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REVIEW

New Names, New Drugs, Better Outcomes in Steatotic Liver Disease

Matthew Peverelle[1], Mzamo Mbelle[1], Deepak Joshi[1,*]

[1]Institute of Liver Studies, King's College Hospital, London, UK
*Correspondence: d.joshi@nhs.net (Deepak Joshi)

Abstract

Steatotic liver disease (SLD) is a growing cause of chronic liver disease, with potential progression to cirrhosis, hepatocellular carcinoma (HCC), and liver failure. Previously known as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), new terminology, including metabolic-dysfunction associated steatotic liver disease (MASLD) and metabolic-dysfunction associated steatohepatitis (MASH), was introduced to improve diagnostic clarity and reduce stigmatization. MASLD is now recognized as the hepatic manifestation of the metabolic syndrome and is the most common cause of liver disease in the UK, affecting up to 20% of adults. The incidence of MASLD-related cirrhosis and HCC is expected to rise significantly by 2030, highlighting the need for early diagnosis and treatment. For over two decades, effective medical therapies for MASLD were elusive. However, recent trials of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), thyroid hormone receptor-β (THR-β) agonist resmetirom, and fibroblast growth factor 21 (FGF21) agonists have shown promising results in reversing steatohepatitis and potentially fibrosis. These agents potentially offer new disease-modifying treatment options for MASLD, with GLP-1 RAs particularly effective in achieving weight loss and all drugs showing promising histological benefits in patients with MASH. This review summarizes nomenclature changes, provides an update on the UK's SLD burden, with a particular focus on MASLD and MASH, and discusses new therapeutic strategies for managing this complex and increasingly prevalent condition.

Key words: nonalcoholic fatty liver disease; hepatocellular carcinoma; cirrhosis; GLP-1 RAs; SLD; MASLD; MASH; metabolic and alcohol related/associated liver disease

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Introduction

Steatotic liver disease (SLD) encompasses a spectrum of liver disorders characterized by the accumulation of fat in liver cells (hepatic steatosis). SLD is the fastest growing cause of liver disease and can progress to cirrhosis, hepatocellular carcinoma (HCC), liver transplantation or death (Fig. 1) (Estes et al, 2018; Estes et al, 2020). The terms non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) were previously used to describe liver disease secondary to hepatic steatosis in the absence of alcohol as a causative factor. Recently, a shift in nomenclature has occurred, leading to the introduction of more specific terms including metabolic-dysfunction associated steatotic liver disease (MASLD), metabolic-dysfunction associated steatohepatitis (MASH), and metabolic and alcohol related/associated liver disease (MetALD) (Fig. 2) (Rinella et al, 2023). These

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terms have replaced the older, more ambiguous nomenclature, with the aim to improve clarity in diagnosis, research, and treatment, and from a patient perspective, reduce confusion and stigmatisation.

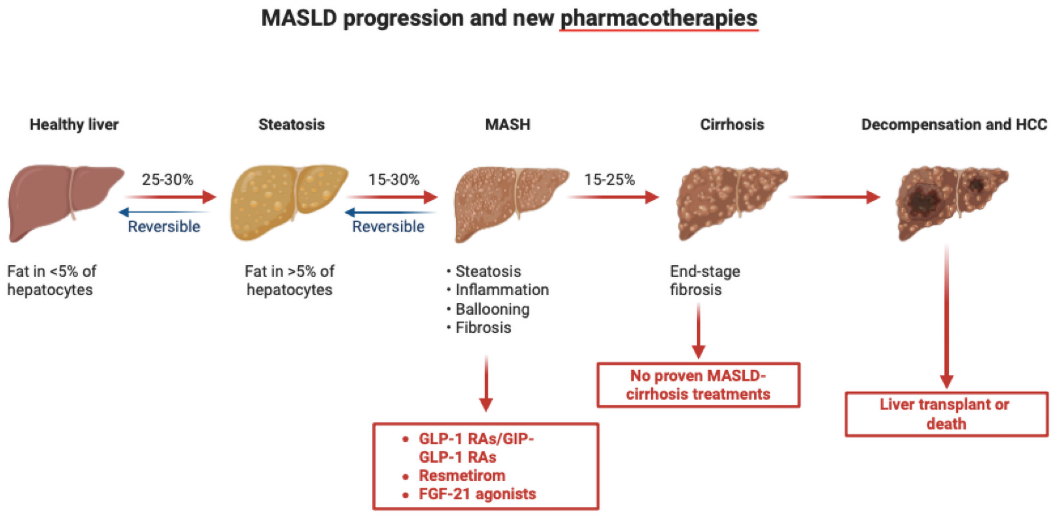

Fig. 1. Progression of MASLD and new pharmacotherapies. Created with BioRender.com. MASLD, metabolic-dysfunction associated steatotic liver disease; GLP-1 RAs/GIP, glucagon-like peptide-1 receptor agonists/glucose-dependent insulinotropic polypeptide; FGF21, fibroblast growth factor 21; HCC, hepatocellular carcinoma; MASH, metabolic-dysfunction associated steatohepatitis.

For over two decades, effective medical treatments for MASLD have remained elusive, with numerous failed drugs creating an often referred to 'graveyard' of MASLD trials. However, the glucagon-like peptide-1 receptor agonists (GLP-1 RAs), thyroid hormone receptor-β (THR-β) agonist resmetirom, and fibroblast growth factor 21 (FGF21) agonists have recently shown ability to attenuate the progression of MASH, and indeed reverse steatohepatitis and fibrosis in a significant proportion of patients, offering promising new disease-modifying options for clinicians.

The purpose of this review is to therefore provide an update on the nomenclature changes that have taken place within the field of hepatology to describe steatotic liver diseases, provide context on its current and projected healthcare burden within the UK, and describe the new disease-modifying drugs that have shown efficaciousness in treating MASLD.

What's in a Name? Recent Nomenclature Changes in Steatotic Liver Disease and Related Conditions

Prior to recent nomenclature updates, NASH and NAFLD had long been used to describe patients with liver disease secondary to components of the metabolic syndrome—hypertension, dyslipidaemia, obesity and type 2 diabetes. However, there was recognition that this diagnosis was driven by 'negative' criteria, i.e., exclusion of excessive alcohol use plus steatosis, as opposed to 'positive' criteria, i.e.,

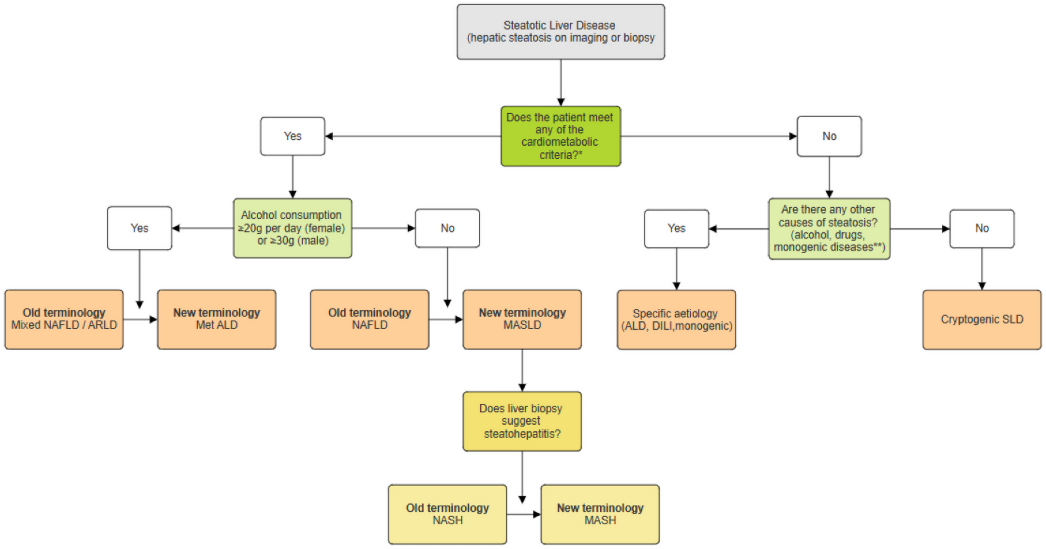

Fig. 2. Summary of steatotic liver disease nomenclature changes and diagnosis flowchart. *Cardiometabolic criteria include overweight/obesity, insulin resistance, hypertension, dyslipidaemia (high triglycerides or low high-density lipoprotein). **Examples of drugs that can cause drug-induced liver injury include steroids, methotrexate, amiodarone, tamoxifen. Monogenic diseases include Wilson's disease, lysosomal acid lipase deficiency (LALD), hypobetalipoproteinaemia. Created with smartdraw.com. NAFLD, non-alcoholic fatty liver disease; ARLD, alcohol-related liver disease; MetALD, metabolic and alcohol related/associated liver disease; ALD, alcoholic liver disease; DILI, drug-induced liver injury; SLD, steatotic liver disease; NASH, non-alcoholic steatohepatitis; MASH, metabolic-dysfunction associated steatohepatitis.

steatosis plus $\geq$1 cardiometabolic risk factor (CMRF) (Zhou et al, 2022). The term NAFLD also incorrectly implied a strict dichotomy between alcohol-related and non-alcohol related liver diseases, whereas in reality, a combination is possible, often leading to clinician and patient confusion as well as stigmatisation (Carol et al, 2022). Further stigmatisation derived from the term 'fatty' was also of concern during debates around nomenclature change (Rinella et al, 2023).

Therefore, following collaborative work between large pan-national liver associations including the European Association for the Study of the Liver (EASL) and the American Association for the Study of the Liver (AASLD), an update on proper nomenclature in the SLD space was published and is now the recommended terminology by these societies (Rinella et al, 2023). Both the overarching term of SLD and its subset MASLD provide a non-stigmatising, affirmative description of the disease rather than a diagnosis of exclusion. Removal of the term 'nonalcoholic' is also designed to focus attention on the metabolic basis for this type of liver disease, which has long been recognised as the hepatic manifestation of the metabolic syndrome (Matteoni et al, 1999). The aim is to ensure that management focuses on optimising the well-established CMRF's such as hypertension, dyslipidaemia and insulin resistance.

Therefore, in brief, the updates to the nomenclature can be summarised as follows:

(1) Steatotic liver disease (SLD): An umbrella term encompassing forms of liver disease characterised by hepatic steatosis related to various aetiologies.

(2) Metabolic-dysfunction associated steatosis liver disease (MASLD): This replaces the term NAFLD and refers specifically to hepatic steatosis in conjunction with one or more CMRF's including overweight/obesity, dyslipidaemia, hypertension and insulin resistance.

(3) Metabolic-dysfunction associated steatohepatitis (MASH): This replaces the previous term NASH and describes the inflammatory subtype of MASLD, characterised by steatosis, inflammation and varying degrees of fibrosis. This can only be diagnosed with a liver biopsy.

(4) Metabolic and alcohol related/associated liver disease: This new term acknowledges the co-pathogenesis that exists between CMRF-related liver damage and alcohol consumption. Within the MetALD group, there exists a continuum across which the relative contribution of MASLD and alcoholic liver disease (ALD) will vary. Patients who consume, on average, 20 g (females) or 30 g (males) alcohol per day have MASLD-predominant MetALD, whereas patients who consume 50 g (females) or 60 g (males) per day have ALD-predominant MetALD. Alcohol consumption in between these values means neither MASLD nor alcohol predominate.

Patients with MetALD have distinctly poorer outcomes than patients with MASLD alone (Israelsen et al, 2024), highlighting the need to simultaneously optimise their CMRF profile and reduce their alcohol consumption.

Whether there exists a safe level of alcohol consumption in patients with MASLD has not been well-defined. A systematic review examined the effects of moderate alcohol consumption (up to 35 units per week in females and 50 units per week in males) among patients with MASLD and found that any level of alcohol consumption increased the risk of liver-related harm (Jarvis et al, 2022). Data pooling was not possible among the six studies included due to heterogeneity; however, the results broadly agreed with the findings of other critical studies (Åberg et al, 2020; Boyle et al, 2018). Prospective studies are needed to examine the association between 'accepted' levels of alcohol consumption and major adverse liver outcomes in patients with MASLD. On the balance of available evidence, however, clinicians should recommend to patients with MASLD to abstain from alcohol consumption to avoid accelerating progression of their liver disease.

The Burden of MASLD in the UK

MASLD has now become the most common cause of chronic liver disease in the UK and is estimated to affect up to 1 in 5 adults (British Liver Trust, 2024a). Liver disease is the only major disease where mortality rates are accelerating and a significant driver of this is the rising burden of MASLD, driven by an increasingly obese and cardiometabolically unhealthy population (British Liver Trust, 2024b). Indeed, Williams et al (2014) reported that death rates from liver disease in the UK in 2014 were four-fold higher compared to 1970, and in England premature deaths from liver disease increased by almost 40% from 2001 to 2022 (10,592 deaths in

2022, 6140 deaths in 2001). By way of comparison, they also found that death rates from cardiovascular disease have roughly halved since 1970.

Concerningly, the majority of the estimated 14.1 million individuals with MASLD in the UK remain undiagnosed, and the prevalence of advanced fibrosis/cirrhosis is expected to double to 1 million individuals by 2030 (Fig. 3) (Estes et al, 2018). The projected increase in the UK is the highest among European countries including France, Germany, Italy and Spain. Furthermore, the incidence of MASLD-related decompensated cirrhosis is expected to approximately double from 6 per 1000-persons to 12 per 1000-persons by year 2030, adding considerable financial burden to the UK healthcare system (Baumeister et al, 2008; Neff et al, 2011; Whalley et al, 2007). The increase in decompensated cirrhosis is expected to proportionately worsen the impact on healthcare resources and the costs associated with the care of these patients (Baumeister et al, 2008; Weinmann et al, 2014). A previous study estimated the cost of MASH in 2018 to be between £2.3 billion (lower prevalence scenario) to £4.2 billion (higher prevalence scenario), and individuals were estimated to experience 94,094 to 174,564 disability-adjusted life years (DALYs) overall (Morgan et al, 2021). The expected rising trend of MASLD in the UK means that these values will invariably increase in the future.

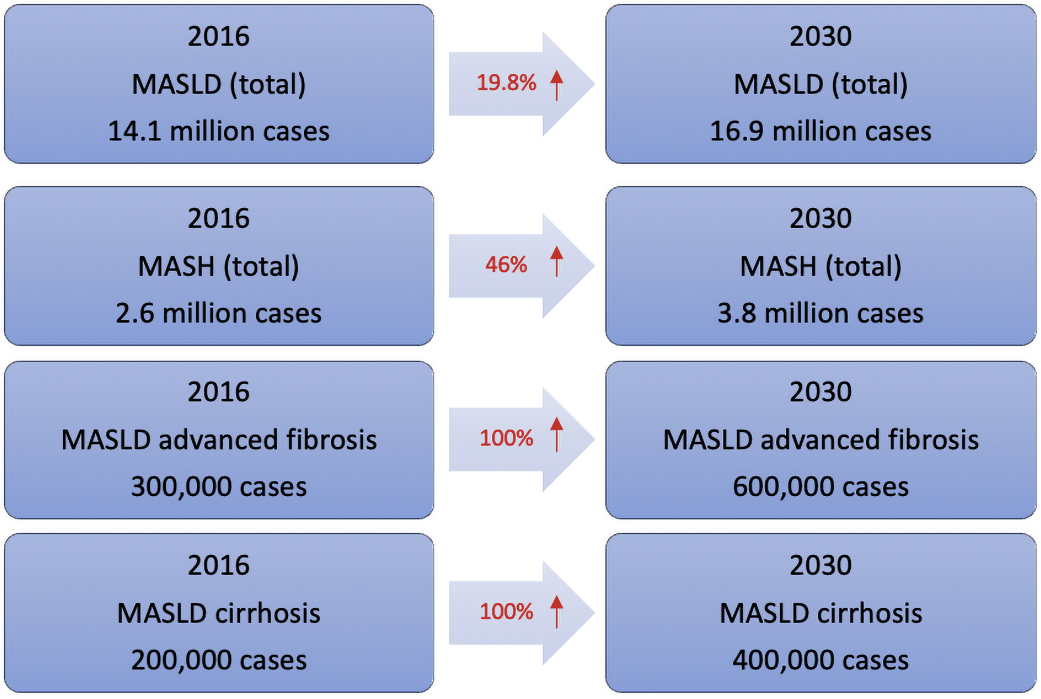

Fig. 3. Projected increase in the burden of MASLD in the UK by 2030. Created with Microsoft Word 2016 (Microsoft, Redmond, WA, USA). MASLD, metabolic-dysfunction associated steatotic liver disease; MASH, metabolic-dysfunction associated steatohepatitis.

The number of HCC diagnoses attributable to MASLD is also growing rapidly and is not limited to those with advanced fibrosis or cirrhosis (Estes et al, 2018; Weinmann et al, 2014). Increasingly recognised are patients with MASLD without advanced liver disease who develop HCC. Indeed, HCC in MASLD occurs in

a non-cirrhotic liver in one-third of cases, and these are often more advanced due to their incidental detection (Vitellius et al, 2024). With the modelled increases in MASLD, it is expected that the incidence of HCC will also double. The associated human cost of HCC is significant—less than 50% of all patients with HCC are alive at 1 year (Burton et al, 2021)—as are the healthcare costs. Treatment options including surgical resection, locoregional therapy, systemic therapy and liver transplantation are all expensive and resource-intensive. A retrospective analysis based on an English registry of HCC between 2010 and 2016 found the median cost per patient over 2 years was £9065. The cost of HCC treatment for England over 5 years was estimated to be £245 million (Cullen et al, 2023). Guidelines still do not recommend routine screening for HCC in patients with MASLD however as the individual-level risk remains too low to justify the associated cost (White et al, 2012).

Timely access to diagnostic tests for MASLD in the pre-advanced stage are therefore critical, as are care pathways to manage those with fibrosis to prevent their progression to advanced disease and HCC. Furthermore, a delicate balance must be struck between improving the identification of patients with MASLD in the general population and referral of select patients to specialised hepatology centres. Guidelines on primary care screening, management and referral pathways to tertiary hepatology centres in the UK have been published by the British Society of Gastroenterology/British Association for the Study of the Liver NAFLD special interest group (McPherson et al, 2022).

Special Populations

Young Patients

Whilst the prevalence of MASLD rises with age and is greatest in those $\geq$60 years, it is becoming increasingly common in young patients. One of the largest studies to analyse the prevalence of MASLD in young adults estimated 25% of adults aged 18–35 years had MASLD (Mrad et al, 2016). However, this study was limited by the broad definitions of MASLD used (alanine aminotransferase concentration greater than 30 international units (IU)/L in men and greater than 19 IU/L in women, and a body-mass index (BMI) greater than 25 kg/m^2) thus limiting its specificity. More recently, a UK based prospective cohort study used transient elastography to estimate steatosis and fibrosis in young adults with a mean age of 24 years, finding steatosis in up to 20% of participants, severe steatosis in 10%, and fibrosis in 2.7% (Abeysekera et al, 2020). Liver fibrosis appeared to be greatest in those who had either harmful drinking patterns or steatosis on transient elastography. Given the cumulative lifetime effect of steatosis on liver and other health-related outcomes, this study suggests that patient education, reduction in alcohol consumption and management of hepatic steatosis represent important targets for intervention in young UK adults.

Lean MASLD

A subtype of MASLD that is prevalent in, though not exclusive to, young individuals is so-called 'lean' MASLD. It occurs in individuals who are of normal weight. The diagnosis is made in individuals with MASLD and BMI <25 kg/m^2 (non-Asian race) or BMI <23 kg/m^2 (Asian race). Thus, it has been postulated that its biological basis may differ from that seen in patients who have 'classic' MASLD (Albhaisi et al, 2019). Patients with lean MASLD represent a challenging scenario where the usual recommendation for substantive weight loss is less applicable, though patients with lean MASLD often have other CMRF's that can be optimised such as insulin resistance and dyslipidaemia.

Up to 20% of the global MASLD population are lean, and among this population, 29% have significant fibrosis and 3% have cirrhosis (Ye et al, 2020). A recent meta-analysis also suggested lean MASLD patients have higher rate of all-cause mortality than non-lean MASLD patients (13.3 deaths per 1000 person vs. 10.6 deaths per 1000 person years); however, liver-related deaths and cirrhosis were lower (3.6 liver-deaths per 1000 person years vs. 7.1 and 2.3 cirrhosis diagnoses per 1000 person-years vs. 5.7) (Huang et al, 2024). The higher mortality was driven by greater cardiovascular and cancer related deaths in the lean MASLD group. Other studies however have suggested lean MASLD patients have similar disease severity and clinical outcomes as their non-lean counterparts (De et al, 2023). Regardless, it is clear from the available evidence that MASLD in lean patients confers both liver and other health-relate adverse outcomes, highlighting the need to study and develop disease-modifying therapies for this special population.

Current management guidelines published by the American Gastroenterological Association (AGA) recommend first excluding other causes of suspected MASLD (viral hepatitis, drug-induced liver injury, autoimmune hepatitis, cholestasis) and then risk stratifying patients with lean MASLD to identify those with 'at risk MASH', advanced fibrosis or cirrhosis using non-invasive tests (FIB-4 score, transient elastography and magnetic resonance elastography) and liver biopsy (Long et al, 2022). In patients deemed low risk, weight loss of 3–5% and exercise followed by reassessment after 1 year are still recommended as they can significantly improve hepatic steatosis. Illustrating this, a large longitudinal study of 2000 lean MASLD patients demonstrated the benefit of modest weight reduction on MASLD resolution (measured by abdominal ultrasound) over 3 years in a dose-dependent manner (Sinn et al, 2021). Supporting this, an randomised-controlled trial (RCT) examined the effect of a 12-month lifestyle intervention on MRI fat fraction in lean and obese MASLD patients, finding that one-half of lean patients had resolution of their MASLD with just 3–5% weight loss (compared to 7–10% in obese patients) (Wong et al, 2018). These studies thus support the role of modest weight reduction in lean MASLD patients. Furthermore, AGA guidelines recommend that in patients with biopsy-proven MASH or who are deemed high risk, 800 IU daily vitamin E in non-diabetics or 30-mg daily pioglitazone can also be considered in addition to weight loss and exercise; however, it is worth noting that a recent EASL clinical practice guideline did not recommend either of these treatments for MASH regardless of lean or obese status (Tacke et al, 2024). Taken together, this highlights the need for

a very individualised approach when managing lean MASLD patients, where the potential benefits, risks and areas of uncertainty need to be clearly discussed with each patient. MASH or high-risk patients should be serially monitored for disease progression every 6–12 months and considered for clinical trials.

New and Emerging Drug Treatments for MASLD

Recent years have seen a paradigm shift in the treatment of MASLD. Lifestyle interventions such as weight loss and dietary improvement were, and still are, the mainstay of management. Weight loss through lifestyle intervention improves biopsy-proven MASH proportionate to the degree of weight loss. A previous study demonstrated that $\geq$5% weight loss after 52 weeks resulted in MASH resolution in 58% of subjects, and a 2-point reduction in the NAFLD activity score (NAS) in 82%, compared to 32% in those who lost $<$5% of their weight ($p < 0.001$) (Vilar-Gomez et al, 2015). The greatest improvements were seen in those who lost $>$10% body weight (90% resolution of MASH and 100% 2-point reduction in NAS).

Effective pharmacotherapeutics have been severely lacking. Multiple agents such as pioglitazone and vitamin E have been trialled, however have either failed to demonstrate robust randomised-controlled trial (RCT)-level evidence, or have been associated with deleterious side effects (e.g., weight gain with pioglitazone) (Sanyal et al, 2010; Staels et al, 2023). In a previous RCT in patients with biopsy-proven MASH, pioglitazone treatment for 96 weeks did not result in a higher rate of improvement in non-diabetic MASH as compared to placebo (34% vs. 19%, $p = 0.04$ with pre-specified significance set at $p = 0.025$). Furthermore, fibrosis scores did not improve after treatment and subjects had a mean weight gain of 4.7 kg ($p < 0.001$ compared to placebo) (Sanyal et al, 2010). In the same trial, vitamin E 800 IU for 96 weeks was more effective at improving MASH compared to placebo (43% vs. 19%, $p = 0.001$), but there was no improvement in fibrosis score ($p = 0.24$). As previously noted, European guidelines have therefore not recommended either drug as MASH-targeted treatments (Tacke et al, 2024). Clearly, there has been an unmet need for therapies that can reverse the progression of steatohepatitis and fibrosis to cirrhosis and HCC. An emerging body of literature suggests that three classes of medication—GLP-1 RAs, THR-β agonists and FGF21 agonists—can reverse this progression, potentially offering new treatment options in the MASLD sphere (Table 1); however, no head-to-head trials comparing these new treatments to existing treatments currently exist.

Glucagon-Like Peptide-1 Receptor Agonists

GLP-1 RAs, single or duel (i.e., glucose-dependent insulinotropic polypeptide [GIP]-GLP-1 RAs) induce weight loss through mechanisms including inhibition of appetite and enhanced post-prandial satiety, mediated both centrally and peripherally via reduced gastric motility (Drucker, 2022). As previously noted, modest weight loss of 5–10% total body weight achieved with lifestyle intervention significantly improves steatohepatitis and fibrosis in patients with MASLD (Vilar-Gomez et al, 2015), thus research has examined whether such benefits can also occur with GLP-1 RAs-mediated weight loss. An early study of liraglutide 1.8 mg/day for 48

Table 1. Summary of key clinical trial results of emerging MASLD pharmacotherapies.

Author (Year)	Study drug	Cohort	Treatment	Primary endpoint(s)	Results	Adverse events
Newsome (2021)	Semaglutide (Phase 2)	320 adults with biopsy-confirmed MASH with NAS of 4 or higher and fibrosis stage F1, F2, or F3	Semaglutide 0.1 mg, 0.2 mg, 0.4 mg weekly, or placebo for 72 weeks	Resolution MASH with no worsening of fibrosis	In patients with F2-F3 fibrosis: MASH resolution occurred in 40% (0.1 mg) vs. 36% (0.2 mg) vs. 59% (0.4 mg) vs. 17% (placebo) ($p < 0.001$). Fibrosis improvement (≥1 stage): N.S in semaglutide (43%) vs. placebo (33%).	GI events, primarily mild to moderate, included nausea in 30–42% with semaglutide (depending on dose) vs. 11% placebo, vomiting in 15–22% vs. 2%, diarrhoea in 20–29% vs. 14% and constipation in 16–22% vs. 12%. Gallbladder-related AE's numerically more common with semaglutide. No cases of acute pancreatitis.
Loomba (2024)	Tirzepatide (Phase 2)	190 adults with biopsy-confirmed MASH with NAS of 4 or higher and stage F2 or F3 fibrosis	Tirzepatide 5 mg, 10 mg, or 15 mg weekly, or placebo for 52 weeks	Resolution MASH with no worsening of fibrosis	MASH resolution: 44% (5 mg) vs. 56% (10 mg) vs. 62% (15 mg) vs. 10% (placebo) ($p < 0.001$). Fibrosis improvement (≥1 stage): 55% (5 mg) vs. 51% (10 mg) vs. 51% (15 mg) vs. 30% (placebo). Trial not powered for this outcome.	GI events, primarily mild to moderate, included nausea in 34–44% with tirzepatide (depending on dose) vs. 12% placebo, diarrhoea in 27–36% vs. 23% and constipation in 15–23% vs. 6%. Discontinuation was similar in both tirzepatide groups (4–8% depending on the dose of tirzepatide) and the placebo group (4%). No cases of pancreatitis.
Sanyal (2024)	Survodutide (Phase 2)	293 adults with biopsy-confirmed MASH and fibrosis stage F1 to F3	Survodutide 2.4 mg, 4.8 mg, or 6.0 mg weekly, or placebo for 48 weeks	Histological improvement (reduction in MASH) with no worsening of fibrosis	MASH improvement: 47% (2.4 mg), 62% (4.8 mg), 43% (6.0 mg) vs. 14% (placebo) ($p < 0.001$). Fibrosis improvement (≥1 stage): 34%–36% with survodutide vs. 22% with placebo. Trial not powered for this outcome.	GI events more common with survodutide and included nausea (63–68% vs. 23%), diarrhoea (41–56% vs. 23%), and vomiting (37–46% vs. 4%). Discontinuation was greater with survodutide (20%) than placebo (3%). Survodutide groups had higher rates of asymptomatic pancreatic enzyme elevation (lipase or amylase level ≥3 times the upper limit of the normal).

Table 1. Continued.

Author (Year)	Study drug	Cohort	Treatment	Primary endpoint(s)	Results	Adverse events
Harrison (2024)	Resmetirom (Phase 3)	966 adults with biopsy-confirmed MASH and fibrosis stage F1B, F2, or F3	Resmetirom 80 mg, 100 mg, or placebo daily for 52 weeks	(1) Resolution of MASH with no worsening of fibrosis (2) Reduction in fibrosis stage by 1 or more with no worsening of NAS	MASH resolution: 25.9% (80 mg), 29.9% (100 mg) vs. 9.7% (placebo) ($p < 0.001$). Fibrosis improvement: 24.2% (80 mg), 25.9% (100 mg) vs. 14.2% (placebo) ($p < 0.001$).	GI events, primarily mild to moderate in severity, were more common with resmetirom than placebo. Nausea occurred in 18.5–22% of patients with resmetirom vs. 12.5% placebo and diarrhoea in 27–33% vs. 16%. Incidence of serious AE's were similar in all groups. Discontinuation of resmetirom was higher in the 100-mg resmetirom group (7.7%) than in the 80-mg group (2.8%) and placebo group (3.4%).
Loomba (2023b)	Pegozafermin (Phase 2b)	222 adults with biopsy-confirmed MASH and stage F2 or F3 fibrosis	Pegozafermin 15 mg or 30 mg weekly, 44 mg every 2 weeks, or placebo weekly or every 2 weeks for 24 weeks	(1) Resolution of MASH with no worsening of fibrosis (2) Reduction in fibrosis stage by 1 or more with no worsening of MASH	MASH resolution: 37% (15 mg), 23% (30 mg), 26% (44 mg) vs. 2% (placebo) ($p < 0.05$ except for 15 mg group). Fibrosis improvement: 22% (15 mg), 26% (30 mg), 27% (44 mg) vs. 7% (placebo) ($p < 0.05$ except for 15 mg group).	AE's were mostly mild or moderate in severity and were predominantly nausea (19–32% with pegozafermin vs. 9% with placebo), diarrhoea (14–24% vs. 6%) or injection site erythema (5–15% vs. 4%). One case of acute pancreatitis related to pegozafermin. Discontinuation was higher with pegozafermin than with placebo (2–6% depending on dose vs. 0).

MASLD, metabolic-dysfunction associated steatotic liver disease; MASH, metabolic-dysfunction associated steatohepatitis; NAS, NAFLD activity score; N.S, not significant; GI, gastrointestinal; AE, adverse event.

weeks showed a higher proportion of histological resolution of MASH in patients treated with liraglutide than placebo (39% vs. 9%) (Armstrong et al, 2016). Following this, the largest phase 2 GLP-1 trial to date enrolled 320 patients and examined the effects of weekly 0.1 mg, 0.2 mg or 0.4 mg semaglutide for 72 weeks in patients with MASH and F1, F2 or F3 fibrosis. The percentage of patients with MASH resolution was as high as 59% in the 0.4 mg semaglutide group compared to 17% in the placebo group; however, there was no difference in the proportion of patients who had an improvement in their fibrosis stage with any dose of semaglutide (Newsome et al, 2021). Adverse events (AEs) were more common with semaglutide than placebo and were predominantly mild to moderate in severity. Nausea, vomiting, diarrhoea, constipation and abdominal pain were the most common AE's. Gallbladder-related disorders including cholelithiasis and cholecystitis were numerically more common with semaglutide (15 events in 239 patients vs. 2 events in 80 placebo patients). There were no cases of acute pancreatitis. A large phase 3 semaglutide study is currently underway, as are trials that combine semaglutide with lipogenesis inhibitors (Alkhouri et al, 2022; Loomba et al, 2021).

Furthermore, the dual glucagon/GLP-1 receptor agonist survodutide has shown promising histological benefits in a phase 2 MASH trial of 293 patients (Sanyal et al, 2024). Among survodutide-treated patients, after 48 weeks of treatment, 43–62% (depending on whether in the 4.8 mg per week group or 6.0 mg per week group) showed improvement in MASH with no worsening of fibrosis compared to 14% placebo. Sub-analysis of those with F2-F3 fibrosis showed that up to 64.5% achieved an improvement in fibrosis by one stage or more compared to 25.9% in the placebo group ($p < 0.001$); however, this finding needs confirmation in a phase 3 trial. AE's were more frequent with survodutide than placebo including nausea (66% vs. 23%), diarrhoea (49% vs. 23%), and vomiting (41% vs. 4%). Discontinuation of study drug was higher with survodutide (20%) compared to placebo (3%) and related mainly to gastrointestinal side effects that occurred during the dose-escalation phase. A phase 3 trial is planned to further elucidate the effects of survodutide treatment on MASH with fibrosis.

Most recently, a landmark phase 2 trial examined the effects of tirzepatide—a dual GIP-GLP-1 RAs—on MASH with associated F2-F3 fibrosis for 52 weeks, and found that among 157 participants with paired pre-post treatment liver biopsies, a dose-response resolution of MASH without worsening of fibrosis was observed—44% in the 5-mg tirzepatide group, 56% in the 10-mg tirzepatide group and 62% in the 15-mg tirzepatide group, compared to 10% in the placebo group (Loomba et al, 2024). The percentage of patients who had an improvement of at least one fibrosis stage without worsening of MASH after treatment was greater with 5 mg, 10 mg and 15 mg of tirzepatide than with placebo (51–55% vs. 30%); however, the study was not sufficiently powered evaluate the effect of tirzepatide on fibrosis. Further limitations include the exclusion of patients with cirrhosis, and the short duration meaning major adverse liver outcomes (decompensation, need for liver transplantation, or death) were not examined. AE's were common in both tirzepatide (92%) and placebo (83%) groups, predominantly mild or moderate in severity, and included nausea in 34–44% of tirzepatide-treated patients compared

to 12% placebo, diarrhoea in 27–36% compared to 23% and constipation in 15–23% compared to 6%. Discontinuation of the study drug due to an AE was similar in tirzepatide groups (4–8% depending on the dose of tirzepatide) and the placebo group (4%). There were no cases of acute pancreatitis. Larger and longer studies are still necessary to confirm its benefits in MASH and evaluate its effects on fibrosis. Nevertheless, it is likely that tirzepatide and similar mechanism of action drugs will be adopted into the MASLD treatment armamentarium.

The effects of these drugs in patients with MASH and established cirrhosis remains uncertain, with a study of 71 patients with compensated cirrhosis showing no benefit on fibrosis or MASH resolution (Loomba et al, 2023a). Reports of liver decompensation following rapid weight loss have been reported (Peverelle et al, 2023), and so there is currently insufficient evidence to recommend GLP-1 RAs as treatments for MASH with established cirrhosis.

Overall, research demonstrates an improvement in histological MASH activity and resolution in patients who are treated with GLP-1 RAs and GIP-GLP-1 RAs. Future clinical practice will see the adoption of these drugs in the management of patients with MASLD to reduce steatohepatitis with the aim of halting fibrotic progression and potentially reversing established fibrosis, though this has yet to be demonstrated in trials. There also remain unanswered questions to guide their use, including whether predictors of treatment response exist, non-histological markers of treatment response and their correlation to histology, optimal dosing that maximises benefit whilst minimising risk of AE's, and duration of treatment. Future clinical trials are also required that are powered to examine whether these drugs can reverse hepatic fibrosis.

Liver-Directed Thyroid Hormone Receptor Agonists

Thyroid hormones reduce hepatic steatosis and can interfere with fibrogenesis by inhibiting TGF-β signalling, providing a rationale for the use of liver-specific thyromimetics in MASLD (Alonso-Merino et al, 2016; Ritter et al, 2020). Resmetirom is an orally-active, liver-specific THR-β agonist that has been approved in the USA for use in MASH. A recent phase 3 trial enrolled patients with MASH and F2 or F3 fibrosis and randomised them to receive 80-mg resmetirom (if bodyweight $<$100 kg), 100-mg resmetirom (if $>$100 kg) or placebo for 52 weeks (Harrison et al, 2024). Patients treated with resmetirom had greater rates of MASH resolution without worsening of fibrosis (25.9% of the patients in the 80-mg resmetirom group and 29.9% of those in the 100-mg resmetirom group, as compared with 9.7% of those in the placebo group [$p < 0.001$ for both comparisons with placebo]) and had greater rates of fibrosis improvement by at least one stage with no worsening of MASH (24.2% of the patients in the 80-mg resmetirom group and 25.9% of those in the 100-mg resmetirom group, as compared with 14.2% of those in the placebo group [$p < 0.001$ for both comparisons with placebo]). Resmetirom is therefore the first MASH-targeted therapy to demonstrate fibrosis regression in treated patients in a phase 3 study. Liver enzymes and serum lipids were also lower with treatment, whilst the effects on glycaemic index and weight were neutral. Gastrointestinal side effects were more common with resmetirom (diarrhoea up to 33% and nausea up

to 22% compared to 16% and 13% in placebo group); however, serious AE's were similar across groups (10.9% in the 80-mg resmetirom group, 12.7% in the 100-mg group and 11.5% in the placebo group). Discontinuation of the drug was higher in the 100-mg resmetirom group (7.7%) than in the 80-mg group (2.8%) and placebo group (3.4%). Liver-related outcome data was not reported and the trial is ongoing to determine these effects. Whilst the results are promising, approximately 70–75% of treated patients did not meet the pre-specified histological criteria, highlighting the need for other MASH-directed therapies. Furthermore, how resmetirom fits into the treatment paradigm of MASLD and its use in combination with other treatments such as GLP-1 RAs is uncertain. Future studies are needed to ascertain this and to determine predictors of who will respond to treatment. Patients with lean MASLD, in whom weight loss and optimising metabolic risk factors are less applicable, also represent a potential group of patients in whom resmetirom could be of benefit and who require future clinical trial data.

FGF21 Agonists

FGF21 modulates lipid and glucose metabolism by enhancing lipogenesis and insulin sensitivity, as well as also regulating energy expenditure (Lee et al, 2014). Owing to its short half-life and poor bioavailability, FGF21 is limited, and thus analogues are being studied. As a drug class, FGF21 agonists show promise in the treatment of MASH. A meta-analysis of eight RCT's involving 963 patients treated with either efruxifermin, pegbelfermin, pegozafermin or placebo reported significantly improved fibrosis with no worsening of MASH (risk ratio [RR] = 1.83) and at least two-point improvement in the NAS with no worsening of fibrosis (RR = 2.85) (Jeong et al, 2024). Side effects of nausea and diarrhoea were higher in treated patients.

Of the three FGF21 agonists developed, the most robust evidence exists for pegozafermin, with the recent phase 2b ENLIVEN trial in MASH with F2 or F3 fibrosis demonstrating that 22–27% of pegozafermin-treated patients improved their fibrosis stage by 1 or more (compared to 7% placebo) and 23–37% had resolution of their MASH (Loomba et al, 2023b). Improvements in liver biochemistry, serum triglycerides, and high-density lipoprotein cholesterol were also found. AE's were more common with pegozafermin treatment than placebo (95% in 15-mg weekly group, 85% in 30-mg weekly group, 67% in 44-mg fortnightly group and 68% in placebo group) but were mostly mild or moderate and predominantly nausea or diarrhoea or injection site erythema. One patient who received a single dose of 44-mg pegozafermin developed acute pancreatitis that was judged to be related to the drug. AE's that led to drug discontinuation occurred in 5% of patients receiving the 15-mg dose of pegozafermin (diarrhoea in one patient), in 6% of those receiving the 30-mg dose (diarrhoea in two patients, nausea in one, and injection-site erythema in one), in 2% of those receiving the 44-mg dose (due to pancreatitis in one), and in no patients receiving placebo. The short duration of follow-up (24 weeks) is a limitation and a single-blind extension study for an additional 24 weeks is therefore ongoing. Furthermore, a large phase 3 RCT—the ENLIGHTEN-Fibrosis trial—is currently underway and will look to build on the results of the ENLIVEN trial.

Conclusion

The new nomenclature in the SLD-space is designed to emphasise the cardiometabolic dysfunction that drives the pathogenesis of MASLD, provide a positive diagnostic criterion for clinicians, and address the stigmatisation that was previously encountered in the NASH and NAFLD era. With the projected human and healthcare system costs in the UK expected to rise dramatically in the next decade, effective disease-modifying treatments are necessary to stave off the accelerating burden of MASLD. Of studied agents, GLP-1 RAs—both single and dual mechanism agonists—as well as the THR-β agonist resmetirom and FGF21 agonists have the strongest accumulation of evidence to date. Future practice will see greater fidelity in using these medications to manage MASH, including potentially in combination with one another, while new drug classes will also emerge to add to the expanding treatment armamentarium.

Key Points

- The terms NAFLD and NASH have now been replaced by the terms MASLD and MASH to highlight the central role that cardiometabolic dysfunction plays in its pathogenesis.
- MetALD encompasses liver disease caused predominantly by alcohol excess also steatosis secondary to cardiometabolic risk factors.
- The human and healthcare burden of MASLD in the UK is high despite the majority of individuals being undiagnosed, and it is expected to increase substantially over the years.
- Young patients with MASLD and patients with so-called ‘lean MASLD’ require special consideration and tailored management strategies.
- A number of emerging pharmacotherapies have shown evidence in reducing steatohepatitis and fibrosis in MASLD, in particular GLP-1 RAs and the liver-specific THR-β agonist resmetirom, with FGF21 agonists also being studied.

Abbreviations

SLD, steatotic liver disease; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MASLD, metabolic-dysfunction associated steatotic liver disease; MASH, metabolic-dysfunction associated steatohepatitis; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; THR-β, thyroid hormone receptor-β; FGF21, fibroblast growth factor 21; MetALD, metabolic and alcohol related/associated liver disease; CMRF, cardiometabolic risk factor; EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of the Liver; ALD, alcoholic liver disease; DALYs, disability-adjusted life years; GIP, glucose-dependent insulinotropic polypeptide; RCT, randomised-controlled trial.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

MP and DJ designed the research study. MP and MM acquired the data. MP, MM and DJ analysed and interpreted the data. MP, MM and DJ contributed to the drafting of the manuscript. MP revised the manuscript for important intellectual content. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Fig. 1 was created using BioRender.com. Fig. 2 was created using smartdraw.com. The authors have no financial or personal relationship with BioRender.com and smartdraw.com, and the use of these tools does not imply any endorsement. The authors declare no conflict of interest.

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