoholic fatty liver (NAFL), also termed as simple steatosis, has a benign prognosis without the increased risk of liver-related mortality, and (2) non-alcoholic steatohepatitis [4] (NASH) which is a more advanced disease form, with evidence of hepatocellular injury and inflammation [5, 6, 7]. NASH can progress to fibrosis through exposure of chronic surplus of energy, which compromises the metabolic pathways and results in lipotoxicity, cell death, inflammation and fibrosis [8]. Despite the global burden of NAFLD estimated to be approximately 25% and 40% in Western and Asian

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populations [9] respectively, there is a suboptimal adherence to existing clinical practical guidelines [10]. Importantly, cardiovascular disease (CVD) remains the leading cause of mortality in NAFLD with an estimated 38.7% and 55.4% of NAFLD experiencing subclinical and clinical coronary artery disease (CAD) respectively [11•]. The incidence rate of CVD mortality in NAFLD is estimated to be 4.8 per 1000 person-years and can occur in the absence of NASH or fibrosis [12].

There is increasing recognition of NAFLD as a multisystem disease [13, 14, 15], with NAFLD perceived to be the hepatic manifestation of metabolic syndrome. Extrahepatic complications of NAFLD has gained much attention [13,16,17], with CVD as the leading cause of mortality in NAFLD patients, followed by extra-hepatic cancers and then liver-associated complications [18, 19, 20]. The severity of CVD also positively correlates with the severity of the NASH [21,22] , with CVD shown to occur earlier in the NAFLD disease spectrum [23] when compared to the occurrence of liver related outcomes. This cardiovascular risk increases two-folds with concomitant type 2 diabetes [24]. The complex interplay of insulin resistance, intrahepatic lipid accumulation, atherogenic dyslipidaemia and altered bile acid metabolism plays an important role in the interdependence and crosstalk between the liver and various organs. The increased cardiovascular risk in NAFLD is related to multiple pathophysiology mechanisms that are beyond the scope of this review.

With chronic energy surplus, the liver becomes overwhelmed and NASH ensues. Energy surplus can result in lipotoxicity, cell death, inflammation and fibrosis. Strategies in the management of NAFLD should involve targeting the root cause of the energy surplus and excess adiposity of downstream anti-inflammatory and anti-fibrotic targeted therapies [25]. The goals of liver directed treatments in NAFLD patients are to prevent the progression of liver-related endpoints, defined by fibrosis staging and disease activity [26]. As NAFLD is a part of a multi-systemic disease, consideration of cardiac-related outcomes should also be considered such as addressing hypertension, dyslipidaemia, glycaemic control, weight loss [27], as well as preventing major adverse cardiac events. Despite the increasing prevalence of NASH, there are no US Food and Drug Administration (FDA)-approved medications. Emerging developments of novel therapeutic agents targeting downstream pathways of NAFLD in the latest clinical trials deliver promise in the advancement of NAFLD therapeutics. This review provides an update on the management of NAFLD.

Weight Loss

Weight loss remains the key intervention in improving liver histology in NASH and a cornerstone in reducing energy surplus. Weight loss through lifestyle measures remains the standard of care and this is achievable with dieting and caloric intake reduction [28]. A ≥ 7% weight loss [29] is associated with improvements in hepatic steatosis and inflammation with a further ≥ 10% body weight loss [30] associated with structural and functional cardiac abnormalities reversal [31, 32, 33]. A reduction of 500 kcal/day is associated with significant weight loss [34]. A multidisciplinary approach with professional guidance by a nutritionist can assist in achieving and maintaining diet-controlled weight loss [35]. A study by Romero-Gómez et al. demonstrated that a 52-week period of lifestyle changes led to 25% of its patients achieving resolution of steatohepatitis, 47% with NAFLD activity score (NAS) reduction and 19% with fibrosis regression [36].

Lifestyle Measures

Exercise is an important component for weight loss with the recommended amount of physical activity at least 30 min per day of exercise 5 times a week [34]. The key to effective weight loss is adherence to an exercise regime that needs to be fitted in the patient's lifestyle. Interestingly, no significant differences were found in overall outcomes between aerobic and resistance exercises, or between high and low intensity exercises [37]. The type of exercise regimen does not predict the amount of improvement in visceral and liver fat through weight loss [37] but important practical considerations remain in the prescription of exercise for NAFLD. Resistance exercises may be more suitable for NAFLD who have poorer tolerance to aerobic exercises. High intensity exercise programmes have a shorter time commitment, which can improve exercise adherence [38]. Patients with NAFLD can also consider subscribing to supervised exercise programmes conducted by trained professionals who can ensure safety for these individuals with significant debilitating comorbidities and improve adherence to lifestyle measures. However, adherence to lifestyle interventions through physical activities and dietary measures is often challenging with a large majority of NAFLD patients returning to their baseline weight within 5 years [39]. An interplay of complex factors can determine the adherence to lifestyle change and is often linked to socioeconomic, cultural and family factors [3]. Psychological impairment associated with NAFLD can also hamper the efficacy of lifestyle measures [40].

Dietary measures and physical activity can have a synergistic effect on weight reduction, liver fat reduction and improved cardiovascular outcomes [41,42]. Diets to be avoided in NAFLD patients include those that are hypercaloric, rich in trans-saturated fats and cholesterol, high in fructose corn syrup as they can promote visceral adiposity and hepatic fat accumulation [34,43,44]. Instead,

low-carbohydrate and low-fat diet have demonstrated benefits in insulin sensitivity and serum alanine aminotransferase (ALT) improvement [45]. The Mediterranean diet remains the most promising in reducing cardiovascular outcomes, although other diets have also been studied for weight loss such as ketogenic diet, intermittent fasting, Nutrisystem and Volumetrics [46].

Given the associated reduced baseline levels of polyunsaturated fatty acids (PUFAs) and increased levels of triglycerides and lipid synthesis in NAFLD, PUFAs can enhance lipid oxygenation and downregulate lipid synthesis. A randomised trial demonstrated that patients on diet intervention with PUFA compared to those only on diet intervention had reduced ALT, triglyceride, tumour necrosis factor alpha (TNF-α) and homeostatic model assessment [47]. Fish oil has also been shown to have significant reduction in hepatic steatosis in a placebo-controlled randomised trial [48]. However, the American Association for the Study of Liver Diseases (AASLD) guidelines [49] recommend the use of fish oil only in the presence of hypertriglyceridemia and not in fatty liver disease. Similar to routine exercise however, ensuring adherence to dietary interventions is often challenging despite the potential beneficial for NAFLD patients [50,51]. Trained dieticians can be employed to counsel patients and family members who are likely to share similar lifestyle related risk factors [52] with the goal in maintaining dietary adherence and weight loss.

Pharmacological Measures

Pharmacological interventions are often indicated in those who are unable to achieve > 5% of total body weight reduction despite lifestyle interventions or are unable to sustain weight reduction, or those with a body mass index (BMI) ≥ 27 kg/m^2 and at least 1 metabolically related comorbidity, or individuals with BMI > 30 kg/m^2 regardless of comorbidities [34]. These medications work by reducing absorption of calories, suppressing appetite or functioning as a stimulant. However, most of these pharmacological agents have not shown clear beneficial effects on liver histology in NASH patients apart from glucagon-like peptide-1 receptor agonists (GLP1-RA). GLP1-RA, particularly liraglutide, have not only shown improvement in weight loss but also demonstrated improvement in liver-enzyme levels and reduction in hepatic adiposity [53], with benefits in histologic resolution of NASH [54]. Semaglutide, through a similar mechanistic pathway as liraglutide, has shown more pronounced metabolic effects than the latter [55, 56, 57] and has been demonstrated to improve liver inflammatory markers [58]. A phase 2 trial involving NASH patients demonstrated that semaglutide use not only led to significantly more weight loss but was also associated with a higher percentage of NASH resolution than placebo [59].

There are several other pharmacological drugs approved by the Food Drug Administration (FDA) for weight loss (Orlistat, Sibutramine, and Dexfenfluramine). However, the initiation of these medications without exhausting lifestyle interventions should be done with caution given its potential side effects. Sibutramine use has been associated with systemic hypertension, tachycardia [60], nonfatal myocardial infarction and nonfatal stroke and hence should not be used by patients with known CVD [61,62]. Dexfenfluramine [63] has been shown to cause pulmonary hypertension by inducing vasoconstriction or may cause cardiac valvular abnormalities. On the contrary, orlistat is generally well tolerated with no known long-term cardiovascular adverse effects. The side effects are associated with its mechanistic action (i.e. increased flatulence, frequent loose stools) but generally did not display any major drug toxicity [64]. However, none of these medications showed clear benefit in liver histology in NASH.

The Gelesis 100 [65], an FDA-approved hydrogel-based matrix that is indicated for weight loss, has been used as a novel and non-invasive mechanical device in limiting energy surplus. This orally administered superabsorbent hydrogel works by occupying space in the stomach, which induces the sensation of satiety and reduces appetite, and has shown to result in weight loss compared to placebo. The advantage of this is the absence of side-effects that are often associated with pharmacological therapy, such as nausea and vomiting. The GLOW study [66] demonstrated that Gelesis 100 doubled the odds for clinically significant weight loss in obese individuals compared to lifestyle interventions alone. More than half (59%) of the Gelesis 100 cohort lost at least 5% of baseline body weight compared to placebo. The exploratory analysis revealed that a significant reduction in the absolute mean change in NAFLD fibrosis score for the hydrogel group compared to the placebo group. Clinical trials are underway to explore the long-term impact of hydrogel pill therapy in the treatment of NAFLD.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been associated with weight loss. There is some evidence of the use of SGLT2i [67, 68•, 69] for NASH. In a meta-analysis by Wong et al of seven randomised controlled trials (RCTs) and three cohort studies, it found significant reduction in hepatic fat content after SGLT2i compared to placebo [67]. In addition, a recent network analysis by Ng et al. found that SGLT2i had the greatest reduction of low-density lipoprotein and increase in high-density lipoprotein cholesterol compared to other antidiabetic medications in NAFLD [69]. SGLT2i decreases de novo lipogenesis and increases lipolysis, which may be the underlying mechanism of the associated improvement in hepatic steatosis observed [70] . SGLT2i also elevates glucagon and alters the insulin-to-glucagon ratio, thus favouring lipolysis and ketogenesis in the liver [71]; this is consistent to the observed trend of

overall significant weight loss and reduced visceral adipose tissue with SGLT2i use [72,73]. Weight loss and improvement in visceral adiposity has been strongly associated with decrease in hepatic fat [74] , which is a key determinant in improvement in liver histology in NASH patients [75]. Furthermore, the reduction in body fat has been associated with an increase in adiponectin levels, which is an adipokine that correlates with improved insulin sensitivity [76]. With this overall improvement in weight loss, cardiometabolic and hepatic profile with SGLT2i use, its benefits extend towards favourable prognosis in terms of reductions in cardiovascular mortality, hospitalisation for heart failure and all-cause mortality [77].

Bariatric Surgery and Endoscopic Therapies

Bariatric surgery and its beneficial effect on cardiovascular outcomes have been well documented with significant weight reduction, and improvement with cardiovascular risk factors such as hypertension, dyslipidaemia and diabetes [78, 79, 80, 81, 82]. Gastric bypass surgery has also improved echocardiographic ventricular geometry of ventricular septum thickness, posterior wall thickness, left ventricular mass, right ventricular end-diastolic area and estimated right ventricular systolic function [83,84]. In NASH, meta-analysis of bariatric surgery in NAFLD found a 40% resolution of fibrosis after surgery with a NAS mean reduction of 2.39 [85]. A recent RCT of bariatric surgery in biopsy proven NASH found a 12.4% and 13.9% reduction in major adverse cardiac events (MACE) at 5 years and 10 years respectively after surgery compared to non-surgical management [86]. Even though bariatric surgery is recommended in weight loss and improvement in the metabolic profile, the risks of surgery should not be discounted. Common post-operative complications such as infections, haemorrhage and high reoperation rates [87] as well as long-term complications such as hypoglycemia need to be considered [88]. Diabetic patients are at an increased risk to post-surgical complications compared to non-diabetic patients [89]. Several studies have also reported the increased risk of unhealthy alcohol use [90], self-harm behaviors [51] and suicide [90] in patients who underwent bariatric surgery compared to those who did not.

In addition, endoscopic bariatric therapies have been effective in the treatment of obesity, metabolic syndrome, improvement in histological characteristics of NASH [91] with significant reduction in liver fat, body fat composition and liver biochemistries [92]. A meta-analysis by Jirapinyo et al. on endoscopic treatment in NAFLD found a mean reduction of NAS and BMI by 2.50 and 5.2 kg/m^2 after endoscopic manipulation respectively [93]. Intragastric balloon therapy has also been associated with improvement in left ventricular function and left ventricular mass in morbidly obese patients [94]. Other minimally invasive mechanical interventions such as intra-gastric balloons and duodenal mucosal resurfacing may benefit weight reduction by limiting energy surplus; however, the current evidence on these mechanical adjuncts and its beneficial effects on liver fibrosis has only been supported by observational studies [95,96]. Several potential mechanisms have been postulated that can contribute to this observation — which includes possible alteration to alcohol metabolism post-surgery that increases risk of alcohol intoxication [97], addictive behaviours towards food might be substituted for substance misuse [98] or increased levels of stress and anxiety post-surgery which can exacerbate pre-existing mental health issues [99,100].

Pharmacological Strategies Targeting NASH

Despite the obesity pandemic and rising prevalence of NASH, with the emerging concerns over its cardiovascular manifestations and burden on the healthcare system, there are currently no FDA-approved treatment for NASH. The Accelerated Approval pathway (subpart H for drugs) has been established by the FDA as an alternative and rapid pathway for approving novel drugs. This allows drug companies to apply for approval with trials using surrogate endpoints, hence reducing the time needed for these drugs to obtain FDA approval. Moreover, certain drugs that may have failed earlier clinical trials are currently undergoing testing as a combination therapy with other drugs. This concerted effort is a push towards developing an FDA-approved therapy for NASH in the near future [25]. At present, there are several pharmacological options targeting NASH as summarised in Table 1. These drugs target several metabolic therapeutic targets including lipid modulation, glucose homeostasis and metabolic modulation (Fig. 1).

Vitamin E

Although not FDA-approved, vitamin E has potent antioxidant properties and can reduce oxidative stress within the liver. At the recommended dose of 800 IU daily, it has been shown to reduce hepatic inflammation, steatosis, ballooning and resolution in NASH [101]. However, the potential increase in all-cause mortality, haemorrhagic shock and prostate cancer has raised concerns over its use [102], although the higher mortality rates observed in these studies may be contributed by the larger percentage of males, with a higher smoking prevalence [25]. Current evidence suggests that only a subgroup of patients, with the haptoglobin2 (Hp2) allele protein, benefits from vitamin E therapy at improving cardiovascular outcomes [103,104]. The Hp protein demonstrates antioxidant effects which has been associated with cardiovascular events. This Hp gene has two common alleles, with the Hp2 allele protein being inferior

Table 1 Potential use of off-label pharmacological therapies for non-alcoholic steatohepatitis

	Effects on NASH	Effects on metabolic parameters	Adverse effects and contraindications
Antidiabetic agents			
GLP-1 agonists	Improves hepatic steatosis and necroinflammation	Improves diabetic control, weight reduction and major adverse cardiovascular events	Gastrointestinal side-effects: Nausea, vomiting, constipation, diarrhoea and dyspepsia. Caution use in acute pancreatitis, acute kidney injury
Pioglitazone	Improves hepatic steatosis, necroinflammation and fibrosis	Improves diabetic control and insulin sensitivity	Weight gain, fluid retention, reduced bone density. Potential increase in bladder cancer. Caution use in heart failure; interactions with CYP2C8 inhibitors
SGLT2 inhibitors	Improves hepatic steatosis, necroinflammation and liver enzymes	Improves diabetic control, weight reduction and major adverse cardiovascular effects. Has cardioprotective and renoprotective effects	Genitourinary infection, euglycemic diabetic ketoacidosis, acute kidney injury, may increase risk of bone fractures and amputations. Contraindicated if estimated glomerular filtration rate < 45 mL/min per $1.73m^2$
Antioxidants			
Vitamin E	Improves hepatic steatosis, necroinflammation. Potential of preventing liver decompensation and mortality in advanced liver fibrosis	Neutral effects	Increased risk of bleeding, prostate cancer, heart failure, hemorrhagic stroke with possible increase in all-cause mortality at high doses. Caution use in those with high cardiovascular risk and bleeding risk
Cardiovascular medications			
Acetylsalicyclic acid	Improves hepatic steatosis, and risk of fibrosis progression	Lowers risk of adverse cardiovascular outcomes	Increased risk of major bleeding
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker	Improves hepatic steatosis and risk of fibrosis progression	Improves blood pressure control. Has renoprotective effects in diabetic patients	Caution use in hyperkalemia, hypotension and kidney failure
Statin therapy	Improves hepatic steatosis and hepatic biochemistry	Improves hyperlipidemia control and atherosclerotic cardiovascular disease	Myalgia is most common adverse effect. The liver damage may occur but is rare
Newer drugs			
Obeticholic acid	Improves hepatic steatosis, liver fibrosis modulation	Improves lipid and glucose homeostasis	Pruritus, increased total cholesterol, low-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol

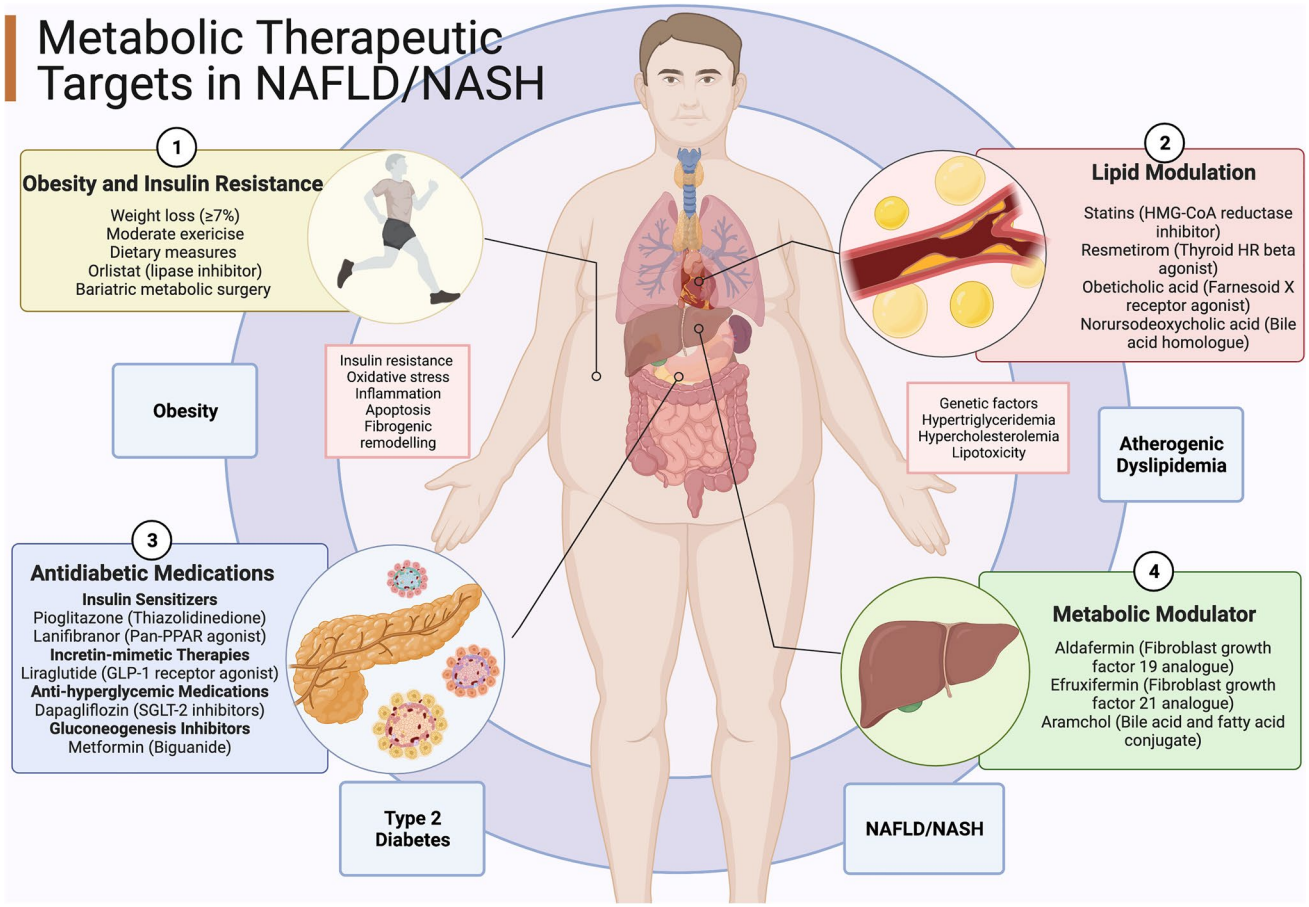

Fig. 1 An illustration of the metabolic therapeutic targets in non-alcoholic fatty liver disease. Obesity, diabetes, atherogenic dyslipidemia and non-alcoholic fatty liver disease have detrimental effects to metabolic health through various pathways. As such, different classes of therapeutic agents have important mechanistic roles targeting each of these individual metabolic components. Four important metabolic therapeutic targets include (1) obesity and insulin resistance, (2) lipid modulation, (3) antidiabetic medications and (4) metabolic modulator

to the Hp1 in antioxidative effects. A significant reduction in nonfatal myocardial infarction, stroke and cardiovascular death has been shown to be observed only in Hp2 individuals treated with vitamin E [105]. Furthermore, vitamin E therapy used in patients with the presence of Hp2 allele protein can have significant improvement in NAS, ALT, aspartate aminotransferase (AST) and cholesterol.

Pioglitazone

Pioglitazone, pan-peroxisome proliferator-activated receptor-γ agonist (PPAR-γ agonist) has been shown to be beneficial for NASH patients [106,107] regardless of diabetic status. The underlying mechanism of PPAR-γ agonist is the improvement of insulin sensitivity and adipocyte fat storage. The Pioglitazone vs Vitamin E vs Placebo for Treatment of Non-Diabetic Patients With Nonalcoholic Steatohepatitis (PIVENS) trial comparing pioglitazone, vitamin E and placebo in nondiabetic patients showed improvement in liver biochemistry, inflammation and fibrosis in patients with pioglitazone [106]. In a RCT by Belfort et al. [108], pioglitazone was found to reduce hepatic fat content, fibrosis and transaminitis. Pioglitazone is also associated with improvements in cardiovascular outcomes. The Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation study compared pioglitazone with glimeride reported decreased coronary atheroma volume in the pioglitazone arm. There were also additional benefits with increment in high-density lipoprotein levels and reduction in median triglycerides [109]. However, the use of pioglitazone needs to be individualised in NASH with careful patient selection. The adverse reactions including weight gain, heart failure and fractures associated with PPAR-γ can be detrimental for NASH patients.

Farnesoid X Receptor Agonist

Obeticholic acid, a farnesoid X receptor agonist, is a promising drug that improves hepatic steatosis with its antifibrotic and antioxidative effects [110]. It acts on a nuclear

receptor that activates bile acid synthesis [111], lipid and glucose homeostasis and liver fibrosis modulation [112]. It was evaluated in the phase 3 Randomised Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment (REGENERATE) trial [113] that demonstrated significant improvement in fibrosis by one stage in obeticholic acid users, compared to placebo. However, despite achieving its primary endpoints, it did not receive FDA approval due to the increased rates of pruritus, increased total cholesterol, increased low-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol [114]. The counteractive adverse effect on cardiovascular outcomes is of concern, and longer-term studies on farnesoid X nuclear receptor agonists and its impact on cardiovascular outcomes will be the next important step for further clarification. Combination therapy of obeticholic acid and atorvastatin has also been evaluated to mitigate the side-effect of hyperlipidemia associated with obeticholic acid. This was examined in the Combination OCA And Statins For Monitoring Of Lipids (CONTROL) trial, which evaluated 4 weeks of the combination of obeticholic acid and atorvastatin, and reported improvement in low-density lipoprotein cholesterol levels [115].

Tropifexor, a non-bile acid farnesoid X receptor agonist in the FLIGHT-FXR phase IIb study, has been reported to have the modest and dose-dependent decrease in hepatic fat and alanine aminotransferase in comparison with placebo at 12 weeks [116]. Several other farnesoid X receptor agonists in phase II trials include Cilofexor [117] and EDP-305 [118]. However, the randomised trial on Nidufexor [119] (LMB763) was terminated.

In addition to tropifexor monotherapy, tropifexor combination therapy is also being examined in a couple of phase II trials. A randomised phase IIb study, TANDEM (NCT03517540), is evaluating the safety and tolerability of the combination of tropifexor and cenicriviroc in NASH patients, compared with monotherapy over a 48-week period. Secondary endpoints include the evaluation of efficacy by ≥ 1-point improvement in fibrosis versus baseline or resolution of steatohepatitis [120]. The Efficacy, Safety and Tolerability of the Combination of Tropifexor and Licogliflozin and Each Monotherapy, Compared With Placebo in Adult Patients With NASH and Liver Fibrosis (ELIVATE, NCT04065841) is a phase II trial that is in the recruiting stage, which seeks to compare combination therapy of tropifexor and licogliflozin versus tropifexor monotherapy with the primary endpoint of ≥ 1-point improvement in fibrosis without worsening of NASH within a 48-week study period [121].

The modified FGF19 agonist (aldafermin) also works on the similar bile acid pathway but regulating bile acid synthesis and lipid homeostasis [122]. It is a promising drug in NAFLD, in view of the deficient FGF19 levels commonly observed in NAFLD patients. A RCT of 78 patients with paired liver biopsies demonstrated higher percentage of NASH resolution with no worsening of fibrosis, and fibrosis improvement with no worsening of NASH in the treatment arm compared to the placebo, although the difference did not reach statistical significance. In a post hoc analysis, significantly higher proportions of patients in the aldafermin treatment arm achieved the combined histological outcome of both fibrosis improvement and NASH resolution compared to the placebo group [123]. Significant improvements in ALT, AST and fibrosis markers were also observed in the aldafermin arm [124,125]. Adverse effects are typically gastrointestinal in nature, but tend to be low in occurrence, and either mild or moderate in severity [123,125].

Drugs Being Investigated in Late-Stage Trials

Several drugs that aim to target downstream pathways of NAFLD are currently being tested in late stage clinical trials. The mechanistic pathways of these drugs involve the inhibition of excess lipid delivery to the liver, de novo lipogenesis, apoptosis, inflammation or fibrogenesis [126].

GLP1-RA GLP1-RA, including liraglutide [127] and semaglutide [128], is another promising class of antidiabetic drug in the treatment of NAFLD [69,129]. A randomised trial reported 39% of its patients on liraglutide demonstrating resolution of NASH, with significantly fewer patients with progression of fibrosis compared to placebo [129, 130, 131]. A recent placebo-controlled phase 2b trial [131] recruited 320 patients with NASH and F1-F3 fibrosis, with significantly greater NASH resolution with semaglutide. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial [132] demonstrated several extrahepatic benefits including weight loss, prognostic improvement in all-cause mortality with reduction in cardiovascular burden. The use of GLP1-RA has also shown significant benefits in reducing the risk of heart failure and chronic kidney disease [133]. Similarly, the phase 2 trial on NASH patients demonstrated that semaglutide led to a significantly higher percentage of NASH resolution compared to placebo, although the randomised study did not report any significant between-group difference in the percentage of individuals with fibrosis stage improvement [59].

PPAR Agonist Beyond thiazolidinediones, which are PPAR-γ agonist, there are other PPAR agonists including lanifibranor [134], which has a well-balanced efficacy for PPARα, δ and γ. It was efficacious in significant resolution of NASH without worsening of fibrosis, improvement of at least 1 fibrosis stage without worsening of NASH, and resolution of NASH with improvement in fibrosis stage of at least 1, when compared to placebo. Liver enzymes and majority of

the lipid, inflammatory and fibrosis biochemical profile also improved with the use of lanifibranor compared to placebo. However, there was an increased rate of peripheral oedema, anaemia and weight gain with lanifibranor use. In addition, Saroglitazar (a PPAR- α/γ agonist) has also been shown to significantly improve ALT, liver fat content, insulin resistance and atherogenic dyslipidaemia in patients with NASH when compared to placebo [135]. However, elafibranor failed the phase 3 Study to Evaluate the Efficacy and Safety of Elafibranor Versus Placebo in Patients With Nonalcoholic Steatohepatitis (RESOLVE-IT) as the study did not meet the predefined primary surrogate efficacy endpoint [136].

FASN Inhibitor The TVB-2640 is a fatty acid synthase (FASN) inhibitor that decreases excess hepatic fat and directly inhibits inflammatory and fibrogenic pathways. 3V2640-CLIN-005 (FASCINATE-1) is a phase 2a randomised, placebo-controlled trial that evaluated TVB-2640 over a 12-week period. In the study, there was significantly increased patients in the TVB-2640 25 mg group (23%) and TVB-2640 50 mg group (61%) who achieved ≥ 30% relative reduction of hepatic fat, compared to the placebo group (11%). Secondary analyses revealed improvements in metabolic, pro-inflammatory and fibrotic markers in the TVB-2640 treatment arm, with good tolerability in its safety profile. This dose-dependent significant improvement in hepatic fat, biochemical, inflammatory and fibrotic profile with TVB-2640 offers promising results for NASH treatment [137].

ACC Inhibitors Acetyl-CoA Carboxylase (ACC) inhibitors (firsocostat) are liver ACC direct inhibitors that decrease de novo lipogenesis and hepatic adiposity [27]. This has been examined in a randomised trial in patients with hepatic steatosis without cirrhosis, which showed 48% of patients demonstrating a reduction of at least 30% from baseline in Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) by 12 weeks, as compared to 15% of patients in the placebo arm [138] ($p = 0.004$). Another RCT showed increased reductions in liver fat fraction ≥ 30% at week 16 with increasing doses of PF-05221304. However, increased triglycerides remain the main adverse effect [139].

FGF21 Analogue Synthetic fibroblast growth factor 21 (FGF21) analogue such as Efruxifermin, works on three FGF receptors (FGFR), FGFR1c, FGFR2c or FGFR3c. The randomised, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Efruxifermin in Subjects With NASH (BALANCED) is a phase 2a randomised trial which demonstrated that the efruxifermin group, at all trial doses (28 mg, 50 mg or 70 mg), reduced hepatic fat by 12–14% and relative fat reduction > 60%. Furthermore, 48% of patients had fibrosis regression by one stage without NASH worsening and 28% had regression by at least two stages, at 16-weeks follow-up. There was also reduction in weight, insulin resistance and hyperlipidaemia in the treatment arm [140]. Pegbelfermin (BMS-986036) [141,142] is a pegylated FGF21 analogue that has shown significant reduction in hepatic fat fraction, compared to placebo, in a phase 2a 16-week trial [143], with phase 2b trials of pegbelfermin in NASH patients underway [144].

Bile Acid Conjugate The bile acid and fatty acid conjugate (Aramchol) downregulates liver steatosis by inhibiting stearoyl-coenzyme A desaturase-1 enzyme. A total of 247 patients were recruited in the phase 2b Clinical Trial to Evaluate the Efficacy and Safety of Two Aramchol Doses Versus Placebo in Patients with NASH (ARREST RCT), and randomised into the treatment and placebo arm for 52 weeks [145]. Aramchol was shown to reduce hepatic fat and improve liver enzymes, with a trend towards higher NASH resolution rates compared to placebo. The Clinical Study to Evaluate the Efficacy and Safety of Aramchol in Subjects With NASH (ARMOR, NCT04104321) is a phase 3 RCT that aims to examine the safety and efficacy of the drug, with its primary outcome being NASH resolution or fibrosis improvement at 52 weeks.

THR Agonists Thyroid hormones regulate several mechanisms involving hepatic triglyceride and cholesterol metabolism that reduce serum cholesterol and liver fat content. The thyroid hormone acts as a ligand to two receptors including thyroid hormone receptor alpha and beta, where thyroid hormone receptor beta is commonly expressed in the liver [146, 147, 148]. Hence, a thyromimetic (resmetirom) that targets the thyroid hormone receptor beta, which is the main receptor expressed in hepatocytes, can help regulate hepatic triglyceride and cholesterol metabolism [146,149,150]. This has been studied in a RCT of 125 patients treated for 36 weeks, which showed that those who received resmetirom had higher rates of relative liver fat reduction on MRI-PDFF at 12 weeks and higher NASH resolution rates at 36 weeks, when compared to placebo. This drug was generally tolerated by the study population, with beneficial effects on atherogenic dyslipidemia associated with NAFLD, and reduction in low-density lipoprotein cholesterol and triglyceride [151]. Evaluation on the efficacy of resmetirom on achieving NASH histologic resolution, and its benefits on dyslipidemia and cardiovascular outcomes are in progress in two large phase 3 randomised trials, namely the Study to Evaluate the Efficacy and Safety of MGL-3196 (Resmetirom) in Patients With NASH and Fibrosis (MAESTRO-NASH, NCT03900429) and MAESTRO-NAFLD-1 (NCT04197479).

Mitochondrial Pyruvate Carrier Inhibitor MSDC-0602K has been studied with its mechanism in targeting mitochondrial pyruvate carrier and minimising binding to PPARγ. The phase 2b EMMINENCE trial [152], a 52-week RCT that evaluated MSDC-0602K in NASH patients with fibrosis stage F1-F3, demonstrated that the primary outcome of 2-point reduction in NAS with at least one point in ballooning without worsening fibrosis was not achieved despite clinically important metabolic improvement (including reduction in fasting glucose, haemoglobin A1c and fasting insulin levels [152]). The role for this agent may potentially demonstrate beneficial metabolic outcomes as a combination therapy rather than a single agent [27].

Other NASH Drug Developments Lysyl oxidase-like 2 (LOXL2) can cause fibrogenesis by catalysing cross-linkage of collagen. Simtuzumab is a monoclonal antibody that functions against LOXL2. However, the double-blind phase IIb of patients with advanced fibrosis caused by NASH reported that simtuzumab was ineffective in reducing hepatic collagen content [153].

Galectin-3 is often associated with NASH and has been shown to contribute to toxin-induced liver fibrosis. Belapectin, an inhibitor of galectin-3, was studied in a phase IIb randomised trial in patients with NASH, cirrhosis and portal hypertension, over a 52-week period. Although 1 year of biweekly infusion of belapectin was safe, it was not found to significantly reduce hepatic vein pressure gradient or fibrosis compared to placebo [154].

Apoptosis signal-regulating kinase 1 (ASK1) also contributes to hepatocyte injury, inflammation and fibrosis in NASH. A phase III randomised trial of selonsertib (STELLAR trial), a selective inhibitor of ASK1, was performed in patients with NASH and bridging fibrosis or compensated cirrhosis. However, 48 weeks of selonsertib monotherapy demonstrated no antifibrotic effect in these patients [155].

Lipotoxicity activates caspases that induce apoptosis and inflammatory cytokine production. Emricasan, a pancaspase inhibitor, reduces serum aminotransferases and caspase activation in NASH patients. However, in a placebo-controlled randomised trial of NASH patients, those who received 72 weeks of emricasan therapy did not display improvement in hepatic histology, but may also have worsened fibrosis and ballooning compared to the placebo arm [156].

Combination therapy

There are several reasons for using combination therapy in the treatment of NASH patients [157]. First, combination therapy may increase response rates compared to monotherapy. The goal of this strategy is to convert partial or non-responders to monotherapy, into responders. With the complex interplay of various mechanistic pathways of the large spectrum of NAFLD, it is important to concurrently target various drivers of NASH. For instance, combining medications targeting metabolic activity and anti-inflammatory activity may further improve the chances of histological resolution. In the Study to Evaluate the Safety and Efficacy of Selonsertib, Firsocostat, Cilofexor, and Combinations in Participants With Bridging Fibrosis or Compensated Cirrhosis Due to Nonalcoholic Steatohepatitis (ATLAS), which compared monotherapy and dual combination regimens of cilofexor, firsocostat and selonsertib, it reported ≥ 1-stage improvement in fibrosis without worsening of NASH, ≥ 2-point NAS improvement, serum ALT and non-invasive fibrosis markers, after 48 weeks of therapy in the combination group (cilofexor and firscostat), compared to placebo [158,159] . Second, combination therapy may maximise response in improving fibrosis and resolution of NASH, compared to monotherapy. The *Study* of *Safety*, *Tolerability*, and *Efficacy* of a *Combination Treatment* of *LJN452* and *CVC* in *Adult Patients* With *NASH* and *Liver Fibrosis* (TANDEM) trial evaluates the combination of cenicriviroc and farnesoid X receptor agonist tropifexor over a 48-week period (NCT03517540 [120]). Third, given the high prevalence of concomitant NAFLD and diabetes, the combination of antidiabetic and anti-NASH drugs can improve both diabetic and liver-related outcomes, whilst improving the metabolic profile such as weight loss and glucose homeostasis [157]. The combination of vitamin E and pioglitazone has been shown to have a numerically greater response in the improvement of fibrosis, although this did not reach statistical significance, when compared to pioglitazone alone [160]. Fourth, combination of drugs can decrease side-effects through the use of lower doses of the individual drugs that can promote tolerability without losing efficacy, as well as the use of a second drug to mitigate the side-effects of the first drug. For example, the use of obeticholic acid can increase low-density lipoprotein cholesterol, and hence the combination with a statin can help ameliorate this side-effect. This was examined in the CONTROL trial which reported improvement in low-density lipoprotein cholesterol levels [161] with combination therapy of obeticholic acid and atorvastatin. In addition, some drugs may lose its therapeutic effects due to physiological adaptive mechanisms, and combination therapy may reduce the rate of escape compared to monotherapy [157]. Future prospective studies on combination therapy are needed to evaluate this hypothesis.

Management of Metabolic Comorbidities

NASH and Diabetes

NASH can preced the onset of type 2 diabetes mellitus. Patients with NAFLD have been shown to have up to a

two-fold increase risk of incident diabetes over time [162]. Therefore, a surveillance strategy with regular screening for type 2 diabetes in NASH patients should be performed. Fasting plasma glucose is a good screening tool in monitoring the development of pre-diabetes or diabetes in NAFLD patients. When the patient develops type 2 diabetes, the treatment strategy should take into account the other comorbidities and risk profile of the patient. Metformin remains the first-line antidiabetic agent in NAFLD patients with diabetes [133]. However, metformin has not been shown to improve histologic or ultrasound features, or biochemical outcomes in NAFLD patients; hence, metformin use has not been specifically recommended in this cohort [163]. However, the role of metformin is still essential in managing the components of metabolic syndrome by targeting lipid metabolism, vascular smooth muscle, cardiomyocyte intracellular calcium shuttling, endothelial function, vasodilation platelet hyperactivity and coagulopathy [102]. The effects of concomitant use of antidiabetic agents are beneficial in controlling diabetes and its metabolic parameters, but its synergistic impact on liver fibrosis regression remains to be studied. To date, there are no studies evaluating the effects of metformin on long-term hepatic outcomes, such as progression of NAFLD to NASH, cirrhosis or death from liver failure [164]. As discussed earlier, GLP1-RA is also an option in patients who have not achieved optimal diabetic control. GLP1-RA has been demonstrated to improve cardiovascular and all-cause mortality in high risk diabetic patients, with the reduction of incident heart failure and chronic kidney disease progression [165]. It is also associated with significant weight loss and improvement in liver histology in NASH patients [166]. SGLT2i also has weight reduction effects, improvement in cardiovascular outcomes and reduction in chronic kidney disease progression [165]. In addition, pioglitazone has shown improvement in NAS and possibly fibrosis in non-diabetic patients. Histological benefits have been recently reported in a trial of NASH patients with type 2 diabetes, although this must be carefully balanced with the risk of weight gain, fluid retention and heart failure exacerbation with the use of pioglitazone [167].

NASH and Hypertension

Patients with concomitant NASH and hypertension tend to display increased severity of NASH [168], although its association with NASH may not be as strong as that seen with concomitant NASH and diabetes [169]. Lifestyle measures and weight loss remain the cornerstone for the treatment of hypertension. Nevertheless, there is a theoretical benefit for the use of angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in NASH patients, especially given the association of NASH, diabetes, chronic kidney disease and hypertension. The activation of the renin angiotensin system (RAS) can precipitate liver fibrosis progression with several studies demonstrating that hypertensive individuals treated with RAS antagonists had a reduction of incident NAFLD [170, 171, 172, 173]. It has been postulated that hepatic stellate cells play a pivotal role in the progression of hepatic fibrosis, as stimulated hepatic stellate cells transform into myofibroblast-like cell and produce large amount of extracellular matrix components that leads to fibrosis formation. The use of ACEI or ARB has demonstrated anti-fibrotic effects in inhibiting hepatic stellate cell activation [174]. NAFLD patients have increased incidence of concomitant cardiovascular risk factors such as hypertension [175], diabetes [176] and chronic kidney disease [177]; thus, ACEI or ARB seems the logical choice of drug for these patients. To date, current guidelines support the first-line therapy with ACEI or ARB in diabetic patients with hypertension and/or chronic kidney disease, regardless if these medications contribute to the treatment of NASH [178]; however, its use for the targeted treatment of NASH alone has not yet been recommended.

NASH and Hyperlipidemia

Patients with NASH display worse lipid profiles compared to non-NASH counterparts, with higher plasma concentrations of very low density lipoprotein, low density lipoprotein and small dense low-density lipoprotein-cholesterol. Statins remain the cornerstone in individuals with coronary artery disease and/or cardiovascular risk factors. Histological improvement in NASH and improvement in ALT levels have been described in patients treated with rosuvastatin [179], but this was not shown with the use of simvastatin [180]. However, there is an underutilisation of statin therapy in NASH patients given the concerns over its safety in those with persistently raised liver enzymes. A paper reported that the diagnosis of NAFLD was a negative predictor of statin use, and this is discordant to guideline recommendations [181]. This misconception has been rebutted by several studies reporting the safety of statin therapy in patients with chronic liver disease [182,183]. Improving awareness amongst physicians, particularly non-hepatologists, in the continuation of statin therapy in NAFLD patients with elevated liver enzymes within an acceptable range, is crucial in reducing the burden of atherosclerotic CVD. Statin therapy is the first-line therapy in treating low density lipoprotein and reducing cardiovascular events. Other lipid-lowering agents such as ezetimibe or PCSK9 inhibitors may be considered if there is suboptimal control of the hyperlipidemia with statins [184].

NASH and Cardiovascular Disease

NASH has been associated with CVD, independent of the competing risk factors associated with metabolic syndrome

such as hypertension, dyslipidaemia, type 2 diabetes and abdominal obesity. Increased fatal and nonfatal CVD events have been reported in patients with NAFLD [185,186]. The severity of hepatic fibrosis, by liver histology, has also been associated with increased liver-related, cardiac-related and all-cause mortality in NASH patients [187, 188, 189]. Increasing severity of NASH has been shown to have higher odds of developing fatal and nonfatal CVD events [190]. These cardiovascular manifestations associated with NAFLD include coronary artery atherosclerosis and disease [191], carotid artery disease [192], cardiac arrhythmias and conduction defects [193, 194, 195, 196], cardiac remodelling and cardiomyopathy [197, 198, 199] and heart valve calcifications [200,201]. The key intervention for patients with CVD is aggressive risk factor control that includes lifestyle measures like smoking cessation, dietary and exercise modifications. Clinicians managing NASH patients should monitor the cardiovascular risk profile using tools such as the atherosclerotic cardiovascular disease (ASCVD) risk calculator on a regular basis. However, there is no current evidence to perform regular coronary artery calcium scoring for all asymptomatic NASH patients.

Cross-sectional data have shown that the use of acetylsalicyclic acid (ASA) can reduce liver fibrosis index levels [202]. A prospective study of biopsy-proven NAFLD patients reported less severe histological characteristics and lower risk of advanced liver fibrosis progression in patients on ASA [203]. The additional benefit of ASA for primary CVD prevention is controversial, although it has been described to lower the risk of adverse cardiovascular outcomes. The main benefit of ASA lies in the secondary prevention of symptomatic atherosclerotic disease [204]. However, careful consideration of the risk-benefit ratio in lowering the antithrombotic risks, and its associated increased major bleeding risks especially in NASH patients, before initiating ASA [205]. The treatment with ASA needs to be individualised to the patient's comorbidities, and current guidelines do not support the use of ASA for the management of NAFLD alone.

Future Directions

Patients with suspected fibrotic NASH should be reviewed by a hepatologist for the consideration of pharmacologic treatment. The choice of therapy is dependent on several factors, such as [1] disease severity (e.g. those with advanced fibrosis may require proven antifibrotic agents), [2] adverse event profile (e.g. those with ischemic heart disease will benefit from most drugs such as GLP1-RA, whilst avoiding others that may worsen hyperlipidaemia) and [3] patient preference (e.g. drugs that require intravenous infusion or subcutaneous injections, without oral alternatives). The response of treatment should be evaluated within 12–18 months to decide if the initiation of combination therapy or a switch in drug class is necessary [206].

Conclusion

To date, there are no FDA-approved medications specifically for NASH, despite its growing prevalence and systemic implications. The early identification and treatment of this multisystem disease remain a priority for the multidisciplinary team. The treatment strategy should encompass both the improvements in liver-related outcomes and the concomitant cardiometabolic profile, with the goal of reducing mortality and morbidity.

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Compliance with Ethical Standards

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