REVIEW ARTICLE

Metabolic Dysfunction–Associated Steatotic Liver Disease

Giovanni Targher, M.D.,[1,2] Luca Valenti, M.D.,[3,4] and Christopher D. Byrne, M.B., Ch.B.[5,6]

In 1980, Ludwig and colleagues described the histologic features of a newly identified chronic liver condition referred to as nonalcoholic steatohepatitis (NASH) and noted that the majority of the patients with the condition had obesity or type 2 diabetes mellitus.[1] NASH represents the progressive form of what has been called nonalcoholic fatty liver disease (NAFLD) and is part of the spectrum of liver disease, which begins with liver-fat accumulation and progresses to liver inflammation with varying levels of fibrosis (i.e., NASH), cirrhosis, and hepatocellular carcinoma.[2]

In recent decades, there has been increasing awareness that metabolic dysfunction is key to the pathogenesis and consequences of NAFLD. In 2020, NAFLD was renamed and reclassified as metabolic dysfunction–associated fatty liver disease (MAFLD), the positive definition of which requires the presence of metabolic abnormalities.[3] There was further iteration of the names and definitions of NAFLD and NASH in 2023 to metabolic dysfunction–associated steatotic liver disease (MASLD) and metabolic dysfunction–associated steatohepatitis (MASH).[2] Because NAFLD and MASLD definitions are almost superimposable in the general population, here we refer to MASLD to define this condition. With improved noninvasive diagnostic tests, care pathways, and promising pharmacotherapies targeting metabolic dysfunction, there is now huge potential to reduce the long-term effect of this complex and burdensome liver disease that has implications for diseases beyond the liver.

This review discusses the global clinical burden and consequences of MASLD as a multisystem disease, briefly describing the natural history, pathophysiology, risk stratification, and case finding of the disease, and focuses on the new and promising metabolism-based pharmacotherapies targeting the liver and coexisting cardiovascular–kidney–metabolic conditions of MASLD. Current areas of uncertainty regarding where further research is needed are also discussed.

Global Burden of a Multisystem Disease with Extrahepatic Implications

MASLD has become the most common chronic liver disease, affecting up to 38% of the adult population worldwide.[4] Although the disease progresses to cirrhosis, end-stage liver disease, or hepatocellular carcinoma in only a small proportion of affected persons, the worldwide number of persons with the disease is so vast that the effect of MASLD on health care providers is considerable. The worldwide prevalence of MASLD is even greater among specific subgroups. For example, in a meta-analysis of 156 studies that included approximately 1.8 million persons with type 2 diabetes, the global prevalence of MASLD was 65% (95% confidence interval [CI], 62 to 68) and of MASH was 32% (95% CI, 17 to 51).[5]

Author affiliations are listed at the end of the article. Prof. Targher can be contacted at giovanni.targher@univr.it or at the Metabolic Diseases Research Unit, IRCCS Sacro Cuore Don Calabria Hospital, Viale Luigi Rizzardi, 4, 37024 Negrar di Valpolicella, Italy

Profs. Targher, Valenti, and Byrne contributed equally to this article.

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CME

KEY POINTS

METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

- MASLD is a multisystem disease that has become a public-health problem worldwide.
- Metabolic dysfunction is key to the pathogenesis and consequences of MASLD.
- The clinical burden of MASLD consists mainly of liver-related disease and death and high rates of fatal and nonfatal cardiovascular disease, chronic kidney disease, type 2 diabetes, and certain extrahepatic cancers, especially extrahepatic gastrointestinal cancers.
- There is a pressing need for drugs to treat MASLD and its more severe form, metabolic dysfunction–associated steatohepatitis (MASH).
- In March 2024, resmetirom, a liver-directed, thyroid hormone receptor beta–selective agonist, was the first drug conditionally approved by the Food and Drug Administration for treating adults with noncirrhotic MASH and moderate-to-advanced fibrosis.
- Incretin-based drugs (especially semaglutide at a dose of 2.4 mg per week) and other metabolism-based pharmacotherapies are showing promise as therapeutic options not only for steatotic liver disease but also for cardiovascular–kidney–metabolic complications that are strongly related to MASLD.

Although there is uncertainty about the accuracy of global estimates of the burden of MASLD, the updated Global Burden of Disease Study 2021 showed increasing rates and trends of point prevalence, annual incidence, and disability-adjusted life-years (DALYs) for MASLD across 204 countries over the past three decades. The largest increases in age-standardized point-prevalence estimates from 2010 to 2021 were observed in China and India; the incidence of MASLD also varied according to the social and economic development of countries (the sociodemographic index [SDI]), peaking at moderate SDI levels. In addition, the global burden of MASLD increased from 1.69 million DALYs (95% uncertainty interval, 1.29 to 2.21) in 1990 to 3.67 million DALYs (95% uncertainty interval, 2.90 to 4.61) in 2021 (i.e., approximately 2.2 times as many DALYs as there were three decades ago).[6]

It is well accepted that MASLD increases the risk of cirrhosis and hepatocellular carcinoma, given that the risk of hepatocellular carcinoma varies according to the development of fibrosis and cirrhosis.[7] A meta-analysis of 64 observational studies showed that the overall pooled incidence rate of hepatocellular carcinoma was an estimated 1.25 per 1000 person-years among persons with MASLD but was approximately 20 per 1000 person-years among persons with MASLD-related cirrhosis.[8] MASLD is a multisystem disease that not only affects the liver but also has the potential to increase the risk of other extrahepatic cardiometabolic diseases.[9] There is now inconvertible evidence that MASLD affects not only the risk of cardiometabolic diseases but also chronic kidney disease (CKD) and certain extrahepatic cancers. Cardiovascular disease is the leading cause of death in persons with MASLD, and MASLD is also a risk factor for new-onset type 2 diabetes, increasing the risk of type 2 diabetes by a factor of 2.2 (and by a factor of 3.4 in the presence of advanced liver disease).[10] Although slightly more contentious,[11] good evidence exists that MASLD is a risk factor for new cardiovascular disease events (although this risk may be attenuated by certain genotypes that increase lipoprotein retention in the liver[12]). A comprehensive meta-analysis showed that MASLD increases the risk of fatal and nonfatal cardiovascular disease events by a factor of 1.5 independent of traditional risk factors; notably, this risk increases further with more severe liver disease (by a factor of approximately 2.5), especially in persons with higher stages of fibrosis.[13] Recent meta-analyses showed that MASLD is also associated with an increased risk of new-onset heart failure,[14] atrial fibrillation,[15] CKD,[16] and certain extrahepatic cancers,[17] increasing the risk of each by a factor of 1.2 to 1.5. Figure 1 shows the relation and strength of associations between MASLD and the incidence of major adverse liver outcomes, fatal and nonfatal cardiovascular events, atrial fibrillation, type 2 diabetes, CKD, and certain extrahepatic cancers (especially extrahepatic gastrointestinal cancers).

Regardless of the term used to define this common liver disease, persons with NAFLD, MAFLD, or MASLD have broadly similar characteristics.[18] MASLD is defined by the coexistence of hepatic steatosis with at least one of the five typical traits of the metabolic syndrome in the absence of clinically significant alcohol consumption and other secondary causes of steatosis (Fig. 1). Be-

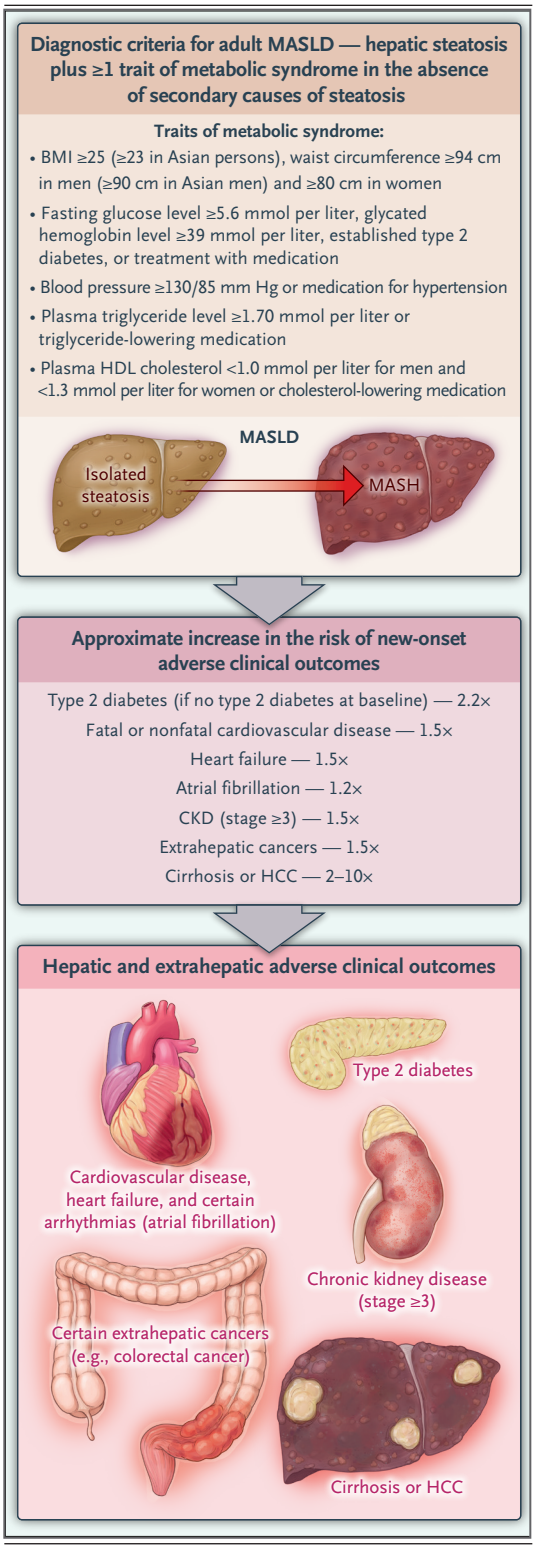

Figure 1. MASLD Diagnostic Criteria and Key Hepatic and Extrahepatic Clinical Outcomes.

Shown are the criteria for establishing a diagnosis of metabolic dysfunction–associated steatotic liver disease (MASLD) in adults and the progression of MASLD to metabolic dysfunction–associated steatohepatitis (MASH). MASLD comprises a variable clinical phenotype that may include combinations of insulin resistance, abdominal obesity, atherogenic dyslipidemia, hypertension, and dysglycemia (which may include prediabetes or established type 2 diabetes). The MASLD phenotype increases the risk of the development of major adverse liver outcomes of cirrhosis and hepatocellular carcinoma (HCC), together with important extrahepatic disease outcomes such as cardiovascular disease (which is the predominant cause of death in persons with MASLD), cardiac remodeling and hypertrophy leading to new-onset heart failure, certain cardiac arrhythmias (mainly permanent atrial fibrillation), new-onset type 2 diabetes, chronic kidney disease stage of 3 or higher, and certain types of extrahepatic cancers, such as colorectal cancer, other nonliver gastrointestinal cancers, and breast cancer. Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. To convert the value for glucose to micrograms per deciliter, divide by 0.05551. To convert the value for triglycerides to micrograms per deciliter, divide by 0.01129. To convert the value for cholesterol to milligrams per deciliter, divide by 0.2586. HDL denotes high-density lipoprotein.

cause persons with MASLD may have differing levels of metabolic dysfunction, as reflected by the presence of one to five metabolic syndrome traits, the risk of serious liver-related and extrahepatic complications may differ according to the severity of the individual patient's metabolic dysfunction. Although additional research is needed, recent data suggest that the greater the number of metabolic syndrome traits present at the time of a diagnosis of MASLD, the higher the risk that new major adverse liver outcomes will develop.[19]

NATURAL HISTORY OF MASLD

The natural history of MASLD is summarized in Figure 2.[20-22] Adiposity — in particular, the accumulation of visceral fat — along with insulin resistance and the severity of metabolic dysfunction are the main drivers of the development and progression of MASLD. The higher the number of coexisting metabolic abnormalities, the higher the risk of advanced MASLD, with type 2 diabetes the predominant metabolic factor followed by obesity and hypertension. Hormonal determinants, especially primary hypothyroidism, may also contribute to the risk of advanced MASLD,[23] whereas estrogens are generally protective.[24] Dietary fac-

tors, such as fructose and alcohol intake (associated with negative effects) and adherence to a Mediterranean dietary style (associated with positive effects), are also involved. Genetic factors play a key role in determining liver-specific involvement, modulated by epigenetics and gut microbiome.[25]

In approximately 30% of persons with MASLD, disease progression is characterized by the development of lipotoxic effects leading to hepatocellular damage and lobular inflammation (features of MASH, which is the main driver of progressive liver disease and which induces faster progression of liver fibrosis).[21] The severity of liver fibrosis is measured on a five-stage scale ranging from least to most severe: F0 (absence of fibrosis), F1

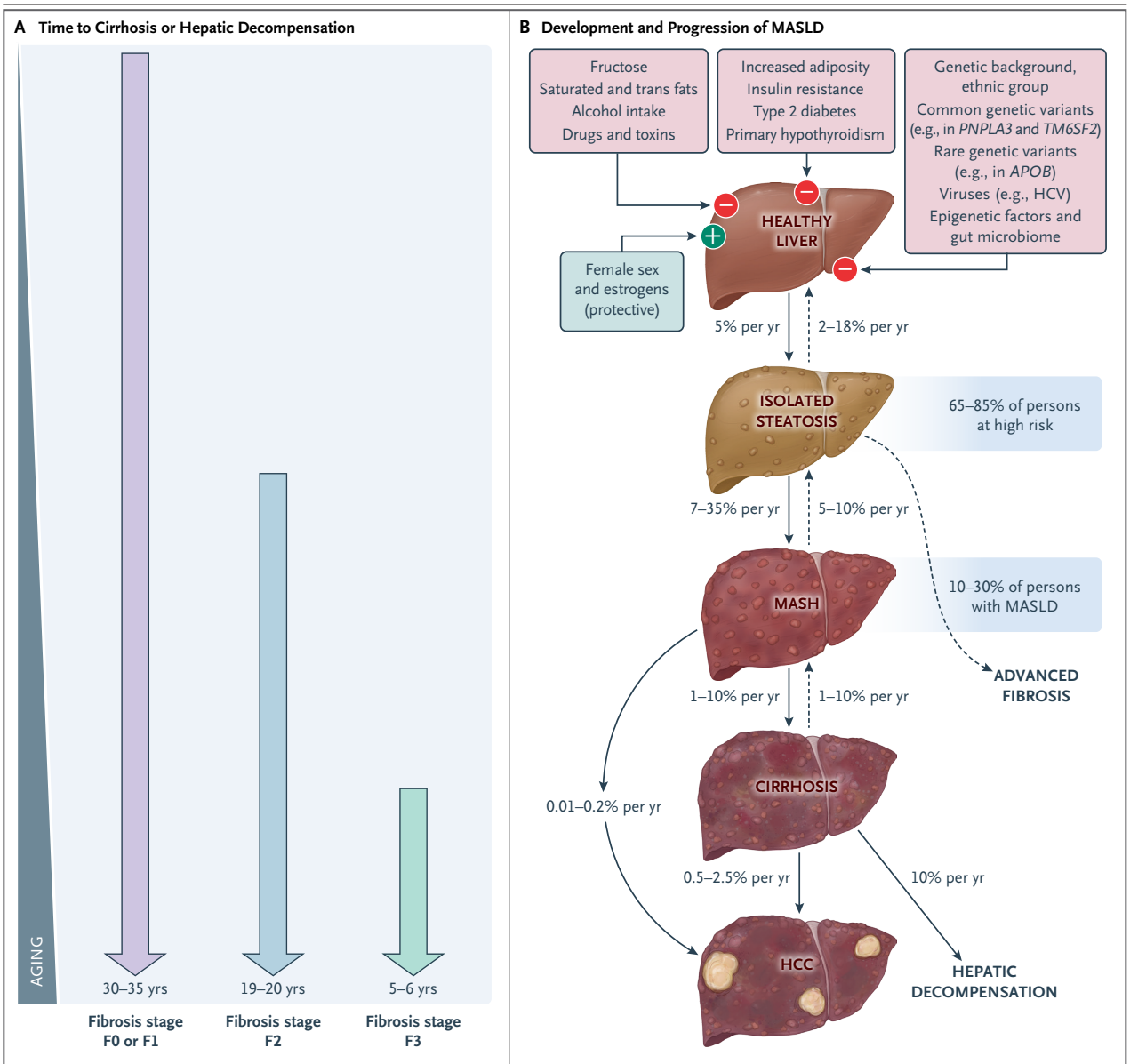

Figure 2. Natural History of Steatotic Liver Disease and MASLD.

Factors related to insulin resistance and metabolic dysfunction, diet and environmental exposures, and genetic and epigenetic factors are the main drivers of MASLD development and its progression throughout the entire spectrum of liver disease (Panel A). Female sex and hormonal factors can also modulate the development and progression of MASLD (Panel B). Ranges for years for disease progression and percentage of patients are approximations. HCV denotes hepatitis C virus.

(perisinusoidal or portal fibrosis), F2 (perisinusoidal and portal or periportal fibrosis), F3 (septal and bridging fibrosis), and F4 (cirrhosis). Clinically significant liver fibrosis (stage ≥F2) is a strong predictor of death from any cause and liver-related complications,[26] and regression of liver fibrosis has been linked to an improved prognosis.[27] Therefore, MASH with clinically significant fibrosis (termed at-risk MASH) is the key treatment indication in clinical trials, whereas MASH resolution without worsening of liver fibrosis and reduction (improvement) in fibrosis by at least one stage without worsening of MASH are the two primary liver-associated end points currently accepted by regulatory agencies for conditional approval of a new drug for the treatment of MASH. A beneficial long-term effect on the risk of major adverse liver outcomes is required for a drug to receive final approval. In individual patients, body-weight changes with related effects on metabolic dysfunction are the primary determinants of disease trajectories leading to MASLD-related cirrhosis.[28]

PATHOPHYSIOLOGY OF MASLD

The hallmark of MASLD is the accumulation of intracellular lipid droplets, organelles able to store both inert lipids and toxic lipids that may trigger the activation of stress pathways.[29] MASLD can, therefore, be viewed as a disorder of hepatic lipid metabolism. Increases in the flux of free fatty acid into the liver (resulting from insulin resistance in adipose tissue), in hepatic lipogenesis, and in lipid uptake from dietary chylomicrons are the three main sources of fatty acids for intrahepatic lipid synthesis. Impaired lipid-droplet remodeling reduces very-low-density lipoprotein secretion and impairs lipid oxidation by mitochondria, thus contributing to the progression of liver disease, cell death with inflammation, activation of fibrogenesis, and carcinogenesis.[25,30,31]

Heritability accounts for approximately 50% of MASLD variability, and genomewide association studies have identified the most common genetic determinants,[25] the mechanisms of which involve interference with lipid and lipid-droplet remodeling.[32] Genetic variations in the patatin-like phospholipase domain–containing 3 gene (*PNPLA3*) and other main genetic determinants of MASLD increase the risk of accumulation of hepatic fat in patients with MASH and liver fibrosis,[33,34] cirrhosis, or hepatocellular carcinoma,[35] thus highlighting the fact that lipid-droplet accumulation is not simply an innocent bystander but is the main driver of liver disease and an important therapeutic target.[36-38] The phenotypic expression of MASLD with genetic risk factors is further influenced by overall adiposity, insulin resistance, alcohol consumption, and diet.[35] Genetic predisposition may also dissociate hepatic and cardiovascular–kidney–metabolic complications of MASLD — for example, having different effects on the risk of cardiovascular disease and hepatocellular carcinoma.[33,39] This genetic predisposition may help identify subtypes of MASLD and make it possible to predict and target liver-specific outcomes in specific patient groups with the use of polygenic risk scores.[40,41]

IDENTIFYING PATIENTS WITH AT-RISK MASH

Major hepatology societies recommend a sequential approach to identifying patients at the highest risk for long-term adverse liver outcomes that starts with general practitioners and specialists in liver and metabolic diseases.[28,42,43] This approach in patients who are deemed to be at risk for adverse liver outcomes (e.g., owing to the coexistence of type 2 diabetes, multiple metabolic risk factors, or MASLD with increased serum concentrations of liver enzymes) is generally based on the first score on the Fibrosis-4 index (FIB-4), a noninvasive, blood-based fibrosis biomarker developed to estimate the presence of advanced liver fibrosis, with the risk of liver fibrosis on the basis of FIB-4 scores categorized as low (score of <1.30), indeterminate (score of 1.30 to 2.67), or high (score of >2.67). The goal is to differentiate between patients whose FIB-4 scores place them in the low-risk category (and who therefore can be treated by nonspecialists and reevaluated over time) and patients whose scores indicate that they are at high risk for adverse liver outcomes. Patients whose FIB-4 scores place them in the high-risk category should be referred for assessment by a hepatologist, and those whose scores place them in the category of indeterminate risk should be referred for additional testing on the basis of liver-specific biomarkers, findings on vibration-controlled transient elastography and the Enhanced Liver Fibrosis test, or liver histologic features.[28,42,43] Management of type 2 dia-

betes and other coexisting metabolic conditions and lifestyle, pharmacologic, or surgical strategies aimed at weight loss are advised in patients who are at intermediate or high risk for advanced liver fibrosis.[28,42,43] The 2024 European guidelines for the management of MASLD have recommended for the first time the possibility of a weight-loss trial, with the inclusion of glucagon-like

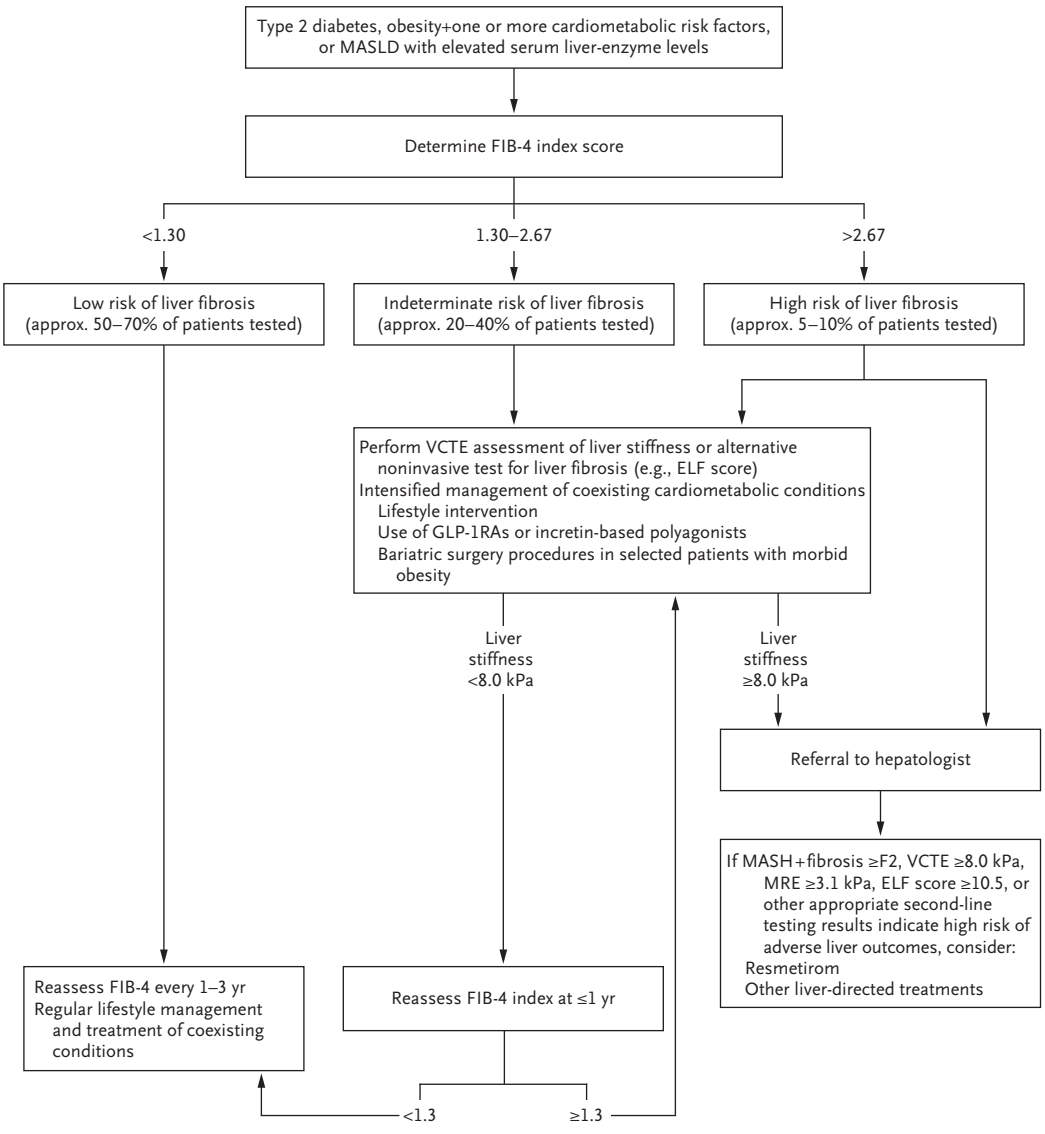

Figure 3. Diagnostic Flowchart for Detection of Advanced Liver Fibrosis in MASLD.

Scores on the Fibrosis-4 index (FIB-4) are calculated with the use of a formula that includes age, serum aspartate aminotransferase level, serum alanine aminotransferase level, and platelet count. The categories of risk and the threshold FIB-4 scores for severe liver fibrosis in persons up to 65 years of age are as follows: low (score of <1.30), indeterminate (score of 1.30 to 2.67), and high (score of >2.67); for persons over 65 years of age, the FIB-4 cutoff score for low risk is 2.0. Percentage ranges for risk are approximations. Severity of liver fibrosis is measured on a histologic five-stage scale ranging from least to most severe: F0 (absence of fibrosis), F1 (perisinusoidal or portal fibrosis), F2 (perisinusoidal and portal or periportal fibrosis), F3 (septal and bridging fibrosis), and F4 (cirrhosis). Vibration-controlled transient elastography (VCTE) measures liver stiffness; 20 to 30% of patients who undergo VCTE have liver stiffness of 8.0 kPa or higher. ELF denotes Enhanced Liver Fibrosis test, GLP-1 glucagon-like peptide-1, and MRE magnetic resonance elastography.

peptide-1 (GLP-1) receptor agonists or other incretin-based polyagonists, followed by reassessment within 1 year before a second-stage evaluation (depending on local resources and logistic factors).[28] Currently, liver-directed pharmacotherapy is advised in patients either with noninvasive biomarkers predicting at-risk MASH or with histologic evidence of the at-risk stage of disease.[44,45] A strategy for identifying patients with at-risk MASH is shown in Figure 3.

PHARMACOTHERAPY FOR MASLD

Lifestyle modifications, including clinically significant weight loss by means of exercise and a hypocaloric diet, are the cornerstone of treatment for MASLD and MASH.[46] Weight loss induced by diet and behavioral therapy should aim for a sustained weight reduction of at least 5% to reduce liver steatosis, 7 to 10% to reduce liver inflammation, and at least 10% to reduce liver fibrosis.[28] However, the adherence to long-term dietary interventions is often insufficient. In this section, we discuss the pharmacologic therapeutic options for MASLD, with a focus on newly approved or promising metabolism-based pharmacotherapies that are currently being evaluated in late-phase randomized, controlled trials for the treatment of this common metabolic liver disease (Table 1), the results of which may beneficially affect patients who have MASLD and its related adverse cardiometabolic and renal outcomes.

RESMETIROM

In March 2024, resmetirom, an oral, liver-directed, thyroid hormone receptor beta–selective agonist, became the first drug to receive conditional approval from the Food and Drug Administration for treating adults with noncirrhotic MASH and moderate to advanced fibrosis (https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-liver-scarring-due-fatty-liver-disease). In the phase 3 MAESTRO-NASH trial, 966 patients with biopsy-proven MASH and stage F1, F2, or F3 fibrosis were randomly assigned to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo for 52 weeks.[47] Both the 80-mg dose and the 100-mg dose of resmetirom were superior to placebo with respect to MASH resolution without worsening of fibrosis and to a reduction in fibrosis by at least one stage without worsening of MASH (Table 1 and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Resmetirom improved plasma concentrations of low-density lipoprotein cholesterol, triglycerides, and lipoprotein(a) but had neutral effects on body weight and insulin resistance and did not induce adverse endocrine events, tachyarrhythmias, or major changes in bone mineral density.[47] Independent of thyroxine-replacement status, resmetirom reduced circulating levels of free thyroxine by approximately 15 to 20%, with no effect on levels of serum thyrotropin or the active thyroid hormone free triiodothyronine. Resmetirom had an acceptable side-effect profile, and the most common adverse events associated with the drug were nausea and diarrhea, which were usually transient and mild or moderate in severity.[47,54] Careful surveillance to detect early endocrine disease that is related to potential thyroid, gonadal, or bone diseases is warranted to avoid any potential risks from long-term treatment.[55] The ongoing phase 3 MAESTRO-NAFLD-OLE trial (Clinical Trials.gov number, NCT04951219) and MAESTRO-NASH-OUTCOMES trial (NCT05500222) are expected to provide answers with regard to the long-term safety and efficacy of resmetirom.

GLP-1 RECEPTOR AGONISTS AND DUAL OR TRIPLE INCRETIN–BASED AGONISTS

GLP-1 receptor agonists were licensed approximately 20 years ago for the treatment of hyperglycemia in persons with type 2 diabetes, and recent evidence indicates that this drug class, as well as dual and triple incretin–based receptor agonists, are beneficial in ameliorating liver disease in patients with MASLD (as discussed below). Persons with MASLD and type 2 diabetes may have a reduced incretin effect and elevated glucagon levels, and the effect of the incretin-to-glucagon ratio in MASLD may be influenced by the presence of coexisting type 2 diabetes. Therefore, the loss of the incretin effect in type 2 diabetes along with the differential influences of GLP-1 and glucose-dependent insulinotropic peptide (GIP) and changes in the incretin-to-glucagon ratio have complex effects on glycemic control in persons with MASLD, particularly in those who have type 2 diabetes.[56] In addition, the mechanisms by which GIP receptor agonism potentially benefits patients with MASLD is also complex, as described in a recent review.[57]

In a phase 2b randomized, controlled trial

Table 1. Trials of Resmetirom, GLP-1 Receptor Agonists, Dual or Triple Incretin Receptor Agonists, and Lanifibranor for Noncirrhotic MASH, Liver Fibrosis, or MRI-Defined MASLD in Adults.*

Drug and Trial	Participants	Size and Duration of Trial	Patients with Resolution of MASH or Reduction in Liver Fat	Patients with Reduction in Liver Fibrosis†‡	Major Metabolic Effects	Adverse Effects
Resmetirom — liver-directed, thyroid hormone receptor beta–selective agonist; phase 3 RCT (MAESTRO-NASH)	966 patients with biopsy-confirmed MASH and fibrosis (stages F1–F3)[47] 86% White, 57% female, mean age of 54.4 yr and BMI of 36.1; 58% with diabetes	Resmetirom at a dose of 80 mg daily (322 patients) or 100 mg daily (323 patients) or placebo (321 patients) for 52 wk	25.9% in 80-mg group, 29.9% in 100-mg group, and 9.7% in placebo group P<0.001 for both comparisons with placebo	24.2% in 80-mg group, 25.9% in 100-mg group, and 14.2% in placebo group P<0.001 for both comparisons with placebo	Resmetirom reduced plasma levels of LDL cholesterol, triglycerides, and lipoprotein(a) Neutral effects on body weight, insulin resistance, and glycated hemoglobin levels	Diarrhea and nausea were more common with resmetirom. Incidence of serious adverse events was similar (11%) in the three groups.
Semaglutide — GLP-1 receptor agonist; phase 2b RCT	320 patients with biopsy-confirmed MASH and fibrosis (stages F1–F3)[48] 77% White, 60% female, mean age of 55 yr and BMI of 35.5; 62% with diabetes	Subcutaneous semaglutide at a dose of 0.1 mg daily (80 patients), 0.2 mg daily (78 patients), 0.4 mg daily (82 patients), or placebo (80 patients) for 72 wk	0% in the 0.1-mg group, 36% in the 0.2-mg group, 59% in the 0.4-mg group, and 17% in the placebo group P<0.001 for semaglutide at a dose of 0.4 mg vs. placebo	49% in the 0.1-mg group, 32% in the 0.2-mg group, 43% in the 0.4-mg group, and 33% in the placebo group P=0.48 vs. placebo	Semaglutide reduced body weight, glycated hemoglobin levels, insulin resistance, and plasma lipid levels	Incidence of transient and mild-to-moderate gastrointestinal events (nausea, diarrhea, constipation, and vomiting) was higher in the 0.4-mg group than in the placebo group.
Semaglutide — GLP-1 receptor agonist; phase 3 RCT (ESSENCE, Part 1)	800 patients with biopsy-confirmed MASH and fibrosis (stage F2 or F3)[49] 67% White, 57% female, mean age of 56 yr and BMI of 34.6; 56% with diabetes	Subcutaneous semaglutide at a dose of 2.4 mg per wk (534 patients) or placebo (266 patients) for 72 wk	62.9% in the semaglutide group and 34.3% in the placebo group P<0.001 for semaglutide vs. placebo	37.0% in the semaglutide group and 22.4% in the placebo group P<0.001 for semaglutide vs. placebo	Semaglutide reduced body weight, glycated hemoglobin levels, insulin resistance, and plasma lipid levels	Transient and mild-to-moderate gastrointestinal events (nausea, diarrhea, constipation and vomiting) were more common with semaglutide.
Tirzepatide — dual GLP-1 and GIP receptor agonist; phase 2b RCT (SYNERGY-NASH)	190 patients with biopsy-confirmed MASH and moderate or severe fibrosis (stage F2 or F3)[10] 85% White, 57% female, mean age of 54.4 yr and BMI of 36.1; 58% with diabetes	Subcutaneous tirzepatide at a dose of 5 mg per wk (47 patients), 10 mg per wk (47 patients), 15 mg per wk (48 patients), or placebo (48 patients) for 52 wk	44% in the 5-mg group, 56% in the 10-mg group, 62% in the 15-mg group, and 10% in the placebo group P<0.001 for all tirzepatide doses vs. placebo	55% in the 5-mg group, 51% in the 10-mg group, 51% in the 15-mg group, and 30% in the placebo group P value for between-group differences not tested	Tirzepatide reduced body weight, glycated hemoglobin levels, insulin resistance, and plasma lipid levels	Incidence of transient and mild-to-moderate gastrointestinal events was highest in tirzepatide groups. Incidence of serious adverse events was similar with tirzepatide and placebo (approximately 6%).

Survodutide — dual GLP-1 and glucagon receptor agonist; phase 2b RCT	293 patients with biopsy-confirmed MASH and fibrosis (stages F1–F3)[51] 70% White, 53% female, mean age of 51 yr and BMI of 35.8; 39% with diabetes	Subcutaneous survodutide at a dose of 2.4 mg per wk (73 patients), 4.6 mg per wk (72 patients), 6.0 mg per wk (74 patients), or placebo (74 patients) for 48 wk	47% in the 2.4-mg group, 62% in the 4.8-mg group, 43% in the 6.0-mg group, and 14% in the placebo group P<0.001 for dose–response curve	34% in the 2.4-mg group, 36% in the 4.8-mg group, 32% in the 6.0-mg group, and 18% in the placebo group P value for between-group differences not tested	Survodutide reduced body weight, insulin resistance, plasma lipid levels, and glycated hemoglobin levels	Incidence of gastrointestinal events was higher with survodutide than with placebo. Treatment discontinuation for adverse events was 20% with survodutide and 3% with placebo.
Retatrutide — triple GLP-1–GIP–glucagon receptor agonist; phase 2a RCT	98 patients with MASLD (assessed by MRI–PDFF ≥10%)[52] 98% White, 47% female, mean age of 46.6 yr and BMI of 38.4; none with diabetes	Subcutaneous retatrutide at a dose of 1 mg per wk (20 patients), 4 mg per wk (19 patients), 8 mg per wk (22 patients), 12 mg per wk (18 patients), or placebo (19 patients) for 48 wk	Mean relative changes from baseline in liver-fat content at 48 wk were –51% (1 mg), –59% (4 mg), –82% (8 mg), –86% (12 mg), and –5% (placebo)‡ P<0.001 vs. placebo for all comparisons	Not available	Retatrutide reduced body weight, insulin resistance, and plasma lipid levels	Transient and generally moderate gastrointestinal events were reported, with higher incidence in the 8-mg and 12-mg groups.
Lanifibranor — pan-PPAR agonist; phase 2b RCT (NATIVE)	247 patients with biopsy-confirmed MASH and fibrosis (stages F1–F3)[53] 95% White, 58% female, mean age of 54 yr and BMI of 33; 42% with diabetes	Lanifibranor at a dose of 800 mg daily (83 patients), 1200 mg daily (83 patients), or placebo (81 patients) for 24 wk	39% in 800-mg group, 49% in 1200-mg group, and 22% in placebo group P<0.01 for 1200-mg group vs. placebo group	34% in 800-mg group, 48% in 1200-mg group, and 29% in placebo group P<0.01 for 1200-mg group vs. placebo group	Lanifibranor increased body weight (by approximately 2.5 kg) but reduced plasma lipid levels, insulin resistance, and glycated hemoglobin levels	Diarrhea, peripheral edema, and weight gain were more common with lanifibranor than with placebo. Discontinuation for adverse events was at a similar rate across the trial groups.

* Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. Fibrosis stages are defined as follows: F0, no fibrosis; F1, mild-to-moderate zone 3 perisinusoidal fibrosis or portal or periportal fibrosis only; F2, zone 3 perisinusoidal fibrosis and portal or periportal fibrosis; F3, bridging fibrosis; and F4, cirrhosis. GIP denotes glucose-dependent insulinotropic polypeptide, GLP-1 glucagon-like peptide-1, LDL low-density lipoprotein, MASH metabolic dysfunction–associated steatohepatitis, MASLD metabolic dysfunction–associated steatotic liver disease, PDFF proton density fat fraction, PPAR peroxisome proliferator–activated receptor, and RCT randomized, controlled trial.
† Percentages reflect participants who had reduction of liver fibrosis by at least one stage.
‡ Most of the reduction in liver-fat content as measured by MRI–PDFF occurred within the first 24 weeks.

involving 320 patients with obesity who had MASH and liver fibrosis, subcutaneous semaglutide at a daily dose of 0.1 mg, 0.2 mg, or 0.4 mg for 72 weeks resulted in a higher percentage of patients with MASH resolution than placebo but failed to reduce the fibrosis stage. At week 72, the mean percent weight loss was 13% in the 0.4-mg group and 1.0% in the placebo group.[48] Semaglutide had an acceptable side-effect profile, with adverse-event rates not exceeding those of placebo except for a higher frequency of transient, mild-to-moderate gastrointestinal events (i.e., nausea, diarrhea, constipation, and vomiting). A subsequent meta-analysis incorporating 11 phase 2 randomized, controlled trials showed that the use of a GLP-1 receptor agonist for a median of 26 weeks reduced liver-fat content (as measured by magnetic resonance imaging [MRI]–based techniques) and was associated with a greater likelihood of resolution of MASH without worsening of fibrosis than placebo. Conversely, there was no meaningful difference among the groups in the percentage of participants who had a reduction in fibrosis by at least one stage.[58] Treatment with GLP-1 receptor agonists reduced body weight, improved insulin resistance, and lowered glycated hemoglobin and plasma lipid levels.[58]

Recently, part 1 of the phase 3 ESSENCE trial (involving 800 adults with obesity who had biopsy-confirmed MASH and moderate-to-advanced fibrosis) showed that semaglutide at a dose of 2.4 mg weekly for 72 weeks was superior to placebo with respect to histologic resolution of MASH without worsening of fibrosis and reductions in liver fibrosis with no worsening of MASH (Fig. 4A). Secondary end points showed that 32.7% of patients treated with semaglutide had resolution of MASH with a reduction in liver fibrosis (as compared with 16.1% of patients who received placebo).[49] In a phase 2b randomized, placebo-controlled trial involving 71 patients with obesity who had MASH-related compensated cirrhosis, semaglutide at a dose of 2.4 mg once weekly for 48 weeks reduced liver-fat content but did not decrease liver fibrosis or resolve MASH.[59] Notably, real-word retrospective cohort studies evaluating the long-term effect of GLP-1 receptor agonists on the risk of adverse liver-related events among persons with type 2 diabetes showed that the use of a GLP-1 receptor agonist was associated with a lower risk of new-onset cirrhosis, hepatic decompensation events, or hepatocellular carcinoma than dipeptidyl peptidase-4 inhibitors or other glucose-lowering medications.[60-63]

In the phase 2b SYNERGY-NASH trial, 190 patients with MASH and moderate or severe fibrosis were assigned to receive subcutaneous tirzepatide (a dual GLP-1 and GIP receptor agonist) at a dose of 5 mg, 10 mg, or 15 mg or placebo once weekly for 52 weeks.[50] All three doses of tirzepatide were more effective than placebo with respect to resolution of MASH without worsening of fibrosis (Fig. 4B). Reduction 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. Participants who received the 15-mg dose of tirzepatide had a mean reduction in body weight of up to approximately 15%. Tirzepatide improved plasma lipid levels, reduced insulin resistance, and reduced glycated hemoglobin levels as compared with placebo. The most common adverse events were gastrointestinal events, most of which were mild to moderate in severity.[50]

In a phase 2b trial, 293 patients with MASH and fibrosis were randomly assigned to receive subcutaneous survodutide (at a dose of 2.4 mg, 4.8 mg, or 6.0 mg) or placebo once weekly for 48 weeks.[51] All three doses of this dual agonist of the GLP-1 receptor and glucagon receptor were superior to placebo with respect to improvement (reduction) in MASH without worsening of fibrosis (Fig. 4C). Reduction in fibrosis by at least one stage was observed in 32% of the participants in the 6.0-mg survodutide group, as compared with 18% of those in the placebo group. Participants in the survodutide groups lost approximately 10 to 15% of their body weight and had lower blood pressure, glycated hemoglobin levels, and plasma lipid levels than participants who received placebo. Adverse events were more frequent with survodutide than placebo and included nausea, diarrhea, and vomiting. Survodutide was also associated with a higher heart rate than placebo. Discontinuation of trial participation owing to adverse events was 20% in the survodutide groups and 3% in the placebo group.[51]

Other phase 2 randomized, controlled trials of other dual GLP-1 and glucagon receptor agonists (cotadutide, efinopegdutide, and pemvidutide) showed that these agents yielded significant reductions in liver-fat content, noninvasive biomarkers of fibrosis, and body weight.[64-66] A phase 2b–3 placebo-controlled trial (NCT05364931) is

ongoing to investigate the long-term efficacy of cotadutide in adults with MASH and liver fibrosis.

In a phase 2a trial, 98 patients with MRI-detected MASLD were randomly assigned to receive subcutaneous retatrutide (an agonist of the GIP, GLP-1, and glucagon receptors) at a dose of 1 mg, 4 mg, 8 mg, or 12 mg or placebo once weekly for 48 weeks. Retatrutide at all doses was associated with significant reductions in liver-fat content at 24 weeks and 48 weeks (Fig. 4D). At the two highest doses, approximately 80% of the participants had at least a 70% relative reduction in liver fat, and more than 85% of the participants had resolution of hepatic steatosis. Adverse effects mainly involved transient and mild-to-moderate gastrointestinal events, which were more frequent among patients in the 8-mg and 12-mg dose groups.[52]

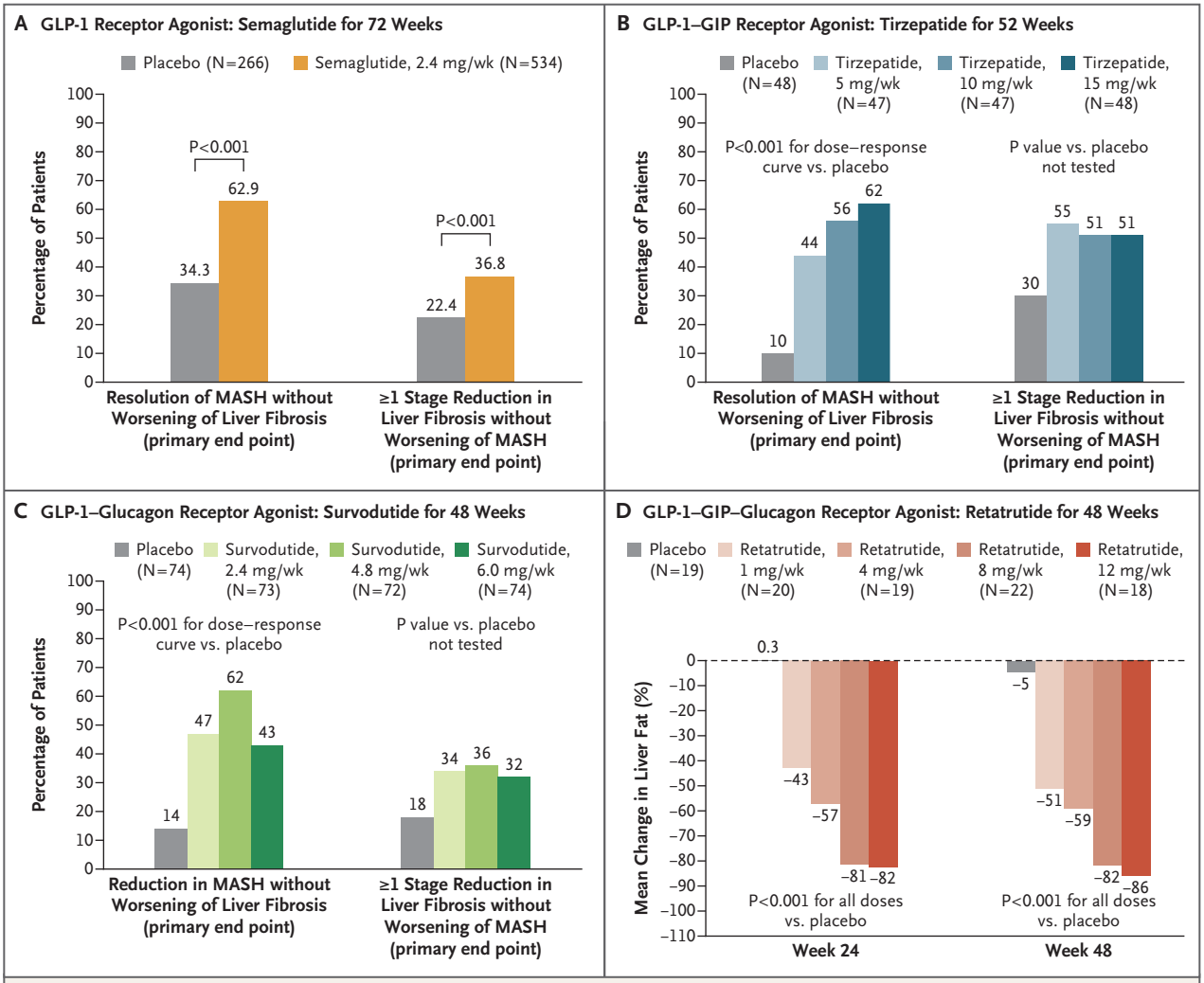

Figure 4. Possible Hepatoprotective Effects of GLP-1 Receptor Agonists or Other Dual or Triple Incretin–Based Receptor Agonists in Adults with MASLD or MASH and Fibrosis.

The results shown were derived from recent phase 2 and phase 3 randomized, placebo-controlled trials of subcutaneous semaglutide, tirzepatide, survodutide, and retatrutide, with a follow-up length of at least 48 weeks. Liver histologic end-point events — resolution of MASH with no worsening of liver fibrosis and reduction in liver fibrosis by at least one stage with semaglutide (Panel A) and tirzepatide (Panel B), reduction in MASH with no worsening of liver fibrosis, and reduction in liver fibrosis by at least one stage with survodutide (Panel C), and reduction in liver-fat content (assessed by MRI–proton density fat fraction) with retatrutide (Panel D) — were assessed in adults with biopsy-confirmed MASH and liver fibrosis or MRI-detected MASLD. Data shown are those reported from each trial (mainly derived from intention-to-treat analyses) without multiple imputation. To date, head-to-head clinical trials comparing the hepatoprotective effects of GLP-1 receptor agonists with those of other incretin receptor polyagonists are lacking.

Collectively, on the basis of the results from the aforementioned randomized, placebo-controlled trials and a recent network meta-analysis,[67] semaglutide and other incretin-based polyagonists have been shown to exert hepatoprotective effects in MASLD and MASH, and these benefits probably occur earlier in the spectrum of liver disease with MASLD. Incretin-based therapies are becoming an attractive and promising treatment option for MASLD and MASH, given that these agents have also shown meaningful benefits with regard to long-term cardiovascular and renal outcomes and that some of these agents could potentially improve the treatment of coexisting cardiometabolic conditions at earlier stages of liver disease. It should be noted that to date, head-to-head clinical trials comparing the hepatoprotective effects of GLP-1 receptor agonists and other incretin receptor polyagonists are lacking. Real-world prospective cohort studies that emulate a hypothetical randomized, controlled trial with the use of observational data are needed to examine whether incretin-based therapies reduce the long-term risk of adverse liver-related events among patients with MASLD. Evaluation of longer-term data from part 2 of the ESSENCE trial (NCT04822181) is ongoing to assess the effects of semaglutide (at a dose of 2.4 mg per week) on liver-related clinical outcomes over a period of 240 weeks.

PEROXISOME PROLIFERATOR–ACTIVATED RECEPTOR (PPAR) AGONISTS

A meta-analysis of five phase 2 randomized, placebo-controlled trials involving approximately 500 patients with MASH and liver fibrosis showed that treatment with the PPAR-γ agonist pioglitazone (at a dose of 30 mg to 45 mg daily) for up to 24 months was associated with a reduction in fibrosis severity and resolution of MASH regardless of the presence or absence of type 2 diabetes. The mean weight gain was 2.7 percentage points greater with pioglitazone than with placebo.[68]

In the phase 2b NATIVE trial, including 247 patients with MASH and fibrosis (stage F1, F2, or F3), the pan-PPAR agonist lanifibranor taken for 24 weeks was associated with greater resolution of MASH without worsening of fibrosis than placebo and reduction in fibrosis by at least one stage without worsening of MASH (Table 1).[53] The incidence of discontinuation for adverse events was less than 5% and was similar across the trial groups. As with pioglitazone,[68] lanifibranor reduced insulin resistance, reduced glycated hemoglobin levels, and improved plasma lipid levels but led to a moderate gain (approximately 2.5%) in body weight.[53] Phase 3 of the NATIVE trial (NCT04849728) is under way to investigate the long-term efficacy and safety of 72-week treatment with lanifibranor in adults with biopsy-confirmed MASH and stage F2 or F3 fibrosis.

FGF21 ANALOGUES

Fibroblast growth factor 21 (FGF21) is a liver-derived hormone that regulates lipid metabolism, insulin sensitivity, and energy homeostasis[69]; therefore, long-acting FGF21 analogues are being evaluated to treat adults who have MASH and advanced fibrosis or compensated cirrhosis.[70-72] A meta-analysis of five phase 2 randomized, placebo-controlled trials involving approximately 600 patients with obesity and biopsy-confirmed MASH and fibrosis of stage F1 to F4 showed that treatment with once-weekly efruxifermin, pegbelfermin, or pegozafermin for 16 to 48 weeks resulted in a higher percentage of participants with MASH resolution and no worsening of fibrosis than placebo and a higher percentage with reduction in fibrosis of at least one stage.[73] These drugs reduced insulin resistance and improved plasma lipid levels but had neutral effects on body weight. The most common adverse events were mild-to-moderate nausea and diarrhea. FGF21 analogues are a promising therapeutic option for the treatment of MASH and advanced fibrosis, but uncertainty remains about the robustness and clinical benefit of these agents.[73]

In the recent phase 2b SYMMETRY trial, which included 181 patients with obesity and biopsy-confirmed MASH-related compensated cirrhosis, treatment with efruxifermin at a weekly dose of 50 mg for 96 weeks led to a reversal of cirrhosis (defined as a reduction in liver fibrosis of at least one stage) without worsening of MASH in a greater percentage of patients than placebo (29% vs. 11%).[74] Although data from longer-term phase 3 clinical trials are needed to evaluate the potential effect of FGF21 analogues on bone health, the use of FGF21 analogues in phase 2 clinical trials of up to 96 weeks has not resulted in meaningful changes in bone mineral density. Phase 3 randomized, controlled trials (NCT06215716 and NCT06318169) are under way to provide further evidence regarding the

long-term safety and efficacy of FGF21 analogues.

SODIUM–GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS

SGLT2 inhibitors, in addition to providing established cardiovascular and renal benefits,[75] also have hepatoprotective effects. A meta-analysis of 12 phase 2 randomized, controlled trials showed that the use of an SGLT2 inhibitor for a median of 24 weeks reduced liver-fat content (as measured by MRI-based techniques) and reduced serum liver-enzyme levels.[76] Recently, a phase 2b randomized, placebo-controlled trial involving 154 adults with biopsy-confirmed MASH with or without type 2 diabetes showed that dapagliflozin at a daily dose of 10 mg for 48 weeks was superior to placebo with respect to MASH resolution (23% of patients vs. 8%) and reduction in liver fibrosis (45% vs. 20%).[77] In addition, a meta-analysis of retrospective active-comparator, new-user cohort studies showed that the use of an SGLT2 inhibitor was associated with lower long-term risk of liver-related events and liver-related death than other glucose-lowering medications (except GLP-1 receptor agonists) in patients with type 2 diabetes.[78]

CONCLUSIONS

MASLD is a multisystem disease that has become a public-health problem worldwide. Addressing the growing clinical burden of MASLD will require the assembly of a multidisciplinary working group and framework to develop and embrace new collaborative ways of working to deliver holistic, person-centered care and treatment of patients with MASLD.[79] Lifestyle modifications should be part of any treatment approach, but resmetirom is the first approved drug for the treatment of adults with noncirrhotic MASH and moderate-to-advanced fibrosis. In addition, incretin-based drugs (especially semaglutide at a dose of 2.4 mg per week) and other metabolism-based pharmacotherapies are showing promise as therapeutic options not only for steatotic liver disease but also for cardiovascular–kidney–metabolic complications that are strongly related to MASLD and MASH.

Many challenges and questions remain regarding long-term pharmacotherapy in MASLD and MASH. Cost-effectiveness studies are needed across different health care systems to help make national and local decisions about diagnostic and treatment strategies with regard to MASLD. In addition to the substantial costs and barriers to access that may widen health inequalities, with regard to the currently approved pharmacotherapy for MASLD and MASH, no reliable predictors are available to identify patients who are likely to have a response to resmetirom therapy. At present, the phase 3 MAESTRO trial of 52 weeks of treatment with resmetirom followed by evaluation of the effect of the drug on noninvasive biomarkers (e.g., a decrease in liver fat of at least 30% or decreases in liver stiffness of 20% or 25% as measured by vibration-controlled transient elastography [e.g., Fibroscan] or magnetic resonance elastography, respectively) is ongoing,[80] but stoppage rules for ineffective medications have yet to be validated.[28,44,45]

Another critical challenge is the treatment of MASLD-related cirrhosis; no liver-directed pharmacotherapies are yet available for this advanced stage of disease. Subcutaneous semaglutide has proved safe in 72-week phase 2 and phase 3 clinical trials,[28] and treatment with GLP-1 receptor agonists results in weight loss and reduces metabolic risk factors in patients who undergo surgery for hepatocellular carcinoma or liver transplantation.[28] However, further studies are warranted in this patient population to assess the safety of GLP-1 receptor agonists in patients with hypercatabolism who are at high risk for both sarcopenia and adverse liver-related events. Furthermore, given the heterogeneity of MASLD and the role of genetic predisposition in tipping the balance toward liver-related complications (as opposed to cardiometabolic complications), assessing whether polygenic risk scores or biomarker panels can reliably identify patients with MASLD who are at higher risk for adverse liver-related events will be important for prioritization and possibly earlier treatment. These polygenic risk scores help to define distinct biologic subtypes of MASLD with different disease trajectories and outcomes in patients with liver disease[12]; therefore, genotyping of inherited variants might be useful in predicting the response to new therapeutic approaches and tailoring the appropriate treatment to the individual patient and should, for these reasons, be examined in clinical studies.

Results of randomized clinical trials of com-

bination treatment in MASLD and MASH are eagerly awaited. Combination treatment will probably be required to tackle this multisystem disease, potentially combining incretin receptor agonists (especially semaglutide at a dose of 2.4 mg per week) with liver-directed pharmacotherapies, such as resmetirom (or PPAR agonists or FGF21 analogues) and possibly also including therapies aimed at genetic targets.[81,82] However, the appropriate therapeutic approaches remain to be defined for patients with MASLD and MASH in whom there have been suboptimal therapeutic responses.[83]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

AUTHOR INFORMATION

[1]Department of Medicine, University of Verona, Verona, Italy; [2]Metabolic Diseases Research Unit, IRCCS Sacro Cuore Don Calabria Hospital, Negrar di Valpolicella, Italy; [3]Department of Pathophysiology and Transplantation, University of Milan, Milan; [4]Department of Precision Medicine, Biological Resource Center Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan; [5]National Institute for Health and Care Research, Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, United Kingdom; [6]National Institute for Health and Care Research, Southampton Biomedical Research Centre, University of Southampton, Southampton, United Kingdom.

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