MASLD as Complication of Diabetes

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Worldwide metabolic dysfunction–associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease. Despite high global prevalence, MASLD is not yet recognized as a noncommunicable disease, although all of the criteria are fulfilled for such a classification. MASLD is strongly associated with type 2 diabetes, cardiovascular disease, chronic kidney disease, and certain extrahepatic cancers. At 65% and 37% the prevalence of MASLD is extremely high in adults and children with type 2 diabetes, respectively. The pathogenesis of MASLD is closely related to that of type 2 diabetes, and diabetes-associated hyperglycemia, hyperinsulinemia, and hyperlipidemia promote progression from simple steatosis to hepatic inflammation and fibrosis. Thus, MASLD is now considered a complication of diabetes. However, there is still a great deal of work to be done to implement screening for and treatment of MASLD in everyday clinical diabetes management. In this article, the major mechanisms involved in the pathogenesis of MASLD and type 2 diabetes are discussed. Furthermore, the heterogeneity in the pathophysiology of MASLD and clusters in MASLD that may be relevant for future stratification of MASLD-associated risk of diseases are addressed. Finally, because of their strong hepato-, cardio-, and nephroprotective effects this article provides support as to why sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor (co)agonists should be used as first-line pharmacotherapies in people with MASLD and type 2 diabetes.

In 2022, 828 million people worldwide aged 18 years or older were diagnosed with diabetes (1). Global diabetes-related mortality steadily increased during the last two decades and today ranks eighth among the diseases with the most years of life lost (2). In countries with high-income populations, 20-year-old people with diabetes lose between 2.5 and 12.9 years of life expectancy, and globally a 10-year-old child with type 1 diabetes loses an alarmingly high 24 years of life expectancy (3,4).

Cardiovascular disease (CVD) is the main cause of death in people with diabetes. However, in people with diabetes considerable premature death is also observed from other causes, such as renal diseases, several cancers, and infectious diseases (5,6). Increased morbidity and mortality are observed not only for people with diabetes but also for those with prediabetes (5,7). Over the past decade, data have emerged showing that metabolic dysfunction–associated steatotic liver disease (MASLD) is highly prevalent in people with diabetes; that the liver is a critical, often underrecognized target of metabolic derangement, with MASLD often developing in prediabetes; and that MASLD is also associated with increased complications in people with diabetes. Furthermore, MASLD is involved in the pathogenesis of diabetes and CVD (8–10). This knowledge resulted in immense interest in the scientific community in better understanding the causes and complications of MASLD, particularly those related to diabetes. Therefore, the main goal of the present article is to synthesize new evidence on the bidirectional nature of diabetes and MASLD and to highlight how this knowledge can be used for better treatment of patients with both diseases.

EPIDEMIOLOGY OF MASLD AND ITS RELATIONSHIP WITH OBESITY, DIABETES, AND PREDIABETES

Worldwide, MASLD became the most common chronic liver disease, affecting up to 38% of the adult population

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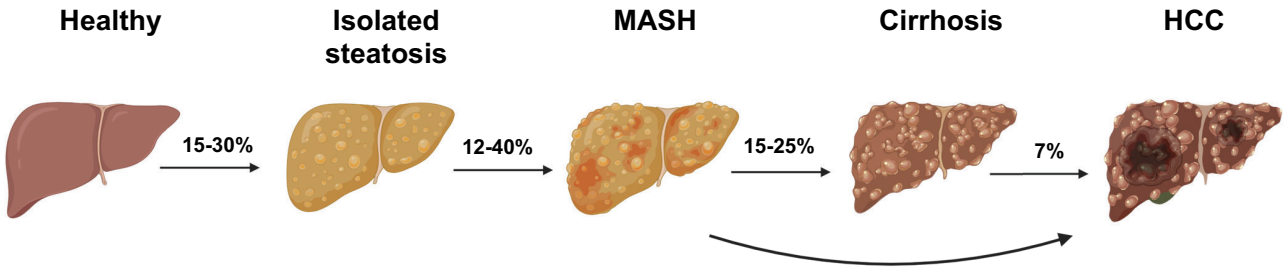

Figure 1—The natural history of MASLD. Information derived from review articles and meta-analyses, including both observational and randomized controlled studies (19–22).

(11). In addition, the global prevalence of MASLD is expected to further increase during the next two decades (12). For example, in the U.S., the prevalence of MASLD is predicted to increase from 34% (86 million people) in 2020 to 41% (122 million people) by 2050 (13). MASLD is an increasingly important contributor not only to liver-related but also to extrahepatic morbidity and mortality worldwide. This observation supports that the clinical burden of MASLD clearly extends far beyond the liver, making it a multisystem disorder. While among people with MASLD <10% develop liver-related complications, the major causes of death are CVD and cancer (11,14).

Today, the highest global pooled prevalence of MASLD is found among people with obesity (75% [95% CI 71–79]) (15) and type 2 diabetes (65% [61–68]) (16). Among people with obesity (34% [28–39]) and people with diabetes (32% [17–51]) there is also a very high prevalence of the advanced form of MASLD, metabolic dysfunction–associated steatohepatitis (MASH) (15,16). Furthermore, at 37% (95% CI 26–48), the prevalence of MASLD is also very high among children and adolescents with type 2 diabetes (17). This very early onset of MASLD may have severe long-term consequences for the liver, such as higher risk for cirrhosis and hepatocellular carcinoma (HCC). In addition, among adults with prediabetes prevalence of MASLD is approximately twofold higher in comparison with people with normal glucose regulation, independently of adiposity (18). The findings that overweight and hyperglycemia are tightly related to MASLD indicate that there are joint pathomechanisms promoting adiposity, hyperglycemia, and MASLD. Furthermore, hyperglycemia may promote hepatic steatosis and inflammation, and the steatotic and inflamed liver may also be involved in the pathogenesis of type 2 diabetes. Thus, there may be a vicious cycle between increased liver fat content and insulin resistance–associated hyperglycemia promoting the progression of both diseases.

SEVERITY OF METABOLIC DYSFUNCTION AND ITS IMPACT ON MASLD DISEASE PROGRESSION

The natural history of MASLD is complex, with a large variability in its progression that can occur over decades. Approximately 15%–30% of people develop isolated hepatic steatosis, and among them 12%–40% progress to MASH. Approximately 15%–25% of people with MASH progress to cirrhosis, and 7% of them develop HCC. However, HCC is also increasingly observed in people with MASH and without cirrhosis (19–22) (Fig. 1).

It has been well established that obesity, particularly abdominal obesity, and impaired glucose metabolism—insulin resistance, prediabetes, and type 2 diabetes—are among the most important risk factors for progression of MASLD (23,24). For example, in people with MASLD, besides MACE, obesity-related cancers, and all-cause mortality, the number of metabolic syndrome traits also considerably influenced the risk and incidence of liver-related outcomes. In comparing MASLD with one versus five metabolic syndrome traits, respectively, with the reference, among 502,381 UK Biobank participants, the adjusted hazard ratios (aHRs) for major adverse liver outcomes were 2.27 (95% CI 1.03–5.00) and 9.19 (4.98–16.95) (24).

Additionally, having type 2 diabetes is associated with increased relative risk of fibrosis progression. For example, in 447 adult participants with MASLD who had paired liver biopsies >1 year apart, aHR for fibrosis progression was 1.69 (95% CI 1.17–2.43) for those with type 2 diabetes in comparison with those without diabetes (25). Furthermore, in a large prospective observational study conducted in 2,016 patients diagnosed with MASLD and fibrosis (by magnetic resonance elastography) and who were followed up for a median time of 3 years, risk was substantially higher for incident hepatic decompensation (aHR 3.29 [2.21–4.90]) (Fig. 2*A*) and incident HCC (aHR 7.72 [95% CI 2.61–22.87]) (Fig. 2*B*) for individuals with type 2 diabetes, in comparison with individuals without diabetes. Importantly, risk remained strongly elevated (aHR for hepatic decompensation 1.90 [1.21–2.96] and HCC 5.50 [1.63–15.67]) after adjustment for liver stiffness on magnetic resonance elastography (26) (Fig. 2*A* and *B*). These findings support the concept that the underlying metabolic abnormalities that lead to insulin resistance and overt type 2 diabetes also contribute to the progression of MASLD. Furthermore, because of the role of high glucose levels activating profibrogenic pathways (27) and the important role of an increased glycolytic pathway in HCC development (28), hyperglycemia puts people with diabetes at very high risk of cirrhosis and HCC. Besides

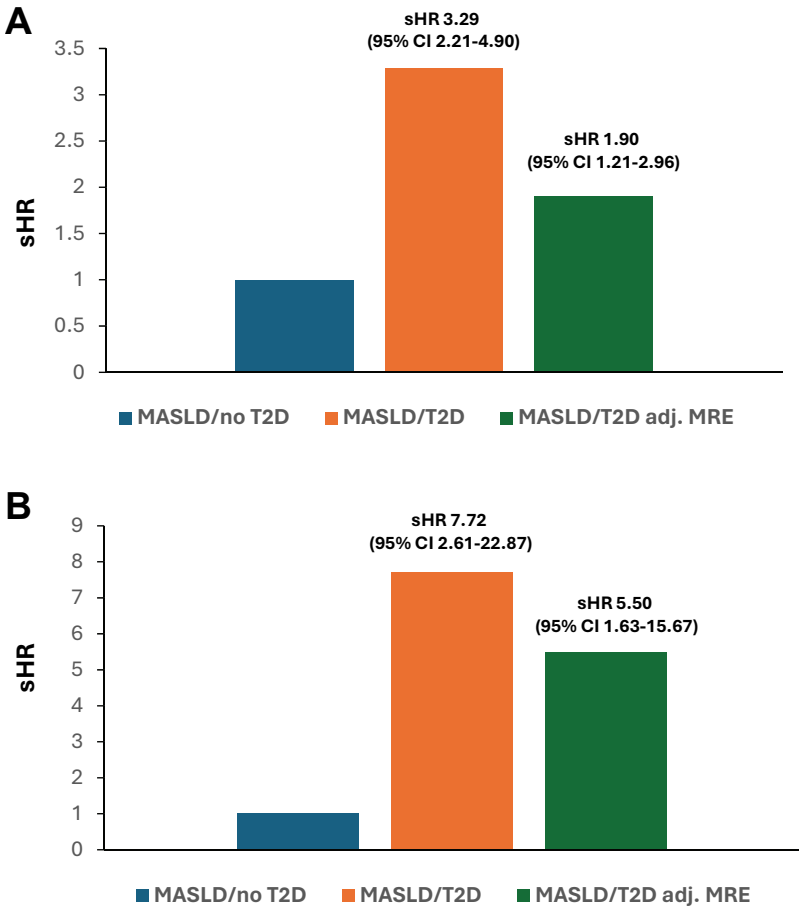

Figure 2—Risk of hepatic decompensation and HCC in people with MASLD, with or without type 2 diabetes (T2D). Data were reproduced from Huang et al. (26). Data derived from 2,016 participants (736 with type 2 diabetes and 1,280 without type 2 diabetes) from six cohorts. Subdistribution hazard ratio (sHR) for hepatic decompensation (*A*) and HCC (*B*). MASLD/T2D adj. MRE, data for those with MASLD and type 2 diabetes after adjustment for liver stiffness on magnetic resonance elastography.

hyperglycemia, the increased release of fatty acids from adipose tissue that is observed in type 2 diabetes may also promote the rapid progression of MASLD in patients with type 2 diabetes. Adipose tissue insulin resistance that is present in most patients with type 2 diabetes results in excess release of fatty acids into the bloodstream. These free fatty acids accumulate in the liver and induce lipotoxic processes (29). Thus, hyperglycemia and adipose tissue insulin resistance may strongly promote hepatic decompensation and HCC in patients with type 2 diabetes.

PATHOPHYSIOLOGY OF MASLD

The pathophysiology of MASLD is complex and has previously been extensively studied and reviewed (30–32). In brief, MASLD is not caused by a single factor but, rather, is caused by multiple simultaneous insults, in which overnutrition (particularly by Western-style diet), sedentary lifestyle, adipose tissue inflammation, metabolic factors (mainly insulin resistance and hyperglycemia), alterations in gut microbial function, and genetic predisposition play a central role (Fig. 3). The key characteristic of MASLD is the accumulation of hepatic lipid droplets that store inert and toxic lipids, triggering activation of stress pathways, inflammation, and cell death, thereby leading to liver damage and fibrosis. Excessive intake of glucose and fructose increases hepatic de novo lipogenesis (DNL). More recently, fructose was also found to potentiate hepatic reesterification of abundant circulating fatty acids and, with follistatin, to potentiate acute MASLD during complete hepatic insulin resistance (33). Together with higher intake of saturated fatty acids, this process results in subclinical inflammation in adipose tissue and the liver, and insulin resistance in adipose tissue, liver, and skeletal muscle. The mechanisms involved include lipotoxicity, mainly brought about by increased signaling via fatty acids, diacylglycerols, and ceramides. The resulting insulin resistance–associated hyperinsulinemia and hyperglycemia amplify hepatic DNL.

Furthermore, increased saturated fatty acids and hyperglycemia promote hepatic mitochondrial dysfunction, increased oxidative stress, and uncoupling of oxidative phosphorylation. In this respect hyperglycemia-associated increase of advanced glycation end products and glucose

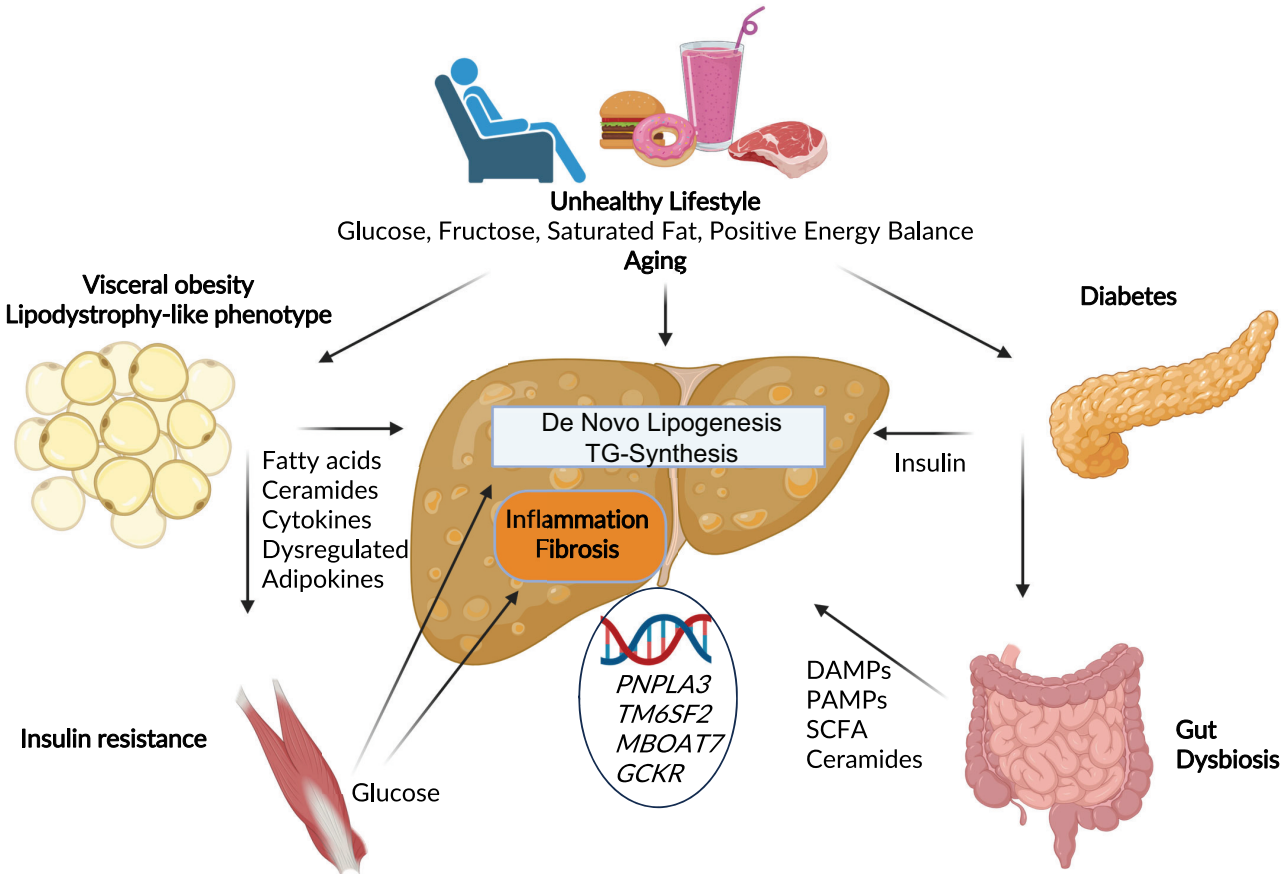

Figure 3—Overview of the key factors in the pathophysiology of MASLD. A positive energy balance with increased caloric intake, particularly of glucose, fructose, and saturated fat, and sedentary behavior results in increased total and visceral fat mass, type 2 diabetes, gut dysbiosis, insulin resistance, and increased hepatic DNL and triglyceride synthesis. Diabetes-associated hyperinsulinemia and hyperglycemia exacerbate hepatic DNL. Gut dysbiosis via increased release of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides, and dysregulated release of short-chain fatty acids (SCFA) and ceramides induce hepatic inflammation and fibrosis. A lipodystrophy-like phenotype with expansion of visceral adipose tissue resulting in increased release of fatty acids and ceramides and a dysregulated pattern of cytokines and adipokines is also involved in the pathogenesis of MASLD. A genetic predisposition for hepatic lipid accumulation, inflammation, and fibrosis also contributes to the pathogenesis of MASLD. *GCKR*, glucokinase regulator; *MBOAT7*, membrane-bound O-acyltransferase domain–containing 7; *PNPLA3*, patatin-like phospholipase domain–containing protein 3; *TM6SF2*, transmembrane-6 superfamily member 2.

flux through the polyol pathway are important. This cell stress and the associated macrophage activation promote a fibrogenic response in hepatic stellate cells that can progress to cirrhosis. In addition to insulin resistance, hyperinsulinemia, and proinflammatory lipid signaling, dysregulated release of adipokines and cytokines from inflamed adipose tissue and exposure to inflammatory mediators from Western diet–induced changes in the gut microbiome further fuel this pathogenic process in the liver (27–30). In most cases these processes are related to increased fat mass. However, they are also relevant for the development of MASLD in people with normal body weight ("lean MASLD") (34,35).

Apart from these global metabolic mechanisms, distinct intrahepatic pathways are involved in the pathophysiology of MASLD. The most important genetic variants associated with MASLD affect pathways that are often involved in the regulation of the mobilization of triglycerides from lipid droplets (*PNPLA3*), assembly and secretion of VLDLs (*TM6SF2*), hepatic phosphatidylinositol acylchain remodeling (*MBOAT7*), DNL (*GCKR*), or as yet unknown mechanisms (*HSD17B13*) (36,37). Adiposity was found to amplify the effects of genetic risk alleles for hepatic steatosis, steatohepatitis, and the progression to cirrhosis but not to other adiposity-associated traits (38). On the other hand, even normal-weight carriers of the *PNPLA3* rs738409 (Ile148Met) GG MASLD risk polymorphism were found to have increased liver fat content (39).

HETEROGENEITY IN THE PATHOGENESIS OF MASLD

Based on the most important detected pathomechanisms of MASLD, as of today, three major causes of MASLD can be identified (32). *1*) MASLD with a dominant hepatic genetic component. People having this phenotype have a strongly increased risk of hepatic steatosis, inflammation,

fibrosis, and HCC. However, they often have only mild insulin resistance and are protected from CVD (people with the *PNPLA3* rs738409 G and *TM6SF2* rs58542926 T MASLD risk alleles that promote a retention of lipids in the liver, resulting in lower circulating lipids). *2*) MASLD with a dominant metabolic component related to increased hepatic DNL. This phenotype is associated with a strong metabolic component characterized by increased hepatic DNL, insulin resistance, hyperglycemia, and hyperinsulinemia. People with this phenotype have not only increased risk of progression from simple steatosis to hepatic inflammation and fibrosis but also increased risk of developing type 2 diabetes and CVD. Third, MASLD with a dominant metabolic component related to adipose tissue dysfunction. People with this phenotype often have severe insulin resistance, hyperglycemia, and hyperinsulinemia. They can have overweight and obesity but can also have a lipodystrophy-like phenotype (40). People with this phenotype also have increased risk of steatosis and progression to hepatic inflammation and fibrosis, and develop type 2 diabetes and CVD (32). In most cases these phenotypes overlap, potentially creating a "synergistic" risk for rapid fibrosis. However, the identification of the predominant phenotype could facilitate management of MASLD.

CLUSTERS IN MASLD

Because of this heterogeneity in the pathogenesis of MASLD, there are efforts to use this knowledge for future stratification of MASLD-associated risk of diseases, as is presently done in the fields of obesity and type 2 diabetes research (41,42). In this respect, data dimensionality reduction strategies have been used to cluster people with MASLD (43–47). Among them, recently, a data-driven cluster analysis, with a simple algorithm based on six widely available traits—age, BMI, HbA_{1c}, ALT, LDL cholesterol, and triglycerides—identified two types of MASLD characterized by distinct clinical trajectories (46). The liver-specific cluster, which was enriched by the *PNPLA3* rs738409 G MASLD risk allele, showed a rapid progression of chronic liver disease but with a relatively low risk of CVD. The cardiometabolic cluster, which was predominantly characterized by elevated glycemia and high levels of triglycerides, had a similar incidence of chronic liver disease but higher risk of CVD and type 2 diabetes.

In a genetically based cluster approach in people with MASLD, two polygenic risk scores were identified, indicating the presence of at least two different types of MASLD phenotypes. The liver-specific phenotype was characterized by more aggressive liver disease but lower risk of CVD. The systemic MASLD phenotype was also associated with a similarly increased risk of more aggressive liver disease, but with a higher risk of CVD (47). These consistent results of the two studies using different cluster approaches (clinical and genetic) further highlight the heterogeneity of MASLD regarding its pathogenesis and risk of diseases. In the future, such data dimensionality reduction approaches might be helpful in improving the prediction of MASLD-associated risk. However, for better stratifying the risk of type 2 diabetes and CVD that is elevated in people with MASLD (8,42) the integration of knowledge about mechanisms of MASLD-mediated cardiometabolic risk—e.g., dysregulated hepatokines (e.g., fetuin-A, fibroblast growth factor 21), dyslipidemia, hypercoagulability (48,49)—will help to better achieve this goal. Furthermore, using liver phenotypes based on imaging and/or noninvasive MASLD-related biomarkers for cluster analyses may improve liver-specific risk prediction (50).

TREATMENT OF MASLD

Lifestyle modifications, including physical exercise and low caloric or Mediterranean diets, are the first-line treatment of MASLD/MASH. Based on medical guidelines to treat MASLD/MASH in adults, dietary and behavioral therapy–induced sustained weight loss of ≥5% should be achieved to reduce liver lipid content, 7%–10% to improve liver inflammation, and ≥10% to improve fibrosis (51–53). In people with lean MASLD, weight loss of 3%–5% is recommended (54). However, for most people living with MASLD, it is difficult to maintain a healthy lifestyle and a reduced body weight. For people with substantial obesity with comorbidities, bariatric surgery is a treatment option, since in patients with MASH it improves hepatic inflammation and fibrosis (55) and reduces the rate of major adverse liver outcomes and major adverse cardiovascular events (56). Furthermore, pharmacological treatment represents an important additional component in the management of MASLD.

To evaluate the efficacy of a drug for treating MASH and liver fibrosis, both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency recommend a long-term composite end point that includes all-cause mortality, histological diagnosis of cirrhosis, hepatic decompensation events, and assessments using the Model for End-Stage Liver Disease (MELD) score. However, because evaluating these long-term clinical outcomes requires considerable time, both agencies also recommend the earlier assessment of intermediate or surrogate histological end points to help accelerate regulatory approval, particularly given the urgent need for effective MASH pharmacotherapies (57).

Over the past decade, many pharmacological compounds tested in trials in people with MASH failed to achieve clinically meaningful improvements in hepatic inflammation and fibrosis or had considerable side effects (58–60). However, in March 2024 and August 2025, resmetirom (an oral, liver-directed, thyroid hormone receptor-β selective agonist) and subcutaneous semaglutide 2.4 mg/week were granted accelerated approval by the FDA for the treatment of adults with noncirrhotic MASH and moderate-to-advanced fibrosis in conjunction with lifestyle modification (9).

Here, pharmacologic therapeutic options for people with MASLD/MASH, with a focus on clinical trials with liver biopsy involving newly approved or promising metabolism-based pharmacotherapies, currently under evaluation in late-phase randomized controlled trials for the treatment of MASLD/MASH and its liver-related and extrahepatic (cardiometabolic) clinical outcomes, will be discussed (Table 1).

Sodium–Glucose Cotransporter 2 Inhibitors

Sodium–glucose cotransporter 2 (SGLT2) inhibitors very effectively not only reduce chronic hyperglycemia in patients with type 2 diabetes but also reduce risk of heart failure events and cardiovascular death for patients with type 2 diabetes, heart failure, chronic kidney disease (CKD), or CVD (61,62). SGLT2 inhibitors lower elevated blood glucose and insulin levels, thereby reducing hepatic DNL, and promote moderate weight loss. Thus, SGLT2 inhibitors may offer therapeutic benefits in the management of MASLD/MASH, particularly in patients with type 2 diabetes. Supporting this, investigators in a randomized, open-label, active-controlled phase 4 trial in adults with biopsy-confirmed MASLD and type 2 diabetes found that tofogliflozin tended to produce greater improvements in steatosis, hepatocellular ballooning, lobular inflammation, and fibrosis in comparison with glimepiride (63). Furthermore, in a phase 3 randomized, placebo-controlled study (the Dapagliflozin Efficacy and Action in NASH [DEAN] trial), including 154 adults with biopsy-confirmed MASH, with or without type 2 diabetes, greater efficacy was demonstrated with dapagliflozin 10 mg daily for 48 weeks than with placebo in achieving MASH resolution (23% vs. 8%, respectively) and fibrosis improvement (45% vs. 20%) (64). In both trials, SGLT2 inhibitors also led to more pronounced reductions in body weight and HbA_{1c} in comparison with placebo.

Glucagon-Like Peptide 1 Receptor Agonists

In addition to SGLT2 inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists revolutionized the treatment of patients with type 2 diabetes. Treatment with GLP-1 receptor agonists has been associated with significant reduction in major adverse cardiovascular events and mortality. GLP-1 receptor agonists improve heart failure, protect against progressive CKD, and are approved for the treatment of obesity. Besides increasing insulin secretion and reducing body weight, GLP-1 receptor agonists reduce systemic low-grade inflammation, mainly through weight loss, neuronal GLP-1 receptor activation, and GLP-1 receptor activation on T cells (65). Semaglutide (0.1, 0.2, or 0.4 mg s.c. daily for 72 weeks) treatment of 320 adults with obesity and biopsy-confirmed MASH and fibrosis stages F1–F3 was associated with larger MASH resolution without worsening of fibrosis in comparison with placebo (40%, 36%, and 59% in patients treated with daily doses of 0.1, 0.2, or 0.4 mg, respectively, compared with 17% in the placebo group) in a phase 2b trial (66). In part 1 of the phase 3 Effect of Semaglutide in Subjects with Noncirrhotic Non-alcoholic Steatohepatitis (ESSENCE) trial, involving 800 adults with obesity and biopsy-proven MASH and fibrosis stages 2 or 3, semaglutide at a dose of 2.4 mg s.c. weekly for 72 weeks was more effective than placebo regarding resolution of MASH without worsening of fibrosis (62.9% vs. 34.3%) and improvement in liver fibrosis with no worsening of MASH (36.8% vs. 22.4%) (67). In both trials, semaglutide significantly reduced body weight and improved plasma lipids, insulin resistance, and HbA_{1c} levels in comparison with placebo. Based on the results of part 1 of the phase 3 ESSENCE trial, on 15 August 2025 the FDA conditionally approved semaglutide 2.4 mg/week for the treatment of adults with noncirrhotic MASH and moderate-to-advanced fibrosis.

GLP-1 and GIP Receptor Coagonists

Tirzepatide, a GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor coagonist, is approved for the treatment of type 2 diabetes and obesity and has additive beneficial metabolic effects in comparison with GLP-1 receptor agonists (68). In a phase 2b trial (SYNERGY-NASH trial) involving 190 participants with obesity and biopsy-confirmed MASH and stage F2 or F3 fibrosis, once-weekly tirzepatide (5, 10, or 15 mg s.c. for 52 weeks), without worsening of fibrosis, was associated with higher percentages of MASH resolution (44% in the 5-mg, 56% in the 10-mg, and 62% in the 15-mg tirzepatide groups) in comparison with placebo (10%). Improvement in fibrosis by at least one stage was achieved in 55% of patients in the 5-mg group, 51% in the 10-mg and 15-mg groups, and 30% in the placebo group. However, the statistical significance of these improvements in liver fibrosis has not been formally tested after adjustment for multiple comparisons. Tirzepatide also more strongly reduced body weight, plasma lipids, and HbA_{1c} levels in comparison with placebo (69).

GLP-1 and Glucagon Receptor Coagonists

GLP-1 and glucagon coadministration is very effective in increasing energy expenditure and hepatic fatty acid oxidation, and decreasing liver fat content (70). In a phase 2b trial involving 293 adults with obesity and biopsy-confirmed MASH and fibrosis stage F1–F3, once-weekly administration of the GLP-1 and glucagon receptor coagonist survodutide at doses of 2.4, 4.8, or 6.0 mg s.c. resulted in significantly greater improvement in MASH with no worsening of fibrosis (47%, 62%, and 43% for the three survodutide doses, respectively) versus placebo (14%). Improvement in liver fibrosis was observed in 34% of the 6.0-mg group compared with 22% in the placebo group. Survodutide also strongly reduced body weight, plasma lipids, insulin resistance, and HbA_{1c} levels (71).

Table 1—Pharmacological treatment studies of biopsy-proven noncirrhotic MASH with focus on agents with beneficial metabolic effects

					Hepatic and metabolic effects						
Mode of action	Name	Population studied	Phase trial status	MASH resolution	Steatosis score	Inflammation score	Fibrosis score	Liver enzymes	Body weight	HbA_{1c}	Insulin resistance
SGLT2 inhibitors	Tofogliflozin 20 mg/day vs. glimepiride 0.5 mg (63)	Biopsy-proven MASLD	Phase 4	Yes	(↓)	(↓)	(↓)	↓	↓	↓	NA
	Dapagliflozin 10 mg/day vs. placebo (64)	Biopsy-proven MASH	Phase 3	Yes	↓	↓	↓	↓GGT	↓	↓	↓
GLP-1 receptor agonist	Semaglutide 0.1, 0.2, or 0.4 mg/day vs. placebo (66)	Biopsy-proven MASH plus liver fibrosis stage F1–F3	Phase 2b	Yes	↓	↓	—/(↓)	↓	↓	↓	NA
	Semaglutide 2.4 mg/week vs. placebo (67)	Biopsy-proven MASH plus liver fibrosis stage F2 or F3	Phase 3	Yes	NA	NA	↓	↓	↓	↓	↓
GIP/GLP-1 receptor coagonist	Tirzepatide 5, 10, or 15 mg/week vs. placebo (69)	Biopsy-proven MASH plus liver fibrosis stage F2 or F3	Phase 2b	Yes	↓	↓	↓	↓	↓	↓	NA
Glucagon/GLP-1 receptor coagonist	Survodutide 2.4, 4.8, or 6.0 mg/week vs. placebo (71)	Biopsy-proven MASH plus liver fibrosis stage F1– F3	Phase 2b	Yes	↓	↓	(↓)	↓	↓	↓	NA
Fibroblast growth factor 21	Pegozafermin 15 or 30 mg weekly or 44 mg once every 2 weeks vs. placebo (73)	Biopsy-proven MASH plus liver fibrosis stage F2 or F3	Phase 2b	Yes	↓	↓	↓	↓	–	–	NA
	Efruxifermin 28 or 50 mg/week vs. placebo (74)	Biopsy-proven MASH plus liver fibrosis stage F2 or F3	Phase 2b	Yes	↓	↓	↓	↓	–	–	↓
THR-β receptor agonist	Resmetirom 80 or 100 mg/day vs. placebo (76)	Biopsy-proven MASH plus liver fibrosis stage F1B, F2, or F3	Phase 3	Yes	↓	↓	↓	↓	–	–	–
PPARs	Pioglitazone (PPARγ) 30 or 45 mg/day vs. placebo (79)	Biopsy-proven NASH	Meta-analysis of phase 2 trials	Yes	↓	↓	↓	↓	↑	↓	↓
	Lanifibranor (PPARα/δ/γ; pan-PPAR agonist) 800 or 1,200 mg/day vs. placebo (81)	Biopsy-proven MASH (76% moderate or advanced fibrosis)	Phase 2b	Yes	↓	↓	↓	↓	↑	↓	↓

↓ or ↑, statistical difference vs. comparator; (↓) or (↑), statistical trend vs. comparator ($P < 0.2$) or no consistent effects among treatment groups; –, not altered. Fibrosis stages: F1, mild fibrosis; F1B, moderate perisinusoidal fibrosis; F2, moderate fibrosis; F3, severe fibrosis. GGT, γ-glutamyl transferase; GIP, glucose-dependent insulinotropic polypeptide; NA, not assessed; MASH, metabolic dysfunction–associated steatohepatitis; PPAR, peroxisome proliferator–activated receptor; SGLT2, sodium–glucose cotransporter 2; THR-β, thyroid hormone receptor-β.

Fibroblast Growth Factor 21 Analogs

The hepatokine fibroblast growth factor 21 (FGF21) is important for the regulation of glucose and lipid metabolism (72). In a phase 2b trial involving 219 patients with obesity with biopsy-confirmed MASH and stage F2 or F3 fibrosis, treatment with pegozafermin at 15 or 30 mg s.c. weekly or 44 mg s.c. every 2 weeks for 24 weeks was associated with a higher MASH resolution (37% for 15 mg/week, 23% for 30 mg/week, and 25% for 44 mg every 2 weeks) in comparison with placebo (2%). Liver fibrosis improved in 25% and 44% of patients in the 30-mg and 44-mg pegozafermin groups, respectively, compared with 7% in the placebo group (73). In a phase 2b trial involving 128 adults with obesity and biopsy-confirmed MASH and stage F2 or F3 fibrosis, efruxifermin at 28 or 50 mg s.c. weekly for 96 weeks was associated with a larger improvement of fibrosis without worsening of MASH (46% and 75%) versus placebo (24%) (74). Changes in body weight and HbA_{1c} levels did not differ significantly between the FGF21 and placebo treatment groups in both trials.

Resmetirom

Activation of the thyroid hormone receptor-β in the liver improves mitochondrial function, resulting in lower hepatic lipid content and lipotoxicity (75). In the phase 3 placebo-controlled MAESTRO-NASH trial, involving 966 patients with obesity and biopsy-confirmed MASH and stage F1b, F2, or F3 fibrosis, 80 and 100 mg resmetirom once daily for 52 weeks were associated with larger MASH resolution without worsening of fibrosis (26% and 30%, respectively) versus placebo (10%). Improvement in fibrosis by one or more stages without worsening of MASH was also significantly greater in the 80-mg (24%) and 100-mg (26%) resmetirom groups than in the placebo group (14%). Resmetirom improved plasma concentrations of LDL cholesterol, triglycerides, and lipoprotein(a) but had neutral effects on body weight, HbA_{1c}, and insulin resistance (76). Based on these results, resmetirom was conditionally approved by the FDA on 14 March 2024, and by the European Medicines Agency on 19 August 2025, for the treatment of adults with noncirrhotic MASH and moderate-to-advanced fibrosis.

Pioglitazone

Activation of the peroxisome proliferator–activated receptors (PPARs) improves glucose and lipid metabolism and inhibits proinflammatory and fibrotic processes. Among the three PPAR isotypes (α, β/δ, and γ) (77), the PPARγ agonist pioglitazone is approved for the treatment of type 2 diabetes, and it is protective against acute myocardial infarction and ischemic stroke (78). In a meta-analysis of five phase 2b randomized trials (315 participants with and without type 2 diabetes) pioglitazone treatment (up to 45 mg/day) for 6–24 months was found to significantly improve liver histology in patients with biopsy-confirmed MASH and liver fibrosis (odds ratio [OR] 3.65 [95% CI 2.32–5.74] for MASH resolution and 4.53 [1.52–13.52] for improvement in advanced fibrosis [stages F3–F4] vs. control groups) (79). Moderate weight gain (up to nearly 2.5% from baseline), especially in subcutaneous fat rather than visceral fat, as also previously documented (80) was observed (79).

Lanifibranor

In a phase 2b placebo-controlled clinical trial in 247 patients with obesity with biopsy-proven MASH and liver fibrosis, the PPARα, PPARδ, and PPARγ (pan-PPAR) agonist lanifibranor (800 or 1,200 mg daily for 24 weeks) was evaluated. A decrease of at least 2 points in the histologic SAF-A score (the activity component of the Steatosis, Activity, Fibrosis [SAF] scoring system that incorporates scoring for ballooning and inflammation) without worsening of liver fibrosis was observed in 55% of patients treated with the 1,200-mg dose of lanifibranor vs. 33% in the placebo group. Improvement in liver fibrosis without worsening of MASH was observed in 48% of patients at the 1,200-mg dose of lanifibranor, compared with 29% in the placebo group. Lanifibranor treatment was associated with improvement of plasma lipids, insulin resistance, and HbA_{1c} levels, and with a moderate increase of body weight (up to nearly 2.5%), compared with placebo (81).

Precision Medicine for MASLD Treatment

While lifestyle intervention and most pharmacological treatment approaches of MASLD/MASH have shown promising results, in most patients with MASLD/MASH no large improvement of the liver phenotype is observed. This may be due to the fact that it is difficult to maintain a healthy lifestyle for a longer period of time and that some medications are discontinued too early due to side effects. In addition, the heterogeneity in the pathogenesis of MASLD may also explain the heterogeneous outcomes of interventions. In the future, this knowledge of heterogeneity in the pathogenesis and cardiometabolic risk of MASLD may also lead to personalized treatments. For example, for people having MASLD with a strong metabolic component related to hepatic DNL a strong focus of the intervention might be decreased glucose and fructose intake and pharmacological treatment approaches to reduce hepatic DNL. For patients with MASLD with a strong metabolic component related to adipose tissue dysfunction the most effective treatment of MASLD/MASH might be PPAR agonists. However, in some people, the pathogenesis of MASLD cannot be clearly determined. In this regard, combination therapies may be considered. First results from phase 1 and phase 2a clinical trials indicate that combination therapies are more effective than single pharmacological approaches in improving clinical parameters of MASLD (82,83).

SPECIFIC RECOMMENDATIONS TO TREAT MASLD IN PEOPLE WITH TYPE 2 DIABETES

There are modifiable and nonmodifiable risk factors of MASLD and its progression to severe liver diseases that

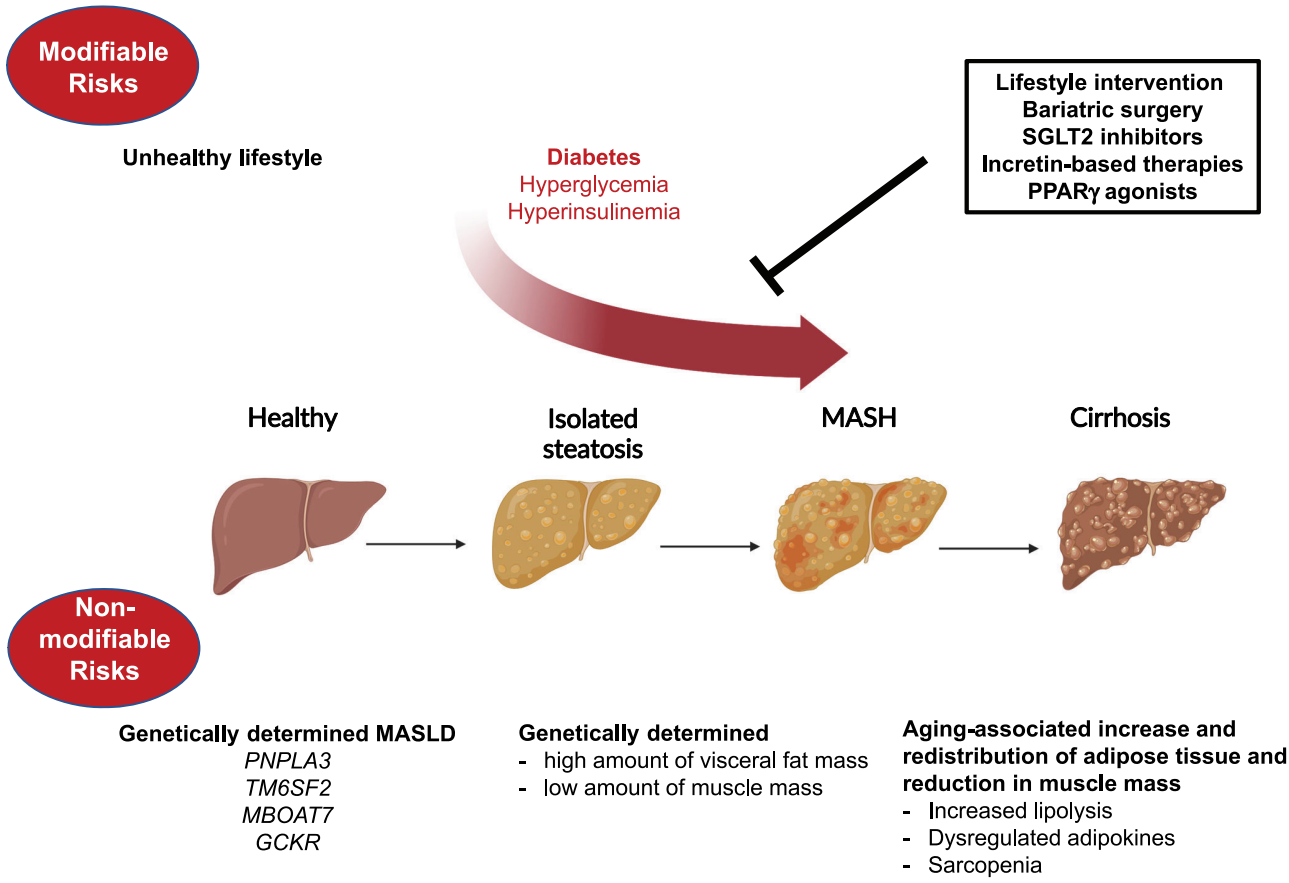

Figure 4—Modifiable and nonmodifiable risk factors of MASLD and treatment strategies of type 2 diabetes that also improve MASLD.

also affect the risk of cardiometabolic diseases in MASLD. Among nonmodifiable risk factors are the most important genetic variants of MASLD, genetically determined fat distribution and muscle mass, and aging-associated increase and redistribution of adipose tissue and decrease in muscle mass. These factors early on predispose people to development of steatosis. Hepatic steatosis is also induced by unhealthy lifestyle, a modifiable risk factor. Type 2 diabetes–associated hyperglycemia and hyperinsulinemia strongly promote hepatic steatosis and the progression of MASLD. However, type 2 diabetes is considered an important modifiable risk factor of MASLD. With the large and powerful portfolio of modern therapies to treat type 2 diabetes (structured lifestyle intervention, bariatric surgery, SGLT2 inhibitors, incretin-based therapies, and PPARγ agonists) it is possible to substantially decrease risk of MASLD progression and its cardiometabolic risk that is observed in people with type 2 diabetes (Fig. 4).

CONCLUSIONS

MASLD is highly prevalent among people with type 2 diabetes, and people with MASLD and type 2 diabetes have a substantially increased risk of hepatic decompensation and HCC. Furthermore, people with MASLD and diabetes have increased risk of CVD. This resulted in several medical associations providing guidelines and consensus reports about the health risks associated with MASLD and its diagnosis and treatment (51,53,84,85). First-line treatment for MASLD includes a weight-reducing and healthy diet, increased physical activity, and effective treatment of obesity, type 2 diabetes, and other metabolic comorbidities. To date, semaglutide 2.4 mg/week s.c. and resmetirom are the only two medications conditionally approved by the FDA for the treatment of adults with noncirrhotic MASH and moderate-to-advanced fibrosis. Because diabetes strongly increases risk of CVD and CKD, in people with type 2 diabetes and MASLD/MASH GLP-1–based therapies and SGLT2 inhibitors that are cardio- and nephroprotective should be used as first-line pharmacotherapies not only to prevent the progression toward advanced liver diseases but also to protect against CVD and CKD.

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