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Metabolic Dysfunction Associated Steatotic Liver Disease in Type 2 Diabetes: A Narrative Review

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ABSTRACT

Metabolic dysfunction associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), affects an estimated 55–70% of adults with type 2 diabetes and is now a leading contributor to cirrhosis and liver transplantation in the United States. The relationship between type 2 diabetes and MASLD is bidirectional: insulin resistance, adipose-tissue dysfunction, and genetic susceptibility drive hepatic steatosis and its progression to metabolic dysfunction–associated steatohepatitis (MASH) and fibrosis, while the resulting hepatokine, inflammatory, and gut-microbial milieu worsens glycemic control and cardiovascular and renal risk. Recognizing this burden, the American Diabetes Association (ADA) Standards of Care in Diabetes recommends systematic risk stratification for advanced fibrosis in all adults with type 2 diabetes or prediabetes using the Fibrosis-4 (FIB-4) index, with reflex noninvasive testing—vibration-controlled transient elastography or the enhanced liver fibrosis test—for indeterminate or high-risk scores, and hepatology referral above defined thresholds. This review synthesizes current evidence on the epidemiology, genetics, and bidirectional pathophysiology linking type 2 diabetes and MASLD/MASH; the strengths and limitations of available noninvasive diagnostic tools; the ADA-endorsed screening and referral algorithm; and the rapidly evolving pharmacologic landscape, including pioglitazone, GLP-1 receptor agonists, the dual GIP/GLP-1 agonist tirzepatide, and the two agents now approved specifically for MASH with fibrosis, resmetirom and semaglutide. Considerations for special populations—type 1 diabetes, chronic kidney disease, older adults, and adolescents transitioning to adult care—and for equitable, system-level implementation are also addressed. Early, systematic identification of at-risk patients, rather than reliance on liver enzymes alone, combined with therapy selected to address glycemic, weight, cardiovascular, and hepatic outcomes concurrently, is central to preventing cirrhosis, hepatocellular carcinoma, and premature death in this population.

INTRODUCTION

Type 2 diabetes and chronic liver disease have converged into one of the most consequential comorbid pairings in contemporary medicine. Metabolic dysfunction–associated steatotic liver disease (MASLD)—the term adopted in 2023 to replace nonalcoholic fatty liver disease (NAFLD) and to better reflect its cardiometabolic origin—describes a spectrum ranging from simple hepatic steatosis to metabolic dysfunction–associated steatohepatitis (MASH, formerly NASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma (1). Because insulin resistance is the central driver of hepatic fat accumulation, type 2 diabetes is both a risk factor for MASLD and an accelerant of its progression to fibrosing liver disease (2).

For much of the past two decades, MASLD was managed as an incidental radiologic or biochemical finding rather than a target of systematic care. Primary care and endocrinology visits for type 2 diabetes have traditionally centered on glycemic control, blood pressure, lipids, and screening for retinopathy, nephropathy, and neuropathy, with the liver addressed only if aminotransferases were markedly elevated or hepatomegaly was noted incidentally. That approach is no longer tenable. Liver-related mortality has risen sharply in parallel with the obesity and diabetes epidemics, and MASH-related cirrhosis has become one of the leading indications for liver transplantation in the United States, having overtaken chronic hepatitis C in several national registries (3). Unlike many other diabetes complications, however, the natural history of MASLD is largely silent until advanced fibrosis or cirrhosis has already developed, which places the burden of early detection squarely on systematic, guideline-based screening rather than on symptom-triggered evaluation.

In recognition of this shift, the American Diabetes Association (ADA) issued a mid-year update to the Standards of Care in Diabetes in 2023 formally incorporating fibrosis risk stratification into the comprehensive medical evaluation of every adult with type 2 diabetes or prediabetes, a recommendation that has been carried forward and refined in subsequent annual Standards of Care updates and that aligns closely with parallel guidance from the American Association for the Study of Liver Diseases (AASLD), the American Association of Clinical Endocrinology (AACE), and the American Gastroenterological Association (AGA) (4,10,11). This review synthesizes the current evidence base including recent pathophysiologic, diagnostic, and pharmacologic developments and the ADA-aligned screening and management pathway for MASLD/MASH in type 2 diabetes, intended for clinicians managing this population in primary care, endocrinology, and hepatology settings.

NOMENCLATURE: FROM NAFLD TO MASLD

In 2023, a multisociety Delphi consensus process replaced the exclusionary term NAFLD with MASLD, defined by hepatic steatosis on imaging or histology plus at least one of five cardiometabolic risk criteria—overweight or obesity, prediabetes or type 2 diabetes, hypertension, hypertriglyceridemia, or low HDL cholesterol—in the absence of other causes of steatosis such as excessive alcohol use, certain medications, or monogenic disease (5). Steatohepatitis with progressive inflammation and fibrosis is now termed MASH rather than NASH. Patients with both significant alcohol consumption and cardiometabolic risk factors fall into a newly defined overlap category, MetALD, which recognizes that alcohol use and metabolic dysfunction commonly coexist and interact rather than representing mutually exclusive etiologies.

The rationale for the terminology change extended beyond semantics. The word 'nonalcoholic' was widely viewed as stigmatizing, defining the disease by what it is not rather than by its actual metabolic drivers, and it complicated communication with patients and across specialties. The new nomenclature also created a diagnostic pathway based on positive criteria—the presence of steatosis plus at least one cardiometabolic risk factor—rather than requiring the exclusion of alcohol use above an arbitrary threshold before a diagnosis could be made, which streamlines diagnosis in busy primary care and diabetes clinics. This review uses MASLD/MASH throughout but retains NAFLD/NASH when directly citing trials, guidelines, or drug labels published under the earlier nomenclature, since the underlying study populations are equivalent and the terminology change is retrospective.

The transition has practical implications for clinicians beyond terminology. Because the MASLD definition requires the presence of at least one cardiometabolic risk factor, essentially every patient with type 2 diabetes and hepatic steatosis will, by definition, meet criteria for MASLD, simplifying diagnostic coding and removing ambiguity that previously arose when a patient with modest alcohol intake and diabetes had steatosis that some clinicians hesitated to label as NAFLD. Electronic health record systems, quality-reporting programs, and drug labeling are transitioning to the new terminology at different rates, so clinicians should expect to encounter both terms in practice for several years and should ensure that problem lists and coding are updated to reflect the current

nomenclature as local systems permit, since consistent coding will also be important for future population-level surveillance and quality-improvement efforts targeting this condition.

EPIDEMIOLOGY AND NATURAL HISTORY

Population-based and cohort studies converge on a prevalence of hepatic steatosis of roughly 55–70% among adults with type 2 diabetes, substantially higher than the 25–30% prevalence in the general adult population, and prevalence rises further with increasing body mass index and duration of diabetes (6,2). Among patients with type 2 diabetes systematically screened in outpatient endocrinology clinics—rather than referred because of known liver disease—clinically significant fibrosis (stage F2 or higher) has been identified in approximately one in five patients using transient elastography, and a substantial proportion of these patients had entirely normal aminotransferases at the time of testing (7). This finding underlies a central message of the current screening paradigm: normal liver enzymes do not exclude clinically important fibrosis in this population, and reliance on alanine aminotransferase alone will miss a substantial share of at-risk patients.

The natural history of MASLD is heterogeneous. Simple steatosis without inflammation carries a comparatively benign hepatic prognosis over years to decades, whereas MASH with fibrosis progresses at a variable rate—commonly estimated at roughly one fibrosis stage per seven to fourteen years on average, though with wide interindividual variability—and a meaningful minority of patients progress considerably faster, particularly those with type 2 diabetes, obesity, and genetic risk variants discussed below (8). Fibrosis stage, rather than the presence of steatosis or even the degree of histologic inflammation, is the dominant determinant of both liver-related outcomes—decompensated cirrhosis, hepatocellular carcinoma, transplantation, and liver-related death—and, independently, all-cause and cardiovascular mortality (9). This is why current guidance stratifies patients by fibrosis risk rather than by steatosis grade or enzyme elevation, and why the term 'fatty liver' alone should not be equated with a benign process in a patient with type 2 diabetes.

Cardiovascular disease, not liver failure, remains the single leading cause of death in patients with MASLD overall, underscoring that hepatic and cardiometabolic risk should be assessed and treated in parallel rather than sequentially. Nonetheless, as fibrosis stage advances, the relative contribution of liver-related mortality rises substantially, and among patients who reach cirrhosis, liver-related complications become a leading cause of death, second only to cardiovascular disease and extrahepatic malignancy in most contemporary cohorts (9,3).

Global trends reinforce the urgency of this issue for diabetes care specifically. The worldwide prevalence of MASLD in the general adult population has risen in parallel with obesity and type 2 diabetes across virtually every region studied, and modeling analyses project continued increases in MASH-related cirrhosis, hepatocellular carcinoma, and liver-related mortality over the coming decades unless screening and treatment are scaled substantially, with the steepest projected increases occurring in regions experiencing the most rapid rises in obesity and type 2 diabetes prevalence, including parts of the Middle East, Latin America, and Asia in addition to the United States (3,6). Because type 2 diabetes is both the strongest single clinical risk factor for MASH and fibrosis and one of the most common chronic diseases managed in primary care, diabetes clinics and primary care practices are positioned as the most efficient point of population-level intervention, rather than hepatology clinics, which by definition see only patients who have already been identified and referred.

BIDIRECTIONAL PATHOPHYSIOLOGY LINKING TYPE 2 DIABETES AND MASLD

The relationship between type 2 diabetes and MASLD is mechanistically bidirectional and multifactorial, involving insulin resistance, adipose tissue biology, genetic susceptibility, gut microbial composition, and systemic inflammation that together create a self-reinforcing cycle of hepatic and systemic metabolic injury.

Insulin Resistance and Hepatic Lipotoxicity

Insulin resistance increases hepatic de novo lipogenesis through persistent activation of sterol regulatory element-binding protein 1c and carbohydrate response element-binding protein, while simultaneously impairing insulin's normal suppression of adipose-tissue lipolysis. The result is increased flux of free fatty acids from peripheral adipose tissue to the liver, where they are esterified into triglycerides and stored as lipid droplets, or metabolized into lipotoxic intermediates—diacylglycerols, ceramides, and other bioactive lipid species—that impair hepatic insulin signaling further and promote endoplasmic reticulum stress, mitochondrial dysfunction, and hepatocyte injury (2,12). This lipotoxic injury, rather than triglyceride accumulation itself, is thought to be the proximate trigger for the inflammatory and fibrogenic cascade that defines MASH.

Adipose Tissue Dysfunction and Hepatokines

Visceral adiposity, which is disproportionately expanded in type 2 diabetes, behaves as an active endocrine and inflammatory organ. Dysfunctional, insulin-resistant adipose tissue secretes reduced amounts of adiponectin—a hepatoprotective, insulin-sensitizing adipokine—alongside increased quantities of proinflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6, and elevated free fatty acid efflux. The steatotic liver, in turn, becomes a source of altered hepatokine secretion—including fetuin-A and fibroblast growth factor 21 resistance—and of subclinical systemic inflammation and impaired hepatic insulin clearance that worsen peripheral and hepatic insulin resistance, closing a bidirectional loop between adipose tissue, liver, and glycemic control (8,12).

Genetic and Epigenetic Modifiers

Genetic susceptibility helps explain why fibrosis severity and progression rate vary substantially among patients with similar metabolic risk profiles. The PNPLA3 rs738409 variant, which impairs hepatic lipid droplet remodeling, is the most extensively replicated genetic risk factor for steatosis, steatohepatitis, and fibrosis progression across populations, and its effect appears to be amplified in the presence of obesity and type 2 diabetes. The TM6SF2 rs58542926 variant similarly increases hepatic triglyceride retention and fibrosis risk while, notably, lowering circulating LDL cholesterol and cardiovascular risk, illustrating a dissociation between hepatic and cardiovascular risk conferred by some genetic variants. Additional modifiers include variants in MBOAT7, associated with increased fibrosis risk, and a common loss-of-function variant in HSD17B13 that appears protective against progression to steatohepatitis and fibrosis. While polygenic and monogenic risk scores incorporating these variants are an active area of research, they are not yet incorporated into routine ADA-endorsed screening algorithms and should be regarded as prognostic refinements rather than first-line clinical tools at this time (13). Composite genetic-clinical risk scores that combine PNPLA3, TM6SF2, and HSD17B13 genotype with routine clinical variables have shown improved discrimination for advanced fibrosis compared with clinical variables alone in research cohorts, and family history of cirrhosis or hepatocellular carcinoma in a first-degree relative with type 2 diabetes may itself be a useful, low-cost proxy for elevated genetic risk in everyday practice even where genotyping is not readily available. Epigenetic modifications, including altered DNA methylation patterns at loci involved in lipid metabolism, have also been described in MASH and may partly explain why fibrosis severity can differ between monozygotic twins with similar metabolic profiles, though clinical application of epigenetic biomarkers remains investigational.

Gut Microbiome and Intestinal Permeability

Alterations in gut microbial composition and increased intestinal permeability have been implicated in MASLD pathogenesis and progression. Dysbiosis can increase circulating bacterial endotoxin (lipopolysaccharide) delivered to the liver via the portal circulation, activating Kupffer cells and hepatic stellate cells and promoting inflammation and fibrogenesis. Altered microbial metabolism of bile acids, choline, and short-chain fatty acids further modulates hepatic lipid handling and systemic insulin sensitivity. Although microbiome-targeted therapies

remain investigational, this axis has generated interest as a potential future biomarker and therapeutic target, and it partially underlies the rationale for dietary pattern interventions, discussed below, that favor fiber-rich, plant-forward diets (14).

Systemic Inflammation and the Cardiovascular-Renal-Hepatic Axis

MASLD is increasingly recognized as a systemic, not merely hepatic, disease. Beyond its association with atherosclerotic cardiovascular disease—now understood to be linked through shared insulin resistance, dyslipidemia (typically an atherogenic pattern of elevated triglycerides, small dense LDL particles, and low HDL cholesterol), and systemic inflammation rather than through hepatic fibrosis alone—MASLD is independently associated with incident chronic kidney disease and with a higher prevalence of diabetic retinopathy and other microvascular complications in patients with type 2 diabetes, likely reflecting shared pathophysiologic drivers rather than a direct causal pathway from liver to kidney or retina in most cases (2,15). This convergence supports a unified, rather than organ-siloed, approach to cardiometabolic risk assessment in patients with type 2 diabetes and MASLD.

CLINICAL PRESENTATION AND DIAGNOSTIC EVALUATION

Most patients with MASLD, including those with established fibrosis, are asymptomatic, or report only nonspecific right upper quadrant discomfort or fatigue that is rarely volunteered without direct questioning. Hepatomegaly may be present but is frequently absent or difficult to appreciate on examination in patients with obesity. Because symptoms and physical examination findings are insensitive and nonspecific, diagnosis and risk stratification depend on systematic biochemical and imaging-based screening rather than on clinical suspicion triggered by symptoms, which is precisely why guideline directed, protocol-driven screening rather than opportunistic case-finding is now recommended for the entire population with type 2 diabetes or prediabetes (4).

When advanced fibrosis or cirrhosis has already developed, findings may include spider angiomata, palmar erythema, splenomegaly, thrombocytopenia identified incidentally on a complete blood count, or, in decompensated disease, ascites, jaundice, or hepatic encephalopathy; however, waiting for these findings to trigger evaluation defeats the purpose of early risk stratification, since by the time they appear, irreversible complications may already be established. Incidental findings that should prompt fibrosis risk stratification even outside the routine periodic screening interval include unexplained thrombocytopenia, an incidentally noted coarsened or nodular liver echotexture on abdominal imaging obtained for another indication, or a rising FIB-4 trend on serial laboratory testing even if the absolute value remains below the high-risk threshold.

Differential Diagnosis

Before attributing steatosis or elevated aminotransferases to MASLD, clinicians should consider and, where clinically indicated, exclude other causes of chronic liver disease, particularly when the clinical picture is atypical (for example, a FIB-4 disproportionately elevated relative to metabolic risk factors, or steatosis without any cardiometabolic risk factor at all). Relevant alternative or contributing diagnoses include hazardous alcohol use, chronic viral hepatitis B and C, hemochromatosis, autoimmune hepatitis, Wilson disease (particularly in younger patients), medication-induced steatosis (for example, from amiodarone, methotrexate, tamoxifen, or corticosteroids), and, less commonly, alpha-1 antitrypsin deficiency. A basic secondary evaluation hepatitis B and C serologies, iron studies, and a directed history of alcohol use and medication exposure is reasonable at the time of initial identification of hepatic steatosis, particularly before hepatology referral, though it should not delay fibrosis risk stratification in patients with clear-cut cardiometabolic risk factors (10,11). A structured, validated alcohol-use screening instrument, such as the AUDIT-C, is preferable to an unstructured verbal inquiry, since patients may underreport alcohol intake, and the distinction between MASLD and the MetALD overlap category

described above has implications for prognosis and for the emphasis placed on alcohol reduction counseling alongside metabolic risk factor management. When the diagnosis remains uncertain after this basic evaluation—for example, a FIB-4 or elastography result substantially out of proportion to the apparent severity of metabolic risk factors—referral to hepatology for consideration of additional testing or liver biopsy is appropriate rather than attributing an atypical presentation to MASLD by default.

SCREENING AND RISK STRATIFICATION FOR ADVANCED FIBROSIS

The ADA Standards of Care recommend risk-stratifying all adults with type 2 diabetes or prediabetes for advanced fibrosis, and extend this recommendation to adults with type 1 diabetes who have obesity or additional cardiometabolic risk factors (4). The recommended first-line, noninvasive tool is the Fibrosis-4 (FIB-4) index, calculated from age, aspartate aminotransferase, alanine aminotransferase, and platelet count—inputs already available in most electronic health records, which allows automated calculation and point-of-care flagging without additional cost or blood draws (10).

Noninvasive Serum Scores

FIB-4 was derived and validated primarily in viral hepatitis cohorts but has been extensively externally validated in MASLD populations and is favored for its simplicity, low cost, and freedom from proprietary calculations. The NAFLD fibrosis score, which additionally incorporates body mass index, diabetes status, and albumin, performs comparably and can serve as an alternative or confirmatory calculation. The AST-to-platelet ratio index (APRI) is simpler still but generally less well validated specifically in MASLD and is used less consistently in current diabetes-focused algorithms. All serum-based scores are optimized to rule out, rather than definitively rule in, advanced fibrosis, and each carries a substantial indeterminate range in which a second-line test is required rather than a binary result being obtainable from serum markers alone (10,11).

Imaging-Based Assessment

Vibration-controlled transient elastography (VCTE, commonly delivered as FibroScan) measures liver stiffness as a surrogate for fibrosis and is the most widely available and best-validated point-of-care imaging tool for second-line risk stratification, with the added benefit of a controlled attenuation parameter that semi-quantitatively estimates steatosis at the same visit. The enhanced liver fibrosis (ELF) test, a serum panel of three direct fibrosis markers, offers a blood-based alternative where elastography is unavailable and performs comparably in several validation cohorts. Magnetic resonance elastography offers superior diagnostic accuracy for fibrosis staging compared with transient elastography and magnetic resonance imaging-based proton density fat fraction (MRI-PDFF) provides the most accurate noninvasive quantification of hepatic steatosis, but both require dedicated MRI capacity, are costlier, and are generally reserved for indeterminate cases, clinical trials, or situations in which VCTE is technically unsuccessful, such as in patients with severe obesity or ascites (16,11). Liver biopsy remains the diagnostic reference standard for grading steatohepatitis and staging fibrosis and continues to have a defined role for diagnostic uncertainty, discordant noninvasive results, suspected concurrent liver disease, or in the context of clinical trials, but its invasiveness, cost, sampling variability, and small but real complication rate preclude its use as a first-line population screening tool (10).

Limitations of Current Tools

No current noninvasive test is perfect, and clinicians should be aware of specific limitations relevant to patients with type 2 diabetes. FIB-4 accuracy is reduced in patients with severe obesity and in older adults, in whom age-adjusted thresholds (using a higher cutoff of 2.0 rather than 1.3 in patients over 65 years) are recommended to reduce false-positive referrals; some recent analyses suggest FIB-4 performance is further attenuated across the

broader population of patients with diabetes and obesity, motivating interest in two-step and sequential algorithms and in emerging biomarker panels (17,18). Because platelet count and transaminases can be affected by conditions unrelated to liver fibrosis (for example, thrombocytopenia from other causes, or transaminase suppression from advanced cirrhosis itself, sometimes termed 'burnt-out NASH'), an isolated FIB-4 result should always be interpreted in clinical context rather than mechanically applied, and unexpected results in either direction warrant clinical correlation or repeat testing.

THE ADA-ALIGNED SCREENING AND REFERRAL ALGORITHM

Integrating the tools above, the ADA- and multisociety-endorsed pathway proceeds as follows. A FIB-4 below 1.3 (below 2.0 in adults over age 65) indicates low probability of advanced fibrosis, and these patients can be managed in primary care or endocrinology with reinforcement of lifestyle measures, optimization of glycemic and cardiometabolic risk factors, and FIB-4 reassessment every one to two years, since risk is dynamic rather than static over time. A FIB-4 of 1.3 or higher warrants a second-line noninvasive test—VCTE where available, or ELF as an alternative. A liver stiffness measurement below 8.0 kPa (or ELF below 9.8) suggests lower fibrosis risk and continued primary care or endocrinology management with interval reassessment; a liver stiffness of 8.0 kPa or higher, an ELF of 9.8 or higher, or a FIB-4 above 2.67 regardless of elastography result, warrants referral to hepatology or gastroenterology for further evaluation, which may include liver biopsy, additional imaging, or assessment for clinical trial eligibility in select cases (11,10).

FIB-4 score	Interpretation	Action
< 1.3 (< 2.0 if age > 65 y)	Low probability of advanced fibrosis	Manage in primary care/endocrinology; repeat FIB-4 every 1–2 years
1.3–2.67	Indeterminate	Second-line test: VCTE or ELF
> 2.67, or LSM ≥ 8.0 kPa, or ELF ≥ 9.8	High probability of advanced fibrosis	Refer to hepatology/gastroenterology

Table 1. ADA-aligned fibrosis risk stratification pathway in type 2 diabetes and prediabetes (4,10,11). FIB-4, Fibrosis-4 index; VCTE, vibration-controlled transient elastography; ELF, enhanced liver fibrosis test; LSM, liver stiffness measurement.

Two practical points merit emphasis. First, this pathway is designed for asymptomatic risk stratification in the general population with type 2 diabetes or prediabetes, not for patients with known cirrhosis, decompensated liver disease, or an established alternative diagnosis, who should be managed under separate, disease-specific pathways. Second, a low-risk FIB-4 result should not be treated as a one-time reassurance; because fibrosis risk evolves with glycemic control, weight trajectory, and age, periodic reassessment is a required, not optional, component of the algorithm.

MANAGEMENT

Management goals in MASLD/MASH complicating type 2 diabetes are threefold: reduce hepatic fat and inflammation, halt or reverse fibrosis progression, and concurrently address the glycemic, weight, and cardiovascular risk that these patients almost invariably share. Therapy should therefore be selected to serve multiple targets simultaneously wherever possible, rather than treating the liver as an isolated problem requiring a separate prescription.

Lifestyle Intervention

Lifestyle intervention remains foundational and should be offered to every patient regardless of fibrosis stage or eligibility for pharmacotherapy. Weight loss of 7–10% of body weight, achieved through a hypocaloric diet and

increased physical activity, produces proportional reductions in steatosis and, at the higher end of this range, histologic improvement in steatohepatitis and fibrosis; weight loss exceeding 10% is associated with fibrosis regression in a majority of patients able to sustain it (19). No single dietary pattern has been shown definitively superior, but a Mediterranean-style diet—emphasizing vegetables, legumes, whole grains, olive oil, and reduced intake of refined carbohydrates, added sugars, and processed meat—has the most consistent supportive evidence and aligns with cardiovascular and glycemic goals, making it a reasonable default recommendation. Reduction of fructose-containing beverages in particular has direct relevance given fructose's specific role in stimulating hepatic de novo lipogenesis. Aerobic exercise reduces hepatic fat even in the absence of significant weight loss, through improved insulin sensitivity and mitochondrial fatty acid oxidation, and resistance training may offer complementary benefit for body composition and glycemic control; current guidance generally recommends at least 150 minutes per week of moderate-intensity aerobic activity, consistent with broader ADA physical activity recommendations for type 2 diabetes. Because sustained behavior change is difficult, structured, multidisciplinary programs incorporating dietitian counseling, behavioral support, and, where available, medical weight management services are more likely to achieve and maintain the magnitude of weight loss associated with histologic benefit than brief counseling alone (19).

Glucose-Lowering Therapies with Hepatic Benefit

Selection among glucose-lowering agents should account for hepatic as well as glycemic and cardiovascular effects, since several diabetes medications now have direct evidence of benefit in MASH.

Pioglitazone, a thiazolidinedione that improves peripheral and hepatic insulin sensitivity through PPAR-gamma agonism, has the longest evidence base for histologic benefit in biopsy-proven MASH in patients with prediabetes or type 2 diabetes, improving steatosis, lobular inflammation, and fibrosis in randomized, placebo-controlled trials with paired liver biopsies (20). Its use is nonetheless tempered by weight gain, fluid retention with a risk of precipitating or worsening heart failure, and an increased risk of bone fracture, particularly in postmenopausal women, which should be discussed explicitly with patients and weighed against the potential hepatic benefit.

GLP-1 receptor agonists, particularly semaglutide, produce dose-dependent reductions in hepatic fat and higher rates of MASH resolution without fibrosis worsening compared with placebo, an effect driven substantially, though likely not exclusively, by their weight-loss effect (21). Given their independently established cardiovascular and, for some agents, renal benefits in type 2 diabetes, GLP-1 receptor agonists are an attractive first-line option in patients with type 2 diabetes, obesity, and MASLD even before fibrosis has been formally staged, since they address glycemic, weight, and cardiovascular risk regardless of the eventual fibrosis result.

The dual GIP/GLP-1 receptor agonist tirzepatide produced high rates of MASH resolution and fibrosis improvement in a phase 2 randomized trial enrolling patients with biopsy-confirmed MASH and stage 2–3 fibrosis, with or without type 2 diabetes, with effect sizes that compared favorably with those reported for GLP-1 monotherapy, plausibly reflecting its larger weight-loss effect and additional GIP-receptor-mediated metabolic actions (22). Tirzepatide is not yet FDA-approved specifically for MASH, but ongoing phase 3 evaluation is expected to clarify its eventual role alongside its established glycemic and weight-management indications.

SGLT2 inhibitors modestly reduce hepatic fat content and aminotransferase levels through mechanisms that likely include weight loss, improved insulin sensitivity, and a shift toward fatty acid oxidation and ketogenesis, and are a reasonable component of a broader cardiometabolic regimen given their robust cardiovascular and renal benefit data in type 2 diabetes; however, evidence for meaningful fibrosis regression with SGLT2 inhibitors is less robust than for GLP-1-based therapy and they should not be regarded as primary liver-directed therapy at this time. Metformin, despite being first-line for glycemic control, has not demonstrated consistent histologic benefit in MASH and should be selected on its established glycemic and safety profile rather than for hepatic effect.

Liver-Directed Pharmacotherapy Approved Specifically for MASH

Two agents are now FDA-approved specifically for MASH with moderate to advanced fibrosis (stage F2–F3), independent of their glycemic effects, and represent the first drugs developed and labeled explicitly for this indication. Resmetirom, an oral, liver-directed thyroid hormone receptor-beta-selective agonist, received accelerated approval in March 2024 after the phase 3 MAESTRO-NASH trial demonstrated MASH resolution without worsening of fibrosis, and fibrosis improvement without worsening of MASH, in roughly a quarter to a third of treated patients versus a substantially lower proportion with placebo, at both the 80 mg and 100 mg once daily doses studied (23). Resmetirom's mechanism selective activation of hepatic thyroid hormone receptor-beta increases hepatic fatty acid oxidation and mitochondrial function while minimizing the systemic thyromimetic effects (such as cardiac and bone effects) associated with nonselective thyroid hormone receptor activation. Common adverse effects include diarrhea and nausea, typically most prominent early in treatment, and monitoring of lipid panels and liver enzymes is recommended given its mechanism and hepatic metabolism.

Semaglutide 2.4 mg received the same indication—MASH with moderate to advanced fibrosis—in August 2025, based on the phase 3 ESSENCE trial, extending its established type 2 diabetes and obesity indications to a formal hepatic one (24,25). This dual approval is clinically significant for patients with type 2 diabetes specifically, because semaglutide can be selected once to address glycemic control, weight, cardiovascular risk, and now MASH with fibrosis simultaneously, reducing pill or injection burden and reinforcing a unified rather than fragmented approach to this patient population. Both approvals were granted for noncirrhotic disease (fibrosis stage F2–F3), and confirmatory trials required under the accelerated approval pathway to verify durable clinical benefit—such as reduction in progression to cirrhosis and hepatic decompensation—are ongoing for both agents; clinicians should counsel patients that these are conditional approvals pending confirmation of long-term outcome benefit, though the histologic effect sizes observed to date are considered clinically meaningful by treating hepatologists and endocrinologists.

Emerging and Investigational Agents

An active pipeline extends beyond the two currently approved agents. Fibroblast growth factor 21 (FGF21) analogs—including efruxifermin, pegozafermin, and efimosfermin—target hepatic and adipose FGF21 signaling to improve lipid metabolism and reduce hepatic fat and fibrosis, and several are in phase 3 evaluation. Survodutide, a dual GLP-1/glucagon receptor agonist, adds glucagon receptor-mediated stimulation of hepatic fatty acid oxidation to GLP-1-mediated weight loss and is being studied in both noncirrhotic and cirrhotic MASH populations, an important distinction since most current trials, and both approved agents, have excluded patients with cirrhosis. Lanifibranor, a pan-PPAR agonist activating PPAR-alpha, -delta, and -gamma isoforms simultaneously, met co-primary histologic endpoints of MASH resolution and fibrosis improvement in a phase 2b trial and is in phase 3 evaluation, with additional favorable effects on insulin sensitivity, lipid profile, and inflammatory markers (26,27). Combination therapy—for example, pairing an incretin-based agent for weight loss with a liver-directed agent such as resmetirom—is an emerging area of clinical interest and trial design, given the different but potentially complementary mechanisms involved, though data guiding rational combination selection are still preliminary.

Bariatric and Metabolic Surgery

Bariatric and metabolic surgery produces the most durable improvement in steatohepatitis and fibrosis of any current intervention, with prospective cohort data demonstrating resolution of steatohepatitis in the large majority of patients and regression of fibrosis in a substantial proportion at long-term follow-up (28). Surgery should be discussed with eligible patients with type 2 diabetes and obesity meeting standard bariatric surgery criteria, particularly those with more advanced fibrosis in whom sustained pharmacologic or lifestyle-driven weight loss is

otherwise difficult to achieve, recognizing that surgery also produces substantial and durable improvement in glycemic control, and in some patients type 2 diabetes remission, independent of its hepatic benefit. Surgical risk, patient preference, and access remain practical barriers, and patients with decompensated cirrhosis generally require careful multidisciplinary evaluation before proceeding given increased perioperative risk.

Management of Cirrhosis and Hepatocellular Carcinoma Surveillance

Once a patient has progressed to cirrhosis, management shifts to hepatology-directed care, including surveillance for hepatocellular carcinoma with ultrasound, with or without serum alpha-fetoprotein, every six months, screening for esophageal varices, and monitoring for decompensation. Type 2 diabetes and obesity independently increase hepatocellular carcinoma risk in patients with MASLD cirrhosis, reinforcing the importance of surveillance adherence in this subgroup. Glycemic management in decompensated cirrhosis requires particular caution given altered drug metabolism, hypoglycemia risk from impaired hepatic gluconeogenesis, and, in some agents, reduced hepatic clearance, and is generally best coordinated jointly between endocrinology and hepatology (11).

Agent/class	Hepatic evidence	Relevant caveats
Pioglitazone	Improves steatosis, inflammation, fibrosis in biopsy-proven MASH (20)	Weight gain, edema/heart failure risk, fracture risk
Semaglutide	FDA-approved for MASH with F2–F3 fibrosis (ESSENCE trial) (24,25)	GI side effects; titrate slowly
Tirzepatide	High rates of MASH resolution/fibrosis improvement in phase 2 (22)	Not yet FDA-approved for MASH specifically
Resmetirom	FDA-approved for MASH with F2–F3 fibrosis (MAESTRO-NASH) (23)	No direct glycemic effect; monitor lipids/LFTs
SGLT2 inhibitors	Modest reduction in hepatic fat/aminotransferases	Less fibrosis outcome data than GLP-1–based agents
Bariatric surgery	Most durable steatohepatitis/fibrosis improvement (28)	Reserve for eligible patients with obesity; caution in decompensated cirrhosis

Table 2. Selected therapies with hepatic evidence in patients with type 2 diabetes and MASLD/MASH. LFTs, liver function tests.

Monitoring Response to Therapy and Long-Term Follow-up

Once a patient has been identified as being at elevated fibrosis risk and started on a lifestyle or pharmacologic intervention, a practical question is how to monitor response over time without resorting to repeat liver biopsy in most cases. Serial noninvasive testing—repeat FIB-4 at each routine diabetes visit, and repeat elastography or ELF testing at an interval of roughly one to two years, or sooner if clinically indicated—provides a reasonable, pragmatic approach to tracking trajectory rather than relying on a single snapshot measurement. A meaningful decline in liver stiffness or in serum fibrosis markers after sustained weight loss or initiation of a liver-directed agent is generally reassuring, whereas a rising trend despite treatment should prompt reassessment of adherence, consideration of an alternative or additional agent, and a lower threshold for hepatology referral even if the absolute FIB-4 or elastography value has not yet crossed the high-risk threshold. For patients treated with resmetirom specifically, package labeling recommends baseline and periodic monitoring of liver enzymes and a lipid panel given the drug's mechanism and hepatic clearance, in addition to routine monitoring of the metabolic parameters already tracked as part of diabetes care. Clinicians should also set explicit expectations with patients that improvement in noninvasive markers, particularly elastography, may lag behind clinical improvement or weight loss by several months, to avoid premature discontinuation of an effective intervention.

COST-EFFECTIVENESS AND HEALTH SYSTEM CONSIDERATIONS

Health-economic analyses of FIB-4-based screening in type 2 diabetes populations have generally found the strategy to be cost-effective or even cost-saving over a lifetime horizon, largely because FIB-4 itself requires no additional laboratory tests beyond those already routinely obtained in diabetes care, and because early identification and referral of the comparatively small proportion of patients with advanced fibrosis avoids substantially higher downstream costs associated with decompensated cirrhosis, liver transplantation, and hepatocellular carcinoma treatment (10). The principal costs in the pathway arise at the second-line testing step—elastography access and reimbursement vary by health system and geography—and at the treatment step, where resmetirom and semaglutide, like most novel branded therapeutics, carry substantial list prices that may require prior authorization or patient assistance programs to access in practice. Health systems implementing this pathway should anticipate and plan for these downstream costs and access barriers at the time of rollout, rather than treating them as an afterthought once patients are identified, since identifying a patient as high risk without a clear, funded pathway to confirmatory testing and treatment provides limited benefit and may increase patient anxiety without a corresponding clinical benefit. Population health approaches, such as embedding FIB-4 calculation and flagging directly into the electronic health record with an associated order set for second-line testing and referral criteria, have been more successful at translating guideline recommendations into completed screening than education-only approaches directed at individual clinicians.

PATIENT COMMUNICATION AND SHARED DECISION-MAKING

Communicating fibrosis risk to patients requires care, given the anxiety that a cirrhosis-adjacent conversation can provoke and the fact that most patients newly identified through screening will fall into the low- or indeterminate-risk category rather than requiring immediate specialist referral. Framing the conversation around actionable, shared risk factors—the same weight, glycemic, and cardiovascular targets patients are already working toward as part of diabetes management—rather than presenting the liver as a separate, frightening new diagnosis, tends to support engagement rather than fatalism, particularly for patients in the low-risk category who will be managed with reinforced lifestyle counseling alone. For patients found to have indeterminate or high-risk results, clearly explaining the stepwise nature of the algorithm—that an elevated FIB-4 indicates a need for further, more specific testing rather than an existing diagnosis of cirrhosis—helps avoid unnecessary distress while the second-line test is arranged. When pharmacotherapy is being considered, shared decision-making should weigh each patient's individual priorities among glycemic control, weight, cardiovascular risk, and hepatic risk, since several available agents, particularly the GLP-1 receptor agonists and semaglutide specifically, offer an opportunity to address multiple of these priorities with a single medication, which can simplify decision-making and improve adherence compared with adding a separate agent for each individual risk domain.

SPECIAL POPULATIONS

Type 1 Diabetes

MASLD is less prevalent in type 1 diabetes overall than in type 2 diabetes, reflecting the lower baseline prevalence of insulin resistance in this population, but risk rises substantially in the presence of obesity, insulin resistance ('double diabetes'), or additional cardiometabolic risk factors. The ADA accordingly recommends fibrosis risk stratification in adults with type 1 diabetes who have obesity or other cardiometabolic risk factors, using the same FIB-4-based pathway, rather than universal screening of all patients with type 1 diabetes regardless of risk profile (4).

Chronic Kidney Disease

Given the bidirectional epidemiologic association between MASLD and chronic kidney disease described above, clinicians should maintain heightened attention to both conditions when either is present in a patient with type 2 diabetes. Practically, this has implications for medication selection, since GLP-1 receptor agonists and SGLT2 inhibitors offer renal as well as hepatic and cardiovascular benefit and are therefore particularly attractive in patients with overlapping MASLD and chronic kidney disease, whereas dose adjustment or avoidance of certain other agents may be required as renal function declines (15).

Older Adults

As noted above, FIB-4 requires an age-adjusted threshold (2.0 rather than 1.3) in patients over 65 years to maintain acceptable specificity, since aminotransferases and platelet counts shift with age independent of fibrosis. Competing mortality risk, frailty, and treatment tolerability should inform how aggressively fibrosis is pursued and treated in the oldest patients, and shared decision-making regarding the intensity of screening and treatment is appropriate in patients with significant comorbidity or limited life expectancy.

Pediatric and Young Adult Transition

MASLD prevalence has risen substantially among children and adolescents with obesity and is expected to become an increasingly important issue in pediatric-to-adult care transition as this cohort ages into adult diabetes and primary care practices. Adolescents with type 2 diabetes and obesity who are transitioning to adult care should have fibrosis risk stratification initiated as part of that transition if it has not already been performed, since screening practices and thresholds validated primarily in adult cohorts are now being adapted, with some modification, for pediatric use, and continuity of hepatic risk assessment across the pediatric-adult transition is easily lost without explicit attention (29).

IMPLEMENTATION, HEALTH EQUITY, AND MULTIDISCIPLINARY CARE

Practical implementation, rather than evidence generation, is now the principal rate-limiting step in translating the ADA screening recommendation into population-level benefit. Automated FIB-4 calculation from existing complete blood count and hepatic panel results, embedded in the electronic health record and flagged at the point of care, allows risk stratification without additional patient burden, additional blood draws, or meaningful added cost, and several health systems have demonstrated that this automation substantially increases screening rates compared with reliance on manual calculation (10). Clinicians should avoid two common errors in practice: treating a normal alanine aminotransferase as reassurance against fibrosis, and deferring any action pending specialist referral when a FIB-4 result is indeterminate rather than proceeding promptly to second-line testing.

Disparities in MASLD prevalence, severity, and access to both diagnostic elastography and emerging pharmacotherapy are increasingly recognized and warrant explicit attention. Hispanic populations in the United States carry a disproportionately high burden of MASLD and MASH, related in part to a higher prevalence of the PNPLA3 risk variant discussed above, while access to transient elastography, hepatology referral, and newer branded therapies such as resmetirom and semaglutide is unevenly distributed by insurance status, geography, and proximity to specialty care. Because the ADA-recommended screening pathway relies on tests already embedded in routine primary care laboratory panels for its first step, it is comparatively well positioned to reduce, rather than widen, these disparities if implemented systematically—provided that referral pathways and affordability of second-line testing and treatment for patients identified as high risk are addressed concurrently (30).

Effective care ultimately requires coordination across primary care, endocrinology, hepatology, dietetics, and, where relevant, bariatric surgery and behavioral health. Formal or informal multidisciplinary clinics or care

pathways that co-locate or closely coordinate these services have been associated with improved adherence to screening and more timely hepatology referral in early implementation reports, and represent a reasonable model for institutions building out MASLD care pathways for their diabetes populations.

FUTURE DIRECTIONS

The approvals of resmetirom and semaglutide for MASH mark an inflection point, but substantial gaps remain. Confirmatory trials are needed to establish that histologic improvement translates into reduced rates of hepatic decompensation, transplantation, and death, the outcomes that ultimately matter most to patients. Head-to-head and rational combination-therapy trials—for example, pairing an incretin-based agent with a liver-directed agent—are needed to guide sequencing and combination decisions that are currently made empirically. Noninvasive diagnostic tools with performance closer to biopsy, potentially incorporating novel serum biomarkers, imaging-derived radiomic features, or polygenic risk information, are an active area of investigation and could eventually reduce reliance on the sequential, sometimes indeterminate, testing algorithm described above. Extension of both diagnostic and therapeutic evidence to patients with compensated and decompensated cirrhosis, who have generally been excluded from pivotal trials to date, is an important unmet need given that this is precisely the population at greatest short-term risk. Finally, implementation research—closing the gap between guideline recommendations and real-world screening rates in primary care and endocrinology practice, and ensuring equitable access to diagnostic and therapeutic advances—will determine whether the considerable recent progress in MASLD science translates into population-level reductions in cirrhosis, hepatocellular carcinoma, and premature death among patients with type 2 diabetes.

Longer term, it is plausible that fibrosis risk stratification will become as embedded in routine diabetes care as retinal photography or urine albumin-to-creatinine ratio testing are today, supported by fully automated electronic health record calculation, standardized referral order sets, and quality metrics tracking screening completion rates analogous to those already used for other diabetes-related microvascular complications. Achieving this level of routinization will require sustained collaboration among endocrinology, hepatology, primary care, and health-system leadership, together with continued refinement of the underlying evidence base summarized in this review.

CONCLUSIONS

MASLD/MASH is a near-universal comorbidity of type 2 diabetes, driven by shared insulin resistance, adipose tissue dysfunction, genetic susceptibility, and gut-microbial and inflammatory pathways, with substantial and previously underrecognized potential for liver-related, cardiovascular, and all-cause mortality. Because the disease is silent until advanced fibrosis has developed and liver enzymes are an unreliable screening tool, systematic fibrosis risk stratification with FIB-4, followed by reflex elastography or ELF testing and hepatology referral when indicated, is now a standard-of-care recommendation from the ADA and should be incorporated into routine comprehensive diabetes evaluation for every adult with type 2 diabetes or prediabetes, and for at-risk adults with type 1 diabetes. Therapeutic selection should prioritize agents—structured lifestyle intervention, GLP-1 receptor agonists, tirzepatide, and, where fibrosis is established, resmetirom or semaglutide—that address glycemic, weight, cardiovascular, and hepatic risk together, reflecting the fundamentally shared metabolic pathophysiology of these two conditions, while bariatric surgery and an expanding pipeline of liver-directed agents offer additional options for patients with more advanced disease. Sustained progress will depend as much on systematic, equitable implementation of existing screening and treatment pathways as on continued pharmacologic innovation.

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