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REVIEW ARTICLE

Nonalcoholic fatty liver disease as a metabolic disease in humans: A literature review

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Abstract

Aims: To conduct a systematic literature review to identify recent epidemiological, biomarker, genetic and clinical evidence that expands our understanding of non-alcoholic fatty liver disease (NAFLD) as a metabolic disorder.

Materials and Methods: We performed a literature search using PubMed to identify trials, observational studies and meta-analyses published in the past 5 years.

Results: A total of 95 publications met prespecified inclusion criteria and reported on the interplay between NAFLD/nonalcoholic steatohepatitis (NASH) and metabolic dysfunction, in terms of disease burden and/or epidemiology (n = 10), pathophysiology, risk factors and associated conditions (n = 29), diagnosis and biomarkers (n = 34), and treatment approaches (n = 22). There is a growing body of evidence on the links between NAFLD/NASH pathogenesis and mechanisms of metabolic dysfunction, through liver lipid accumulation, insulin resistance, inflammation, apoptosis, and fibrogenic remodelling within the liver. The frequent co-occurrence of NAFLD with obesity, metabolic syndrome and type 2 diabetes supports this premise. Therapeutic approaches originally envisaged for type 2 diabetes or obesity (such as glucagon-like peptide-1 receptor agonists, sodium-glucose co-transporter-2 inhibitors, insulin sensitizers and bariatric surgery) have shown promising signs of benefit for patients with NAFLD/NASH.

Conclusions: Given the complex interplay between NAFLD and metabolic dysfunction, there is an urgent need for multidisciplinary collaboration and established protocols for care of patients with NAFLD that are individualized and ideally support reduction of overall metabolic risk as well as treatment for NASH.

KEYWORDS

fatty liver disease, GLP-1, insulin resistance, pharmaco-epidemiology, type 2 diabetes

1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a chronic and increasingly common liver disorder among adults in Western countries.^{1,2} NAFLD encompasses a heterogeneous spectrum of disease, but is histologically categorized into nonalcoholic fatty liver, characterized as $\geq 5\%$ liver steatosis with no evidence of injury to hepatocytes and no evidence of fibrosis,¹ and nonalcoholic steatohepatitis (NASH),^{1,2} defined as $\geq 5\%$ liver steatosis including inflammation and injury to hepatocytes with or without fibrosis, although fibrosis is typically observed.¹⁻³ NASH is associated with increased risk of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality, especially when fibrosis is present.¹⁻³ Advancing fibrosis stage exponentially increases the risk of liver-related mortality.⁴

Diagnosis of NAFLD requires detection of liver steatosis, exclusion of other liver diseases, and absence of alcoholic causes.⁵ NAFLD is often identified by abdominal ultrasonography during routine health checks, and ultrasonography is an acceptable screening procedure for steatosis.⁵ However, liver biopsies remain the only definitive technique to determine and then monitor the stage and severity of NAFLD.⁶ Biopsies are invasive, costly, and allow for considerable sampling error^{5,6}; thus, noninvasive diagnostic and staging methods are under continued investigation. Vibration-controlled one-dimensional transient elastography, also known as Fibroscan®, provides a liver stiffness measurement and controlled attenuation parameter, which can indicate the level of liver fibrosis and steatosis, respectively.⁷ This method is considered an effective noninvasive procedure for NAFLD screening.⁷ Development of the XL probe has also improved Fibroscan® reliability in patients with obesity.⁷ The commercial biomarker panels SteatoTest, ActiTest, NashTest-2 and FibroTest have been validated for diagnosis of NAFLD, NASH and/or fibrosis; however, the validation cohorts only included a minority of patients with type 2 diabetes mellitus (T2DM).⁸ All panels were found to underperform in a population of patients with T2DM, suggesting that studies in nondiabetic populations should not be directly extrapolated to patients with T2DM.⁸ Other proposed methods for detecting and assessing fibrosis stage in patients with NAFLD include various biomarkers and composite scores of clinical assessments such as NAFLD fibrosis score, fibrosis-4 index and the aspartate transaminase (AST) to platelet ratio index; studies assessing these have found varying performance.⁹⁻¹¹ The National Institute for Health and Care Excellence has recommended the Enhanced Liver Fibrosis score for assessing advanced fibrosis in NAFLD.¹² Noninvasive imaging methods, such as magnetic resonance imaging-derived proton density fat fraction and magnetic resonance elastography (MRE), have been suggested for liver fat and fibrosis detection, respectively.^{13,14} Recently, combining liver stiffness measurement and controlled attenuation parameter by Fibroscan® with AST level, known as FibroScan-AST (FAST), demonstrated good performance in identifying patients at risk of progressive NASH (NASH with NAFLD Activity Score ≥ 4 and fibrosis stage ≥ 2).¹⁵ The positive predictive value for FAST was 83% in the

prospective UK derivation cohort, and 69% in the pooled global validation cohorts.¹⁵ The MRE combined with FIB-4 (MEFIB) index (MRE ≥ 3.3 kPa and FIB-4 ≥ 1.6) demonstrated positive predictive values of 97% and 91% for detection of fibrosis stage ≥ 2 in the University of California at San Diego derivation cohort and Japan validation cohort, respectively.¹⁶

Accumulating evidence supports a bidirectional association between NAFLD and components of metabolic syndrome (MetS).^{1,17,18} NAFLD is accompanied by a number of pathophysiological changes: (i) increased de novo lipogenesis (DNL) and very low-density lipoprotein production; (ii) reduced hepatic fatty acid oxidation; (iii) unrestrained lipolysis in adipose tissue; and (iv) impaired insulin-mediated suppression of hepatic glucose production, leading to liver steatosis, hypertriglyceridaemia, and hyperglycaemia.^{19,20} At the molecular level, selective hepatic insulin resistance (IR) is thought to be a common factor driving these processes, resulting in development of both hepatic and peripheral metabolic dysfunction.²¹

The prevalence and incidence of IR, obesity, T2DM and NAFLD are also closely linked.²² NAFLD and T2DM share multiple cardiometabolic risk factors and proinflammatory and profibrotic pathways.²³ The prevalence of comorbid conditions with NASH has been reported in a meta-analysis to be 82% for obesity, 72% for hyperlipidaemia, 71% for MetS (various definitions were included), 68% for hypertension, and 44% for T2DM.¹⁷ Patients with T2DM frequently also have NAFLD and have a higher risk of developing NASH, suggesting there is a bidirectional interplay of risk factors between NAFLD and T2DM.²⁴

While NAFLD was formally described over 40 years ago, it is only in recent years that NAFLD has become recognized as an urgent unmet medical need, and an appropriate histological classification, regulatory pathway and clinical endpoints have been in place to enable effective clinical research and drug development.²⁵ As yet there are no approved treatments for NAFLD or NASH, but a consensus workshop between the American Association for Study of Liver Diseases and the US Food and Drug Administration (FDA), published in 2015, established a framework for critical components of the drug development process enabling more rapid progress.²⁶ This literature review focuses on the current evidence supporting NAFLD as a metabolic disease and part of a process of systemic metabolic dysfunction, the efforts to establish noninvasive diagnostic techniques, particularly in patients with NAFLD and T2DM or obesity, and the current evidence supporting pharmacological therapies under investigation for NAFLD or NASH that target metabolic dysfunction.

2 | METHODS

The objective of the literature review was to identify evidence that advances the understanding of NAFLD, including NASH, and its relationships with components of MetS, with a focus on the most recent evidence generated in the past 5 years.

2.1 | Search strategy

A literature search of the PubMed electronic database was conducted on 16 November 2020 to identify clinical studies, clinical trials, comparative studies, controlled clinical trials, meta-analyses, observational studies and randomized controlled trials, restricted to human participants only and in English language, published from January 2014. The full search strategy is presented in the Supplementary Appendix S1. Articles outside of the PubMed search were also included, if relevant.

2.2 | Study selection

Articles were included in the full-text review if they reported on disease burden, epidemiology, association with metabolic abnormalities or other diseases (eg, cancer), pathophysiology, diagnosing methods, and treatment and management of NAFLD or NASH.

3 | RESULTS

A total of 168 articles and abstracts underwent full-text review from the PubMed search (Figure 1). After removal of 73 ineligible articles, there remained 95 articles that met the criteria for inclusion in this review (Table S1), and 84 are further discussed. Selected articles (Figure 1) were categorized according to the type of data they reported, as follows: disease burden and/or epidemiology (10 references); the interplay with metabolic

abnormalities and/or relationships with other diseases (29 references); diagnosis and biomarkers (34 references); and treatment (22 references).

3.1 | Global burden of NAFLD and NASH

The prevalence of NAFLD has grown consistently over the last three decades in the United States, in line with similar increases in the prevalence of obesity and T2DM.²⁷ Seven of the retrieved studies reported on the burden of NAFLD in the context of metabolic abnormalities. A cross-sectional analysis of 1948 adults in China identified a prevalence of NAFLD of 35.5% during general health checks.²⁸ A large, well-designed meta-analysis of 24 studies including 35 599 patients with T2DM reported a pooled prevalence of NAFLD of 59.7%.²⁹ This finding is consistent with the prevalence of NAFLD in three recent observational studies in populations with metabolic risk factors: 65.7% in South Indian patients with morbid obesity undergoing bariatric surgery (of which 33.6% had histological features of NASH),³⁰ 64.5% in premenopausal women who have overweight/obesity from Greece,³¹ and 64.7% in patients with T2DM from Bangladesh.³² Parameters of metabolic dysfunction (including body mass index [BMI], waist-hip ratio, glycated haemoglobin [HbA1c], fasting plasma glucose, low-density lipoprotein [LDL] cholesterol, triglycerides, total cholesterol, and hypertension) were consistently found to be significantly associated with an increased prevalence of NAFLD across the studies identified.^{28–34} The 34 retrieved studies related to the diagnosis and monitoring of NAFLD and NASH are discussed in the Supplementary Appendix S1.

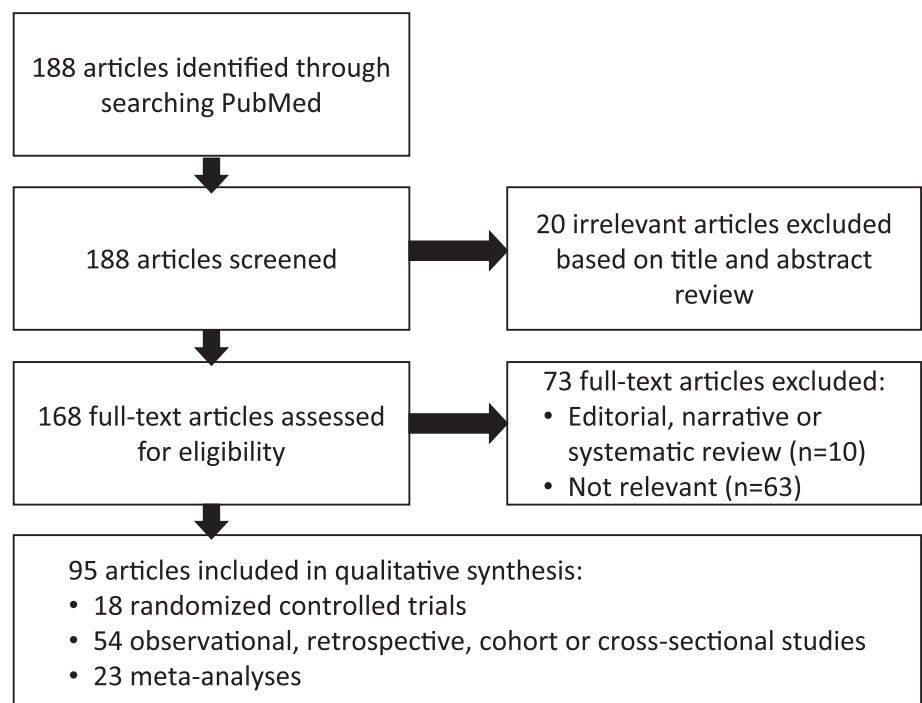


FIGURE 1 Diagram of included and excluded publications

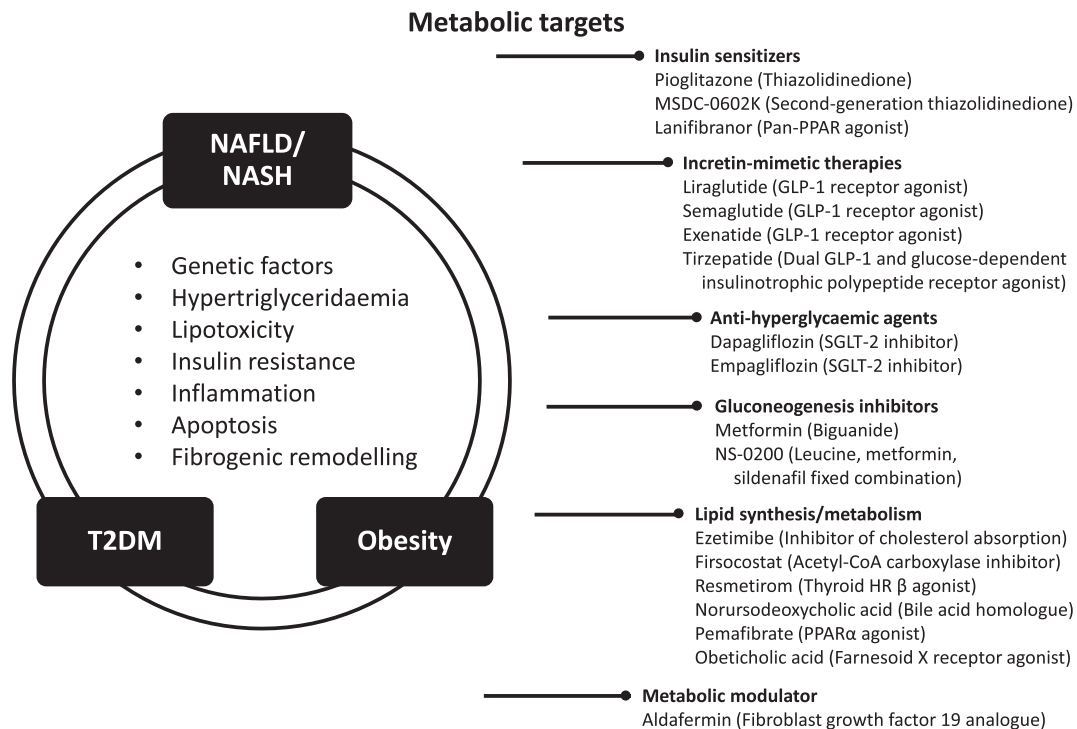


FIGURE 2 Potential mechanisms by which nonalcoholic steatohepatitis (NASH) causes hepatic and extrahepatic metabolic dysfunction and current metabolic therapeutic targets. Acetyl-CoA, acetyl co-enzyme A; GLP-1, glucagon-like peptide-1; HR, hormone receptor; NAFLD, non-alcoholic fatty liver disease; PPAR, peroxisome proliferator-activated receptor; SGLT2, sodium-glucose co-transporter-2; T2DM, type 2 diabetes mellitus

3.2 | Metabolic risk factors and the pathophysiology of NAFLD

The current view of NAFLD pathogenesis encompasses abnormal lipid metabolism, apoptosis, hepatic inflammation, and fibrogenic remodelling in the liver and has been an active area of research in recent years (Figure 2).

3.2.1 | Metabolic dysfunction

A number of meta-analyses carried out in the past 5 years have evaluated the interplay between metabolic diseases and NAFLD, and what is now understood to be a “vicious cycle” between NAFLD and T2DM, in which NAFLD increases the risk of incident T2DM and then T2DM increases the risk of liver fibrosis. Many of the publications identified reinforce the association of NAFLD with components of MetS and IR first reported 20 years ago,^{35,36} although few studies evaluated longitudinal changes in liver histology.

Large meta-analyses consistently demonstrate that patients with NAFLD have a significant risk of T2DM and MetS.^{37,38} Currently it is uncertain whether the incidence of T2DM increases with worsening severity of liver disease in NAFLD. An updated meta-analysis that incorporated a total of 19 observational studies in nearly 296 500 individuals (30% with NAFLD diagnosed via imaging) and captured nearly 16 000 cases of incident T2DM over a median follow-up of 5 years concluded that NAFLD was associated with an

approximate doubling of risk of T2DM (random-effects hazard ratio 2.22, 95% confidence interval [CI] 1.84-2.60).²³ In this study, risk of T2DM appeared to increase further with greater severity of NAFLD in the four eligible studies that used either noninvasive fibrosis scores or ultrasonographic severity of steatosis. In a cohort study of 12 853 South Koreans a significantly increased risk of incident T2DM at 5-year follow-up was reported among patients with baseline fatty liver on ultrasonography (odds ratio 2.42, 95% CI 1.74-3.36; $P < 0.0001$), even after adjustment for established risk factors.³⁹ There is also some evidence of worsening metabolic dysfunction with increasing severity of NAFLD in patients with MetS.⁴⁰ The IT-DIAB observational study in patients with prediabetes found that the Fatty Liver Index (a proxy of liver steatosis comprising triglycerides, gamma glutamyl-transferase [GGT], BMI, and waist circumference) was associated with new-onset diabetes independent of age, gender, diabetes risk score, HbA1c, and fasting plasma glucose.⁴¹ Besides T2DM, patients with obesity also have an increased risk of NAFLD.^{42,43} Finally, it should be noted that NAFLD can occur in lean individuals, especially in Asian populations, who display increased visceral adipose tissue and IR at lower BMI thresholds (see below).⁴⁴

On the other side of the coin, several studies have demonstrated that metabolic diseases, especially T2DM, are independent factors of the severity of NAFLD. A recent prospective cohort study designed to reflect the full spectrum of disease and overcome potential lead time bias by including patients with NAFLD, borderline NASH and definite NASH has provided insights into liver histology over a mean of

4.9 years between biopsies, reporting that MetS was significantly associated with progression to advanced fibrosis ($P = 0.03$).⁴⁵ Moreover, T2DM is an independent risk factor for severe steatosis (relative risk 2.04, 95% CI 1.10-3.76; $P = 0.023$) and severe fibrosis (relative risk 4.57, 95% CI 1.37-15.20; $P = 0.013$) compared with patients without T2DM.⁴⁶ A meta-analysis found that T2DM was associated with a more than twofold increased risk of incident severe liver disease events in the general population at risk of NAFLD or with diagnosed NAFLD (adjusted hazard ratio 2.25, 95% CI 1.83-2.76; $P < 0.001$).⁴⁷ In the same study, obesity as defined by BMI alone had a less marked association with increased risk of incident severe liver disease outcomes (adjusted hazard ratio 1.20, 95% CI 1.12-1.28; $P < 0.001$).⁴⁷ A separate meta-analysis found that BMI-defined obesity was significantly associated with liver fibrosis in patients with NAFLD (odds ratio 3.22, 95% CI 2.13-4.87; $P < 0.001$), but not necessarily with advanced fibrosis.⁴⁸

In light of the association between NAFLD and metabolic disorders, an international panel of experts proposed that defining fatty liver disease based on the presence or absence of metabolic dysfunction, independent of alcohol consumption, may be more relevant to the condition.⁴⁹ Metabolic dysfunction-associated fatty liver disease (MAFLD) has been suggested as an alternative term to better represent patient heterogeneity,^{49,50} and to account for the possibility of coexisting liver diseases which may be associated with alcohol consumption.⁴⁹ It is also suggested that a higher alcohol intake threshold should be considered when enrolling patients into clinical trials, to address the current difficulties faced in patient recruitment.⁴⁹ The proposed key diagnostic criteria for MAFLD comprise hepatic steatosis together with at least one of the following: overweight/obesity; T2DM; or two or more metabolic risk abnormalities.⁴⁹ The presence of metabolic risk factors in the absence of overweight/obesity enables diagnosis of MAFLD in the nonobese or lean population.

A recent meta-analysis confirmed that BMI should not be a mandatory criterion for MAFLD/NAFLD diagnosis, with approximately 40% of global NAFLD cases classified as nonobese and approximately 20% as lean.⁵¹ Obese and lean NAFLD share many pathophysiological characteristics. For example, some individual components of MetS, such as high blood pressure, plasma glucose levels and serum triglycerides, appear to be similar between patients with obese or lean NAFLD, although MetS overall is more prevalent in obese cases.⁵² The frequency of NASH and stage ≥ 2 fibrosis in nonobese NAFLD is 40% and 30%, respectively,⁵¹ and neither appear to correlate with obesity.⁴⁸ However, obese NAFLD may predict worse long-term prognosis due to higher transaminase levels, a higher degree of hepatic steatosis, and increased risk of metabolic complications and fibrosis, relative to nonobese NAFLD.⁴⁸ Lean NAFLD appears to be more common in Asian populations and possible predisposing factors include visceral adiposity, fructose- and cholesterol-rich diets, and genetic components.^{44,53} Indeed, presence of the G allele of *PNPLA3* rs738409 appears to be more frequent in nonobese NAFLD than in obese cases.⁴⁸ Evidence for effective pharmacological treatment approaches in lean NAFLD is lacking⁴⁴ and inclusion of lean NAFLD

individuals in clinical trials for pharmacological treatment of NAFLD is recommended.^{48,51} In terms of current disease management, similar approaches to those taken for NAFLD patients with obesity are suggested, such as weight loss in those individuals with visceral obesity and dietary restrictions (also see below).^{44,53}

3.2.2 | Pathological mechanisms

Multiple parallel events are thought to lead to the pathogenesis of NAFLD, starting with accumulation of fatty acids and triglycerides and development of IR both in the liver and in adipose and skeletal muscle. Through a combination of multiple-stable-isotope analysis and liver biopsies, sources of intrahepatic triglycerides have been attributed mainly to circulating fatty acids (approximately 59%), DNL (approximately 26%) and dietary fatty acids (approximately 15%) in NAFLD.^{54,55} DNL is estimated to be threefold higher in NAFLD compared with controls, whereas the production of fatty acids from adipose tissue has not been found to be significantly different.⁵⁵ It has been proposed that all individuals may have a genetic and environmentally determined limit to their capacity for adipose tissue expansion and that, once this is reached, lipids accumulate in other tissues, and this promotes IR and inflammation both within and outside of the liver in a process known as lipotoxicity.⁵⁶ A cross-sectional study in 137 normoglycaemic participants from Mexico reported that disruption in regulation of acylcarnitines and amino acids predicts development of inflammation, obesity, NAFLD, and IR.⁵⁷ IR is thought to exacerbate lipotoxicity through stimulation of lipolysis in adipose tissue and a process of positive feedback that escalates the metabolic imbalance, for example, through accumulation of ceramides, long-chain acylcarnitines and diacylglycerols (DAGs) that promote inflammation and impact further on insulin signalling.^{58,59} Adipose tissue macrophages are thought to be key contributors to IR and impaired adipose tissue function.⁶⁰ Increased fatty acid levels activate toll-like receptor 4 (TLR4) signalling in adipose tissue macrophages, resulting in polarization from an anti-inflammatory M2 state into the proinflammatory M1 phenotype.⁶¹ M1 macrophages produce the cytokines tumour necrosis factor- α and interleukin (IL)-6, both of which are associated with development of IR.⁶² Adipose tissue hypertrophy can result in reduced oxygen supply to the tissue; hypoxia has also been implicated in the infiltration of adipose tissue by M1 macrophages and as a potential mechanism of IR.^{60,62} Insights into the relationship between metabolic dysfunction and NAFLD from genome-wide analyses in recent years are discussed in the Supplementary Appendix S1.

3.2.3 | Inflammation, oxidative and endoplasmic reticulum stress, and apoptosis

Insulin resistance and lipid accumulation in the liver trigger a cascade of mitochondrial dysfunction and activation of cytochrome p450 2E1-mediated lipid peroxidation that generates reactive

oxygen species and degrades mitochondria and other hepatocellular structures.⁶³ Mitochondrial damage decreases cellular energy production and increases accumulation of metabolic intermediates, which adds to the stress on endoplasmic reticulum caused by excess free cholesterol. These processes lead to release of proinflammatory cytokines, hepatocellular injury, apoptosis and fibrogenesis, which can ultimately progress to fibrosis and cirrhosis.⁶³ Several studies have assessed the key putative mechanisms responsible for hepatic IR and hepatic lipid accumulation. Hepatic lipid accumulation has been implicated in the development of IR, but translational evidence in humans is limited.⁶⁴ Intracellular lipid metabolites, such as DAG, ceramides and acylcarnitines, are claimed to be involved in the pathogenesis of IR in skeletal muscle.⁶⁵ The severity of liver cell injury and degree of NAFLD activity are also thought to contribute to hepatic IR independent of the amount of intrahepatic triglycerides and lipid intermediates.⁶⁵ Studies have consistently shown the key role of hepatocellular DAG and protein kinase C ϵ (PKC ϵ) activation in the pathogenesis of IR in humans.⁶⁴⁻⁶⁶ DAG in hepatic cytosol has been shown to be a predictor for insulin inhibition of glucose production, and DAG-associated IR is characterized by PKC ϵ translocation.⁶⁴⁻⁶⁶ In a study of the human liver lipidome in 125 liver biopsy samples, *PNPLA3* I148M variant allele carriers had significantly higher liver fat content and no features of IR (as determined from homeostatic model assessment of IR [HOMA-IR], serum lipids and adiponectin concentrations), compared with noncarriers.⁶⁷ IR in the human liver is associated with increased concentrations of saturated and monounsaturated free fatty acids and triacylglycerols (TAGs) as well as ceramides from the de novo ceramide synthetic pathway.⁶⁷ This is not observed in NAFLD with the *PNPLA3* I148M variant, which instead is characterized by increased concentrations of polyunsaturated TAGs that can be attributed to known functions of the I148M variant in in vitro studies.⁶⁷

Several identified studies highlighted the relationship between inflammation and NAFLD.⁶⁸⁻⁷⁰ In a cross-sectional analysis, patients with NAFLD had significantly lower circulating levels of anti-inflammatory mediators such as adiponectin, endogenous soluble receptor for advanced glycation end products, and IL-10, and high concentrations of proinflammatory oxidized LDL, CD40 ligand, and endogenous thrombin potential compared with patients without NAFLD, suggesting that the inflammation may be accelerated by the presence of MetS.⁶⁸ Leukocyte cell-derived chemotaxin-2 (LECT2) has been identified as a secretory protein that modulates inflammatory responses, but is also implicated as playing a key role in IR.⁷¹ Significantly higher plasma levels of LECT2 were found in patients with NAFLD versus those without, and were associated with obesity, lipid profile and high-sensitivity C-reactive protein (hsCRP) in individuals with MetS.

It is thought that sublethal lipid-induced hepatocyte stress and dysfunction is able to trigger proinflammatory cascades through the generation of undead hepatocytes (which includes ballooned hepatocytes and hepatocytes with Mallory-Denk bodies' inclusions) and extracellular vesicle release.⁷² This generates a feed-forward loop, intensifying hepatocyte injury and maintaining a proinflammatory

microenvironment within the liver.⁷² Decreased liver fat and heat shock factor 1 may impair heat shock protein-70-dependent anti-inflammation, further exacerbating inflammation leading to oxidative stress during progression of the disease.⁷⁰ Adipose tissue secretes regulatory proteins known as adipokines that may play a role in development of MetS and NASH through involvement in the hepatic and systemic inflammatory response and in IR. Patients with NAFLD have decreased levels of circulating anti-inflammatory adipokine adiponectin⁷³ and underexpression of adiponectin receptors in visceral fat, while overexpression of adiponectin receptors in the liver appears to be associated with the degree of liver damage.⁷⁴ A systematic review assessed the relationship between novel adipokines and liver histology in patients with NAFLD, including 31 cross-sectional studies evaluating seven adipokines.⁷⁵ Chemerin, resistin, and adipocyte-fatty-acid-binding protein (also known as FABP-4) were identified as potentially being involved in NAFLD pathogenesis and/or progression, warranting further evaluation.

Inflammasomes are large multiprotein complexes that promote or sustain inflammation, and intriguing evidence in a mouse model of NASH suggests that saturated fatty acids can upregulate the inflammasome in hepatocytes.⁷⁶ Elevated serum uric acid (UA), an end product of purine metabolism, is a feature of inflammasome activation that has been observed in MetS and cardiovascular (CV) disease. The associations between UA, components of MetS, obesity and NAFLD were assessed in a cross-sectional study in 10 069 Chinese participants.⁷⁷ The prevalence of NAFLD was significantly higher among individuals with elevated UA across subgroups of patients with BMI <25 and ≥ 25 kg/m², and there was a strong additive interaction between obesity and elevated UA to increase the risk of NAFLD.⁷⁷

3.2.4 | Impact on CV disease

As T2DM occurs very frequently with NAFLD, and T2DM is an established risk factor, it has been uncertain until recently whether the presence of co-existing T2DM confounds the relationship between NAFLD and CV disease. Wild et al⁷⁸ recently performed a retrospective cohort analysis using linked population-based routine data for people aged 40 to 89 years diagnosed with T2DM in Scotland between 2004 and 2013 who had one or more hospital admission records. Adjusted hazard ratios for NAFLD versus no record of liver disease were 1.70 (95% CI 1.52-1.90) for CV disease and 1.60 (95% CI 1.40-1.83) for all-cause mortality. Moreover, a recent meta-analysis showed that NAFLD was independently associated with a higher incidence of CV disease in patients with T2DM,⁷⁹ providing evidence that T2DM is unlikely to confound the relationship between NAFLD and CV disease, as a similar strength of relationship between NAFLD and CV disease exists in patients both with and without T2DM. Another meta-analysis found a significant association between presence of NAFLD and diastolic cardiac dysfunction, suggesting the need for careful observation for CV comorbidities in patients with NAFLD.⁸⁰ The risk of atrial fibrillation (AF) has been found to be doubled in

cross-sectional studies of patients with NAFLD, independent of other risk factors for AF; this risk was elevated even further in those with T2DM.⁸¹ It has been suggested that the relationship between NAFLD and AF is likely attributable to shared risk factors and pathological mechanisms such as obesity, activation of the renin-angiotensin system and proinflammatory and oxidative states.⁸² A causal relationship between the two, however, has not been confirmed.^{81,82} In a retrospective analysis of the longitudinal CARDIA cohort, NAFLD was shown to correlate with subclinical myocardial remodelling and dysfunction, resulting in left ventricular stiffness that was independent of established risk factors for heart failure, suggesting common pathophysiological links perhaps via IR, systemic inflammation, and/or myocardial lipotoxicity.⁸³ In a prospective observational study, NAFLD was significantly correlated with systemic markers of inflammation and higher all-cause mortality in patients with heart failure with preserved ejection fraction.⁸⁴ Another study found that NAFLD incidence was significantly higher among patients with versus those without coronary artery disease ($P = 0.013$), and greater degrees of liver steatosis were observed in patients with Grade 3 versus those with Grade 0 to 1 coronary artery disease ($P = 0.038$).⁸⁵ However, a cohort study including 30 239 participants in the United States reported no clear association between NAFLD and risk of ischaemic stroke, suggesting that although the risk factors for stroke, atherosclerosis, and coronary disease are similar, the role of liver inflammation across the spectrum of atherosclerotic CV diseases remains to be clarified.⁸⁶

3.2.5 | Impact on oncogenesis

Nonalcoholic fatty liver disease is associated with an elevated risk of HCC, colorectal adenoma and colorectal cancer, with the risk increasing with NAFLD severity, potentially as a result of excess advanced glycation end products and proinflammatory cytokines that can elicit oxidative stress and hepatic stellate cell activation.⁸⁷ A retrospective, long-term analysis of outcomes in Japanese patients with NAFLD found that incidences of HCC and both liver and nonliver-related mortality were increased in individuals with advanced fibrosis compared with those with mild fibrosis.⁸⁸ In a meta-analysis of 21 observational studies, NAFLD was associated with increased risk of incident colorectal adenoma/colorectal cancer, while severe NAFLD also elevated the risk of incident colorectal adenoma/colorectal cancer compared with mild and/or moderate NAFLD.⁸⁷ A cohort study in 1793 participants from China reported that NAFLD and MetS were independently associated with elevated risk of colorectal neoplasm ($P = 0.001$ and $P = 0.001$, respectively) and colorectal cancer ($P = 0.005$ and $P = 0.001$, respectively), and the authors suggested that patients with NAFLD and MetS should undergo regular colonoscopy assessments.⁸⁹ Another meta-analysis found that NAFLD may elevate the risk of developing cholangiocarcinoma, particularly intrahepatic cholangiocarcinoma.⁹⁰ Finally, a meta-analysis of 19 studies including 168 571 participants without cirrhosis reported that patients with NASH have a higher risk of developing HCC compared with patients with other aetiologies of liver diseases.⁹¹

3.3 | Managing NAFLD and NASH by treating liver disease and targeting metabolic risk: Current and emerging strategies

Lifestyle modification consisting of diet, exercise and weight loss is advocated for patients with NAFLD.^{1,92,93} Assessment of dietary and physical activity habits is part of comprehensive NAFLD screening²; however, no recommendations exist on any particular type of diet or intensity, volume and type of exercise required.^{1,92,93} Exercise may independently improve hepatic steatosis without weight loss, but weight loss is usually required for NASH resolution.^{92,93} There is evidence of reversal of liver fibrosis with weight loss, but the effect is dependent on the degree of weight reduction and baseline BMI. A 7% to 10% decrease in body weight is thought to be required for resolution of NAFLD in patients with obesity; however, only 10% to 20% of individuals are able to achieve a weight loss of $\geq 10\%$ with lifestyle change over 1 to 2 years.⁹⁴ It should be underlined that similar weight loss is less effective in reaching NASH resolution in people with diabetes compared with those without diabetes.⁹⁵

In terms of exercise, a study in 32 patients with NAFLD found that 8 weeks of individualized aerobic training improved some metabolic variables, and in particular decreased alanine transaminase (ALT) and AST levels.⁹⁶ Conversely, a randomized controlled trial in 24 patients with NASH found that 12 weeks of exercise without weight loss had no significant effect on inflammation or fibrosis markers including ALT and AST, or on noninvasive scores of liver disease. The study did, however, report significant reductions in hepatic and circulating triglycerides, and visceral fat, after the 12-week programme.⁹⁷ Interestingly, a cross-sectional study found that individuals with NASH are physically deconditioned, with significantly reduced aerobic power and capacity in NASH patients with obesity and overweight, compared with untrained sedentary control subjects.⁹⁸ NASH subjects in this study had fitness levels comparable to those of the least fit subset of control subjects.⁹⁸ Regarding diet, a meta-analysis reported that a carbohydrate-restricted diet may be more effective in reduction of hepatic steatosis than simply a low-fat diet,⁹⁹ possibly due to reduced fructose content.⁵⁵ Excessive consumption of fructose has been implicated in the development of NAFLD through increased plasma triglycerides and hepatic DNL.^{55,100} Increased fatty acid consumption in the form of omega-3 polyunsaturated fatty acids (PUFA) has been linked to reduced hepatic steatohepatitis, triglyceride content and IR.^{100,101} However, a randomized controlled trial reported no histological improvement in NASH after 1 year of N-3 PUFA treatment, despite a reduction in hepatic fat content.¹⁰² However, the inconsistent effects of omega-3 fatty acids on NAFLD and/or NASH may depend on the composition and purity of omega-3 fatty acids used in the study and on the severity of liver disease. Previous studies have often used mixtures of eicosapentanoic (EPA) and docosahexanoic acid (DHA) with different degrees of purification. Sanyal et al¹⁰³ showed no improvement of NAFLD Activity Score after supplementation with purified EPA in patients with NASH. Only one clinical trial, the WELCOME study (Wessex Evaluation of fatty Liver and Cardiovascular markers in NAFLD with OMacor thErapy), has

assessed erythrocyte EPA and DHA enrichment to assess compliance during the study.¹⁰⁴ Using erythrocyte DHA percentage enrichment or erythrocyte EPA percentage enrichment, the authors were able to test the specific contribution of each omega-3 fatty acid. Thus, it was possible to test associations between percentage DHA enrichment (or percentage EPA enrichment), and changes in liver fat percentage measured by magnetic resonance spectroscopy. In this study, the authors showed an independent association between a decrease in liver fat percentage and enhanced erythrocyte DHA enrichment, but not with erythrocyte EPA enrichment, with purified omega-3 fatty acid treatment. High-fibre diets have demonstrated benefits in NAFLD subjects and so are recommended for improvement.^{100,101} Dietary supplements and homeopathic remedies are also discussed in the Supplementary Appendix S1.

3.3.1 | Potential pharmacological treatment approaches targeting metabolic dysfunction

There are currently no FDA-approved pharmaceutical treatments for patients with NAFLD or NASH; however, some international guidelines do recommend some therapeutic approaches (Supplementary Appendix S1). To date, none of the treatments assessed in NASH have provided efficacy across the heterogeneous patient population and the lack of simple inexpensive tests to assess treatment response and predictors of likelihood of response is a major challenge for drug development.

Treatment approaches for NAFLD based on a range of metabolic targets have been evaluated, including glucagon-like peptide (GLP)-1 receptor agonists, sodium-glucose co-transporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, insulin sensitizers and the inhibitor of gluconeogenesis metformin, fibroblast growth factor (FGF)-21 and FGF-19 agonists and analogues, and an acetyl-CoA carboxylase (ACC) inhibitor. While insulin therapy could be useful to inhibit adipose tissue lipolysis and thereby reduce liver steatosis,¹⁰⁵ insulin often promotes weight gain in patients with T2DM, so delayed introduction or intensification of insulin is preferred in patients with NAFLD or obesity.¹⁰⁶ Given the ongoing challenges in identifying and categorizing NAFLD, the current basis for drug development is to identify clinically meaningful outcomes and optimal surrogates for disease regression.

3.3.2 | Insulin sensitizers and metformin

Thiazolidinediones directly bind to and activate the peroxisome proliferator-activated receptor (PPAR)- γ and have been evaluated in a number of studies in NASH.¹⁰⁷ A meta-analysis including patients with biopsy-confirmed NASH found that pioglitazone was significantly associated with reversed advanced fibrosis and resolution of NASH, regardless of the presence of T2DM.¹⁰⁸ Another recent meta-analysis comparing antidiabetic drug classes in patients with NAFLD reported that only the thiazolidinediones and liraglutide have shown an improvement in liver histology.¹⁰⁹ However, thiazolidinediones are

associated with weight gain, and their use (and associated risks and benefits) needs to be carefully considered in patients with NASH.^{108,110} Other adverse events associated with first-generation thiazolidinediones include bone fractures, congestive heart failure, cancer, hypoglycaemia and lower-limb oedema.^{107,108,110} MSDC-0602K, a second generation of thiazolidinedione that targets the mitochondrial pyruvate carrier, did not demonstrate significant effects on primary and secondary liver histology endpoints in a randomized, double-blind, placebo-controlled phase 2b study.¹⁰⁷ However, the effects on noninvasive measures of liver cell injury and glucose metabolism support further exploration of the safety and potential efficacy of MSDC-0602K in patients with T2DM and liver injury.¹⁰⁷ Adverse events typically associated with thiazolidinediones were not observed more frequently with MSDC-0602K than placebo.¹⁰⁷ A phase 3 study assessing resolution of NASH with MSDC-0602K in patients with NASH and T2DM (NCT03970031) is planned.

Other next-generation insulin sensitizers, such as elafibranor and seladelpar, which act via the PPAR family, showed initial promise in NAFLD but have not been able to demonstrate significant improvements in liver histology to date,^{107,111–113} and clinical development of elafibranor (a dual PPAR- α / δ agonist) and seladelpar (a PPAR- δ agonist) in NAFLD has halted. Lanifibranor, a pan-PPAR agonist, was evaluated for the treatment of NASH in the phase 2b NATIVE study.¹¹⁴ A press release in June 2020 announced that significantly more patients achieved a decrease of ≥ 2 points in the Steatosis Activity Fibrosis score (combining assessments of hepatocellular inflammation and ballooning) from baseline with lanifibranor 1200 mg/d versus placebo (49% vs 27%; $P = 0.004$).¹¹⁵ Resolution of NASH and no worsening of fibrosis was also observed in 45% of patients receiving lanifibranor 1200 mg/d versus 19% receiving placebo ($P < 0.001$).¹¹⁵ Modest weight increase and peripheral oedema were observed with lanifibranor treatment.¹¹⁵ On the basis of these promising results, a phase 3 programme is planned for lanifibranor in NASH.

Pemafibrate is a highly selective PPAR- α agonist that promotes the induction of genes involved in fatty acid oxidation, lipid mobilization and energy metabolism.^{116,117} In a clinical trial in patients with T2DM and hypertriglyceridaemia over 24 weeks, pemafibrate was shown to significantly reduce fasting serum triglycerides ($P < 0.001$) and HOMA-IR score (0.4 mg/d, $P < 0.05$; 0.2 mg/d, $P < 0.01$) compared with placebo.¹¹⁸ Incidence of adverse events was similar with pemafibrate or placebo.¹¹⁸ Most clinical trials of pemafibrate have been in Japan,¹¹⁶ including the ongoing phase 2, placebo-controlled trial investigating the efficacy and safety of pemafibrate in patients with NAFLD (NCT03350165). The large-scale phase 3 clinical trial, PROMINENT (NCT03071692), is investigating effects of pemafibrate on CV outcomes in patients with T2DM and combined dyslipidaemia across multiple countries worldwide.

Metformin has a modest benefit on weight loss and, in studies in NAFLD, has generally not demonstrated significant improvements over comparator therapy in serum markers of liver injury, liver fat content, or in histological inflammation and fibrosis.¹¹⁹ In a study of 85 patients with T2DM and NAFLD, 24 weeks of either metformin or liraglutide significantly improved weight, BMI, and waist

circumference versus gliclazide (all $P < 0.01$)¹²⁰; however, there was a significant reduction in intrahepatic fat content with liraglutide versus gliclazide ($P = 0.001$), but not with metformin.¹²¹ NS-0200, a fixed-dose combination of leucine, metformin, and sildenafil, has been assessed in a phase 2 randomized controlled trial of patients with NAFLD. No significant differences were seen versus placebo, but high-dose NS-0200 (1.1 g leucine/0.5 g metformin/1.0 mg sildenafil) twice weekly for 16 weeks significantly reduced hepatic fat content compared with placebo in a subgroup of patients with high baseline ALT ($P < 0.005$).¹²² Adverse events associated with metformin typically include gastrointestinal effects such as nausea and diarrhoea.¹²³ In patients with severe hepatic, renal or cardiac dysfunction, metformin use is discouraged due to subclinical increases in lactic acid and potential lactic acidosis in a small subset of patients.¹²³

3.3.3 | GLP-1 receptor agonists

Liraglutide, a once-daily GLP-1 receptor agonist, is licensed for T2DM (maximum dose: 1.8 mg/d) and weight management in adults with metabolic disorders who have overweight or obesity (maximum dose: 3.0 mg/d). Liraglutide was shown in the phase 2 Lira-NAFLD study (dose: 1.2 mg/d) to significantly reduce body weight and liver fat content ($P < 0.0001$) after 6 months of treatment in patients with NAFLD and T2DM.¹²⁴ In a meta-analysis, patients with NASH (particularly those with T2DM) had improved liver histology, aminotransferase levels, and obesity in response to treatment with GLP-1 receptor agonists liraglutide or exenatide.¹²⁵ In the phase 2 LEAN randomized controlled study, more patients treated with liraglutide achieved histological resolution of NASH compared with patients receiving placebo ($P = 0.019$), while fewer patients treated with liraglutide had progression of fibrosis compared with patients receiving placebo ($P = 0.04$).¹²⁶ Recently, the once-weekly GLP-1 receptor agonist semaglutide has also been shown to significantly reduce ALT and hsCRP levels in a dose-dependent manner in patients with obesity or T2DM.¹²⁷ In a recent phase 2 trial of semaglutide in patients with NASH, the primary endpoint of NASH resolution with no worsening of liver fibrosis was met ($P < 0.001$).¹²⁸ Significant reductions in ALT and AST have also been reported with the investigational dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist tirzepatide.¹²⁹ Adverse events associated with GLP-1 receptor agonists are typically gastrointestinal, such as nausea, vomiting, diarrhoea, abdominal discomfort and appetite suppression.¹²⁵

A phase 2a study of the dual GLP-1/glucagon receptor agonist cotadutide has demonstrated beneficial effects in patients with T2DM and excess body weight.¹³⁰ Over a 42-day period, there were significant reductions in blood glucose levels ($P < 0.0001$), body weight ($P = 0.0008$), and liver fat ($P = 0.0172$) with cotadutide treatment, compared with placebo.¹³⁰ Gastrointestinal disturbances and decreased appetite occurred more frequently with cotadutide than with placebo.¹³⁰ It is thought that the GLP-1 receptor agonism effects of reducing plasma glucose should counterbalance any hyperglycaemic effects from glucagon receptor agonism, while allowing beneficial

effects such as increased energy expenditure, satiety, hepatic lipolysis and fatty acid oxidation.^{131,132}

3.3.4 | DPP-4 inhibitors

Dipeptidyl peptidase-4 is a serine protease involved in metabolism and immune function, and GLP-1 is among its peptidase targets.¹³³⁻¹³⁵ As such, DPP-4 has been evaluated in relation to T2DM and NAFLD. A cross-sectional study found significant correlations between DPP-4 activity and ALT ($r = 0.4637$, $P = 0.0038$) and GGT ($r = 0.4491$, $P = 0.0017$) levels, and a direct correlation between DPP-4 activity and HOMA2-IR ($r = 0.5295$, $P = 0.0026$).¹³⁴ A more recent cross-sectional study corroborated these findings by concluding that, not only do patients with NAFLD have increased DPP-4 activity ($P = 0.02$) irrespective of obesity, but there is also a linear relationship between DPP-4 activity and the severity of liver steatosis ($P = 0.04$) and lobular inflammation ($P = 0.03$).¹³³ DPP-4 has therefore been identified as a possible marker of disease progression in NAFLD.¹³³⁻¹³⁵ While it has been suggested in one small open-label randomized controlled trial that sitagliptin, a DPP-4 inhibitor, improved NAFLD Activity Score irrespective of diabetes status,¹³⁶ additional larger double-blind randomized controlled trials are warranted to confirm the potential benefit of DPP-4 inhibitors in NASH. DPP-4 inhibitors have a good safety profile and the most frequent adverse events observed are nasopharyngitis and, more rarely, skin lesions (bullous pemphigoid).¹³⁷

3.3.5 | SGLT2 inhibitors

The established antidiabetic SGLT2 inhibitors are known to reduce body weight and body fat, mainly by increasing urinary glucose excretion. In the EFFECT-III study, the SGLT2 inhibitor dapagliflozin, in combination with omega-3 carboxylic acids, significantly reduced liver fat content ($P < 0.05$), and decreased markers of hepatocyte injury including plasma FGF-21, compared with placebo.¹³⁸ Empagliflozin, another SGLT2 inhibitor, was shown in the E-LIFT study to significantly reduce liver fat versus standard treatment ($P < 0.0001$).¹³⁹ A recent phase 4 study provided evidence that empagliflozin effectively reduces liver fat content compared with placebo, but has no major effects on tissue-specific insulin sensitivity.¹⁴⁰ Exploratory analyses also revealed a marked decrease in serum UA and a rise in serum high molecular weight adiponectin levels.¹⁴⁰ These effects occurred in the presence of moderate weight loss and despite only minor changes in glycaemia in a cohort of patients with metabolically well-controlled T2DM and a short disease duration.¹⁴⁰ There is currently a need to better understand the mechanism of action of SGLT2 inhibitors in the liver and to further characterize potential benefit in patients with NAFLD, particularly on liver histology. The most common adverse effects associated with SGLT2 inhibitors are mycotic genital infections¹⁴¹ and, particularly in individuals with type 1 diabetes, diabetic ketoacidosis.¹⁴²

3.3.6 | Other potential pharmacological treatment approaches based on metabolic dysfunction

It has been proposed that combining GLP-1 analogues with an SGLT2 inhibitor and/or a specific statin could potentially reduce the risk of CV-related morbidity and mortality, as well as liver-related morbidity in patients with NASH,¹⁴³ while combining GLP-1 analogues such as liraglutide or exenatide with thiazolidinediones also has the capacity to reduce hepatic fat content in patients with NAFLD and T2DM.¹⁴⁴

The farnesoid X receptor (FXR), a metabolic nuclear receptor that is critically involved in regulating bile acid, lipid, and glucose metabolism,^{145,146} is a potential therapeutic target because serum bile acid levels have been shown to correlate with disease severity in NAFLD.¹⁴⁷ Obeticholic acid, an FXR agonist, provided significant histological improvement in fibrosis versus placebo among patients with NASH and F2-3-stage fibrosis as part of a planned 18-month interim analysis of a phase 3 REGENERATE randomized controlled trial (NCT02548351); this study is ongoing to assess clinical outcomes.¹⁴⁸ Pruritis and elevated LDL cholesterol have been reported as common adverse effects of obeticholic acid.¹⁴⁸⁻¹⁵⁰ Given the association with elevated LDL cholesterol levels, combination of statins with obeticholic acid has been suggested.¹⁵⁰ The phase 2 CONTROL study found that coadministration with atorvastatin reversed the effects of obeticholic acid on LDL cholesterol concentration in patients with NASH and fibrosis.¹⁵⁰

Norursodeoxycholic acid is a synthetic bile acid homologue which has been assessed in a dose-finding phase 2 trial in individuals with NAFLD.¹⁵¹ A dose-related reduction of serum ALT was reported after treatment with norursodeoxycholic acid, as were reductions in AST and GGT, compared with placebo.¹⁵¹ The most common adverse events reported were headaches, infections and gastrointestinal effects.¹⁵¹ A phase 2b trial on the safety and efficacy of norursodeoxycholic acid in NAFLD is currently underway (EudraCT number 2018-003443-31).

Fibroblast growth factor-19 has been implicated in multiple metabolic pathways in the pathogenesis of NASH. Aldafermin (NGM282), an FGF19 analogue, has been shown in a phase 2 randomized controlled trial in patients with biopsy-confirmed NASH to significantly reduce liver fat content ($P < 0.0001$), ALT and AST ($P < 0.0001$), and some fibrosis biomarkers (Pro-C3 and TIMP-1; $P < 0.05$) versus placebo after 12 weeks.¹⁵² Reported adverse events included injection site reactions, gastrointestinal symptoms and abdominal pain.¹⁵² A phase 2b dose-ranging study is ongoing to further assess the potential of aldafermin in patients with NASH and liver fibrosis (NCT03912532).

The intestinal cholesterol absorption inhibitor ezetimibe was assessed in a randomized controlled pilot study of 50 patients with biopsy-confirmed NASH, but did not significantly improve liver fat, histology, enzymes, or stiffness versus placebo.¹⁵³ No significant side effects were found compared with the placebo arm.¹⁵³

Acetyl-CoA carboxylase catalyses the rate-limiting step in DNL. Firsocostat (GS-0976), a small molecule inhibitor of ACC isoforms

1 and 2, has been shown to significantly reduce hepatic steatosis ($P = 0.002$), metalloproteinase 1 (a marker of fibrogenesis; $P = 0.022$), and multiple plasma acylcarnitine species ($P < 0.001-0.009$).¹⁵⁴ Commonly reported adverse events were nausea, abdominal pain and diarrhoea.¹⁵⁴ Firsocostat is currently being investigated in combination with antifibrotic agents in patients with NASH (NCT02781584).

Resmetirom, a selective thyroid hormone receptor- β agonist, is the first thyroid hormone analogue investigated for use in treatment of NASH.¹⁵⁵ A phase 2 randomized, double-blind study in patients with biopsy-confirmed NASH reported significant reductions in hepatic fat after treatment with resmetirom compared with placebo ($P < 0.0001$).¹⁵⁵ Resmetirom treatment also reduced levels of triglycerides, cholesterol and other lipids.¹⁵⁵ A higher incidence of transient mild diarrhoea and nausea was observed with resmetirom versus placebo. A phase 3 trial for the treatment of NASH with resmetirom is ongoing (NCT03900429).

The impact of bariatric surgery on NAFLD is discussed in the Supplementary Appendix S1.

4 | CONCLUSIONS

Type 2 diabetes, obesity and MetS are well established as major global health challenges associated with significant economic impact. NAFLD very commonly co-occurs with other metabolic disorders, meaning that patients typically have multiple health challenges and greatly increased risk of serious clinical consequences. Although not yet widely adopted, the term MAFLD has been proposed by an international expert panel when describing hepatic steatosis associated with metabolic dysfunction, in recognition of the specific characteristics of NAFLD in comparison with other liver diseases.⁴⁹ Many patients with NAFLD may be primarily under the care of nonhepatology specialists, including diabetologists, cardiologists, endocrinologists, and primary care physicians, and at this interface between metabolic and hepatic medicine, optimal patient care requires effective multidisciplinary collaboration and joint protocols.¹⁵⁶ It seems likely that a combined approach of pharmacotherapy (including systemic glucose and lipid management) with lifestyle and behavioural interventions will prove most successful, given the complex multifaceted nature of metabolic disorders. In the future, it would be preferable to establish treatment options with known benefits for both NAFLD and the other metabolic disorders with which patients typically present. The increased risk of CV complications and gastrointestinal tumours in addition to HCC suggests a need for proactive assessment and rapid intervention of comorbidities by the relevant specialist clinician. There is an opportunity to build on the chronic disease management approach that is already being implemented in some healthcare systems for patients with T2DM or obesity. Our growing understanding of the natural history and pathogenesis of NAFLD and NASH, focused efforts on new diagnostic and interventional approaches, and ability to deliver optimal multidisciplinary care provide opportunities to improve outcomes for patients with NAFLD and NASH and reduce the impact on healthcare systems.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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