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Metabolic Dysfunction–Associated Steatotic Liver Disease

Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most common chronic liver disease in the United States. It is characterized by steatosis in the liver and is potentially reversible. Risk factors include obesity, type 2 mellitus, and other metabolic disorders. Metabolic dysfunction–associated steatohepatitis (MASH), a more severe form of MASLD, puts patients at risk for cirrhosis, liver decompensation, and liver cancer. Diet, exercise, and weight loss are the cornerstones of management. Although only 1 medication has been approved for treatment of MASH, other pharmacotherapies and surgeries that aid weight loss and optimize metabolic risk factors can be used. Early diagnosis and intervention are important to prevent progression to cirrhosis and its complications, including cancer.

Risk Factors, Screening, and Prevention

Diagnosis

Management and Treatment

Practice Improvement

CME/MOC activity available at Annals.org.

Physician Writers
Sajjadh M.J. Ali, MD
Michelle Lai, MD, MPH
Department of Medicine, Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts (S.M.J.A., M.L.)

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What is metabolic dysfunction–associated steatotic liver disease, and how common is it?

Metabolic dysfunction–associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), is the most common liver disease in adults and children in the United States. It affects more than 80 million adults, or 25% to 30% of the U.S. population (1–3), and this number is projected to increase to approximately 100 million by 2030 (4). Roughly one third are estimated to have the more severe subtype, metabolic dysfunction–associated steatohepatitis (MASH). MASH-related cirrhosis is the leading cause of liver transplant in women and adults older than 65 years (2, 5, 6).

MASLD is defined as the presence of liver steatosis (liver fat) with at least 1 of 5 cardiometabolic risk factors: obesity, central obesity (increased truncal subcutaneous fat and visceral fat), insulin resistance, hypertension, and dyslipidemia. The "MASLD" nomenclature, introduced in June 2023, replaces "NAFLD" or "nonalcoholic fatty liver disease," which had been defined as the presence of liver steatosis in more than 5% of hepatocytes in the absence of alcohol consumption above a certain threshold (20 g/d in women and 30 g/d in men); nonalcoholic steatohepatitis (NASH) was the more severe subset of NAFLD (**Table 1**) (1). The "MASLD" nomenclature highlights the metabolic basis and adds a new category for increased alcohol intake (MetALD) to capture people with metabolic derangements who also consume high amounts of alcohol (>140 g/wk for women and >210 g/wk for men). "MASH" replaces the term "NASH"; both are characterized by inflammation and hepatocellular injury in addition to hepatic steatosis, with or without fibrosis. MASH can lead to progressive fibrosis of the liver and eventually cirrhosis (defined by fibrosis and cirrhotic nodules) (1). After progression to cirrhosis, the steatosis and inflammation can become less prominent on histology as the liver becomes "burnt out" (**Figure 1**).

Table 1. **Types of MASLD**

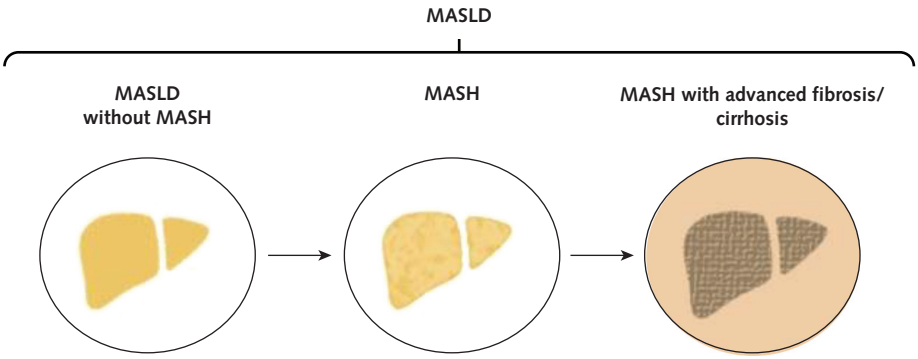
Name	*Definition*
MASLD	Liver steatosis in ≥5% of hepatocytes plus 1 of the following cardiometabolic risk factors: • Elevated BMI* • Hyperglycemia† • Hypertension‡ • Hypertriglyceridemia§ • Low HDL cholesterol level‖ Replaced "nonalcoholic fatty liver disease" (NAFLD), which required liver steatosis but in the absence of an alternative cause of steatosis, including high alcohol intake (<20 g/d [women] or <30 g/d [men])
MASH	More severe subset of MASLD complicated by lobular inflammation and ballooning hepatocytes Formerly known as "nonalcoholic steatohepatitis" (NASH)
MetALD	MASLD in the setting of high alcohol intake, defined by weekly (vs. daily) intake ≥140 g in women and ≥210 g in men

BMI = body mass index; HDL = high-density lipoprotein; MASH = metabolic dysfunction–associated steatohepatitis; MASLD = metabolic dysfunction–associated steatotic liver disease; MetALD = MASLD with increased alcohol intake.
** BMI ≥25 kg/m^2 (≥23 kg/m^2 in Asian persons) or waist circumference ≥94 cm (males) or ≥80 cm (females) (thresholds vary among Asian persons).*
† Fasting serum glucose level ≥5.6 mmol/L (≥100 mg/dL) or 2-hour postload glucose level ≥7.8 mmol/L (≥140 mg/dL) or hemoglobin A_{1c} level ≥5.7% or type 2 diabetes mellitus or treatment for type 2 diabetes mellitus.
‡ Blood pressure ≥130/85 mm Hg or specific antihypertensive drug treatment.
§ Plasma triglyceride level ≥1.70 mmol/L (≥150 mg/dL) or lipid-lowering treatment.
‖ Plasma HDL cholesterol level ≤1.0 mmol/L (≤40 mg/dL) (males) or ≤1.3 mmol/L (≤50 mg/dL) (females) or lipid-lowering treatment.

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Figure 1. **Spectrum and progression of MASLD.**



The term "MetALD" is used if cardiometabolic criteria are met and weekly alcohol intake is ≥140 g (women) or ≥210 g (men). MASH = metabolic dysfunction–associated steatohepatitis; MASLD = metabolic dysfunction–associated steatotic liver disease.

MASLD-related adverse outcomes can be mitigated through identification of high-risk patients with MASLD and early intervention to prevent progression to cirrhosis and liver failure and other cirrhosis-related complications. The *Standards of Care in Diabetes—2024* from the American Diabetes Association (ADA) provide detailed guidance on how to screen for and manage patients with or at high risk for MASLD (7).

Because the new "MASLD" nomenclature was just adopted in June 2023, all of the MASLD-related studies cited in this article (including those that estimated prevalence) used prior definitions of NAFLD and NASH. An analysis of a large European registry of patients with NAFLD showed that 98% of the existing cohort would meet the new criteria for MASLD (8). Thus, we will hereafter use the term "MASLD."

What is the natural history of MASLD?

The approximately 60% to 70% of patients with MASLD who do not have MASH usually do not progress to end-stage liver disease; however, patients without MASH initially can develop MASH over time if their metabolic profile worsens (for example, from weight gain). Those diagnosed with MASH are at increased risk for fibrosis, and approximately 10% to 30% will progress to cirrhosis over several years (9–11). Conversely, weight loss or improvement in metabolic profile in patients with MASH can lead to resolution of inflammation, hepatocellular injury, steatosis, and even fibrosis. The progression from MASH through the stages of fibrosis to cirrhosis is typically slow, usually taking more than a decade; however, more rapid progression (≤10 years) has been reported in 5% to 18% of patients who do progress to cirrhosis (11). Rapidity of progression depends on disease severity, comorbidities, and genetic and environmental factors (1). About 10% to 30% of patients with MASH develop cirrhosis (stage 4 fibrosis) (11).

As in the general population, the most common causes of death among patients with MASH are cardiovascular disease and nonhepatic cancer; however, these show higher rates in patients with MASH than in the overall population (1). The subset of patients with MASH who develop stage 2 liver fibrosis (F2, defined by periportal fibrosis with few septa) are also at higher risk for liver-related morbidity and mortality. Among those with advanced liver fibrosis (stage 3 to 4 [F3 to F4], defined by bridging fibrosis or cirrhosis), cirrhosis-related complications, such as ascites, variceal bleeding, and encephalopathy, occur at a rate of 3% to 20% and are the leading cause of mortality (12).

11. Singh S, Allen AM, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol. 2015;13:643-654. [PMID: 24768810]
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Risk Factors, Screening, and Prevention

Who is at increased risk for MASLD?

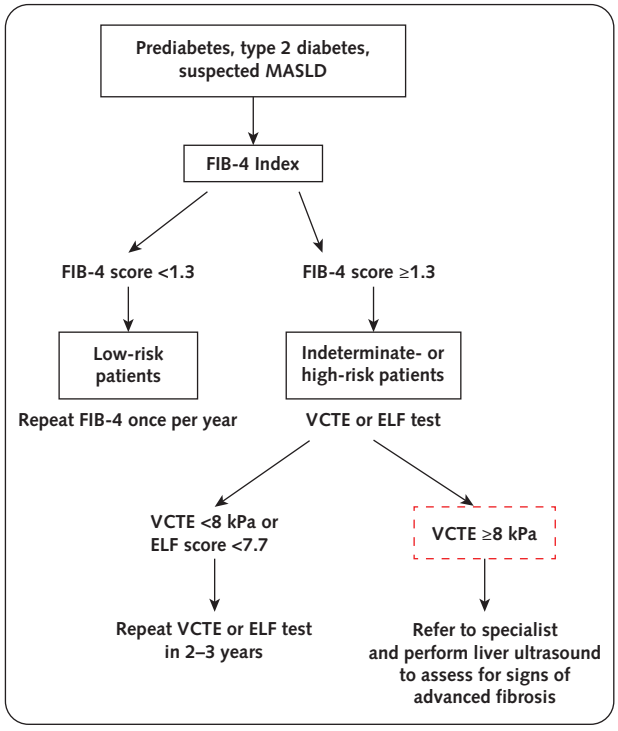
Patients with any of the cardiometabolic risk factors listed in Table 1 (obesity, central obesity, hypertension, atherogenic dyslipidemia, and particularly prediabetes and type 2 diabetes mellitus [T2D]) are at increased risk for MASLD, with multiple abnormalities adding risk (1). Family history of MASLD is a risk factor and likely reflects a combination of both genetic and environmental factors (13). Evidence also suggests that those with genetic single-nucleotide polymorphisms and family history of MASLD and those from certain racial and ethnic groups are more likely to develop MASLD at lower body mass indices (BMIs) (14). Because Asian populations develop obesity-related metabolic diseases (including MASLD) at lower BMIs, the World Health Organization Asia-Pacific region guideline for Asian persons defines overweight as a BMI of 23 to 24.9 kg/m^2 and obesity as a BMI above 25 kg/m^2 (15).

Who should be screened for MASLD, and with what test?

Patients with T2D are at especially high risk for MASLD, with an estimated prevalence of 70% to 75%; patients with T2D and MASLD are also at higher risk for MASH with fibrosis (16–18). Moreover, patients with T2D and MASH have 3 times the risk for hepatocellular carcinoma (HCC) of patients without T2D who have MASH (19).

In a study that systematically screened 561 adults who had T2D and no diagnosis of MASLD in the primary care or endocrinology outpatient setting with transient elastography, the prevalence of steatosis was 70%, and the overall prevalence of any fibrosis (F1 to F4) was 21%, with 10% having precirrhosis (F3) or cirrhosis (F4) (20).

Figure 2. **Screening and monitoring algorithm.**



Data are from reference 15. ELF = Enhanced Liver Fibrosis; FIB-4 = Fibrosis-4 Index; MASLD = metabolic dysfunction–associated steatotic liver disease; VCTE = vibration-controlled transient elastography.

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Thus, ADA guidelines (7) recommend that patients with T2D should be presumed to have MASLD and should be stratified by their risk for advanced fibrosis at baseline and every 2 to 3 years, as these patients are at risk for liver-related complications. The ADA recommends initial screening using the Fibrosis-4 (FIB-4) Index, calculated as (age × aspartate aminotransferase [AST] level) / (platelet count × [square root of alanine aminotransferase {ALT} level]). Patients with a FIB-4 score of 1.3 or higher should then undergo further evaluation (see **Figure 2** and the Diagnosis section).

Can MASLD be prevented?

There are no published data on specific interventions to prevent MASLD per se. However, given that MASLD is etiologically linked to obesity, T2D, and metabolic dysfunction, preventing and treating overweight and obesity and optimizing metabolic health, including through a healthier lifestyle, are believed to be beneficial (see the Management and Treatment section). Additional guidance on treatment and prevention of obesity is provided in a recent In the Clinic article on obesity (21).

Risk Factors, Screening, and Prevention... MASLD, the most common chronic liver disease in the United States, is characterized by liver steatosis and is potentially reversible and preventable. Risk factors include obesity, T2D, and other metabolic disorders. The more severe MASH puts patients at risk for progression to cirrhosis, liver decompensation, and liver cancer. Because a majority (>70%) of patients with T2D have MASLD, the ADA guidelines (7) recommend screening these patients for liver fibrosis, beginning with the FIB-4 Index.

CLINICAL BOTTOM LINE

Diagnosis

What are the characteristic symptoms of MASLD?

Most patients with MASLD are asymptomatic but may rarely present with fatigue, malaise, and vague right upper abdominal discomfort (22). Patients often present with incidental findings of elevated liver enzymes or hepatic steatosis on imaging. Pruritus, jaundice, and sarcopenia suggest liver decompensation in patients with cirrhosis. Once the disease has progressed to cirrhosis, symptoms are similar to those in other patients with cirrhosis, regardless of the cause (1).

What should the history and physical examination include?

A thorough history should include any risk factors for MASLD, including T2D and other cardiometabolic risk factors (**Table 1**), family history of metabolic syndrome or MASLD, alcohol use history, and weight history. The history should also evaluate for secondary causes of liver disease, including a detailed medication and drug history.

The physical examination should assess weight and height (to calculate BMI), blood pressure, and stigmata of cirrhosis and liver failure, such as scleral icterus on eye examination; a hard, nodular, and shrunken liver; presence of fluid wave or splenomegaly and caput medusa on abdominal examination; spider telangiectasia; asterixis; muscle wasting; gynecomastia; and testicular atrophy.

How is MASLD diagnosed, and what other conditions should clinicians consider?

MASLD is often suspected when elevated liver enzymes are noted incidentally or through screening via the FIB-4 Index. A definitive diagnosis requires confirmation of hepatic steatosis on imaging or liver biopsy with the presence of 1 of the cardiometabolic risk

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Table 2. **Differential Diagnosis of Chronic Liver Disease**

Disorder	*Work-up to Help Rule Out Disorder*	*Characteristics Suggestive of Disorder*
Alcoholic liver disease	Social history; calculation of AST–ALT ratio (>2); serum phosphatidylethanol measurement	History of substantial alcohol use
Hemochromatosis	Ferritin test (↑); transferrin saturation test (↑); *HFE* gene testing	Increased skin pigmentation; diabetes; testicular atrophy and decreased libido; cardiomegaly
Chronic viral hepatitis	HCVAb test; HBsAg test If results are positive, send HCV and HBV viral load	CDC recommends universal screening of adults
α_1-Antitrypsin deficiency	α_1-Antitrypsin phenotyping	Associated lung disease; vasculitides
Autoimmune liver disease	Antinuclear antibody test (↑); anti–smooth muscle antibody test (↑); serum IgG measurement (↑)	History of other autoimmune disorders (type 1 diabetes mellitus, Graves disease, ulcerative colitis)
Wilson disease	Ceruloplasmin test; measurement of urinary copper excretion	Young age; associated neuropsychiatric symptoms; Kayser–Fleischer rings
Drug-induced liver injury	Detailed medication/toxin exposure history with detailed timeline of medication initiation and withdrawal	Elevation of liver enzyme levels after medication use (e.g., amiodarone, tamoxifen, corticosteroids, methotrexate, 5-fluorouracil, irinotecan) and normalization of levels after discontinuation of medication Some drug-induced liver injuries require treatment with steroids

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDC = Centers for Disease Control and Prevention; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HCVAb = hepatitis C virus antibody.

factors listed in **Table 1**. However, because of its high prevalence in the setting of obesity and/or T2D, a presumptive diagnosis can be made without confirmation of hepatic steatosis in this setting, particularly if liver enzyme levels decrease with weight loss or increase with weight gain. If there is high clinical suspicion of substantial alcohol use and patient underreporting (which is common) (23), an alcohol use biomarker, such as serum phosphatidylethanol, can be measured. Patients with substantial alcohol consumption should undergo a trial of complete abstinence to see whether liver enzymes normalize. Certain drugs may cause hepatic steatosis, including amiodarone, tamoxifen, corticosteroids, methotrexate, 5-fluorouracil, and irinotecan, and use of these drugs should be elicited.

If liver enzyme levels do not correlate with weight change or if the clinical presentation is atypical, evaluation for other causes or referral to a specialist for further work-up for less common causes is indicated (**Table 2**). Less common causes include celiac disease, autoimmune liver diseases, and other rarer toxic or metabolic diseases, such as Wilson disease, refeeding syndrome, hypobetalipoproteinemia, lysosomal acid lipase deficiency, severe starvation, or rapid weight loss (1).

What laboratory tests should be ordered as part of the initial evaluation for MASLD?

Initial evaluation should include ALT, AST, bilirubin, and alkaline phosphatase levels; platelet count; international normalized ratio (INR); metabolic profile (hemoglobin A_{1c} and lipid panel); and diagnostic tests to exclude other causes. ALT and AST levels can be elevated in MASLD, usually with the AST–ALT ratio below 1, but some patients with MASLD may have a predominantly cholestatic pattern with an elevated alkaline phosphatase level. An AST–ALT ratio above 1 raises the possibility of either alcoholic liver disease or cirrhosis. A low platelet count or elevated INR suggests advanced liver disease.

Patients with abnormal liver enzyme levels (ALT level >19 IU/mL [females] or >30 IU/mL [males]) should have viral serologic testing and iron studies to rule out viral hepatitis and iron overload, respectively (1). Initial tests include

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Table 3. **Performance of Serum Tests for Prediction of Advanced Fibrosis (Stage 3 to 4) in Patients With MASLD***

Test	*Details*	*Diagnostic Cutoff*	*Sensitivity, %*	*Specificity, %*
Nonproprietary				
FIB-4 Index	Calculated as (age × AST level) / [platelet count × (square root of ALT level)]	Low risk: <1.3 High risk: >2.67	Low risk: 70 High risk: 31	Low risk: 60 High risk: 97
NAFLD Fibrosis Score	Calculated as −1.675 + (0.037 × age) + (0.094 × BMI) + (1.13 × 1 [if hyperglycemia present]) + (0.99 × ratio of AST to ALT) − (0.013 × platelet count) − (0.66 × albumin level)	Low risk: <−1.455 High risk: ≥0.676	Low risk: 77 High risk: 27	Low risk: 55 High risk: 91
APRI	Calculated as AST level (IU/L) / upper limit of normal AST level (IU/L) / platelet count (10^9/L) × 100	High risk: 0.5–1	High risk: 40	High risk: 82
Proprietary				
ELF test	Score based on 3 direct markers of fibrosis: hyaluronic acid, procollagen III amino-terminal peptide, and TIMP-1	Low risk: <7.7 High risk: ≥9.8	Low risk: 85 High risk: 76	Low risk: 38 High risk: 87
FIBROSpect	Incorporates TIMP-1, hyaluronic acid, and α2-macroglobulin	High risk: ≥17	High risk: 79	High risk: 75
FibroTest	Score based on age and sex with 6 serum markers: α2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total bilirubin, and ALT	High risk: >0.3	High risk: 72	High risk: 69
Hepascore	Incorporates age and sex with bilirubin, GGT, hyaluronic acid, and α2-macroglobulin	Low risk: <0.6 High risk: >0.8	Low risk: 63 High risk: 59	Low risk: 92 High risk: 96
FibroMeter (NAFLD version)	Incorporates age and weight with platelet count, AST, ALT, ferritin, and glucose	High risk: >0.59	High risk: 65%	High risk: 86%

ALT = alanine aminotransferase; APRI = aspartate aminotransferase–platelet ratio index; AST = aspartate aminotransferase; BMI = body mass index; ELF = Enhanced Liver Fibrosis; FIB-4 = Fibrosis-4; GGT = γ-glutamyl transpeptidase; MASLD = metabolic dysfunction–associated steatotic liver disease; NAFLD = nonalcoholic fatty liver disease; TIMP-1 = tissue inhibitor of metalloproteinase 1.
** Data are from references 25, 66, 67, 68, 69, and 70. Sensitivities and specificities are for advanced fibrosis (F3 to F4).*

anti–hepatitis C virus antibody; hepatitis B surface antigen, surface antibody, and core antibody; plasma iron, plasma ferritin, and total iron binding capacity; and antitissue transglutaminase IgA antibody with total IgA levels to evaluate for viral hepatitis infection, iron overload, and celiac disease. If these tests do not identify an underlying cause and liver enzymes do not improve with weight loss and alcohol abstinence, patients may be referred to specialists for further work-up.

What noninvasive and nonimaging tools are available to risk-stratify patients with MASLD?

The most important predictor of liver-related morbidity and mortality in patients with MASLD is advanced fibrosis. However, fibrosis cannot be detected on ultrasound and requires invasive procedures or elastography to measure liver stiffness. Thus, the next step after presumptive diagnosis of MASLD is to use noninvasive or nonimaging tools to stratify patients into low, intermediate, or high risk for liver fibrosis before they proceed to further evaluation.

Several blood-based noninvasive tests can estimate risk for advanced fibrosis, including the FIB-4 Index, the NAFLD Fibrosis Score (NFS), the AST to Platelet Ratio Index (APRI), the Enhanced Liver Fibrosis (ELF) score, and other commercial patented biomarker panels (**Table 3**). FIB-4, NFS, and APRI are free clinical scoring systems that can be calculated based on readily available clinical information, such as platelet count, AST level, ALT level, age, presence of diabetes, albumin level, and BMI. As discussed, the FIB-4 Index is recommended by the ADA because of its superior performance and low cost (**Table 3**). Patients with an intermediate-risk (1.3 to 2.67) or high-risk

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(>2.67) FIB-4 score are then referred for an elastography-based assessment or to a specialist (**Figure 2**) (1, 7).

In a meta-analysis of 37 studies (n = 5735) using liver biopsy as the gold standard reference comparator, an algorithm combining the FIB-4 score and liver stiffness measurement by vibration-controlled transient elastography (LSM-VCTE) sequentially that used lower thresholds to rule out advanced fibrosis (FIB-4 score <1.3; LSM-VCTE <8.0 kPa) and higher thresholds to diagnose cirrhosis without liver biopsy (FIB-4 score ≥3.48; LSM-VCTE ≥20.0 kPa) had specificity of 95% and would reduce the need for liver biopsy from 33% to 19% (24).

The ELF test, a blood test that measures elements of matrix turnover, reliably identifies patients with increased risk for progression to cirrhosis (with a threshold score >9.8) (25). It can be used for secondary assessment and prognostication in suspected advanced fibrosis, especially when elastography is not available. If secondary risk assessment is consistent with intermediate or high risk, patients should be referred to specialty care for management. Magnetic resonance imaging (MRI)–based tools, such as magnetic resonance elastography (MRE) or corrected T1, can be used to stratify risk in patients in whom noninvasive tests have shown indeterminate results (1).

What is the role of imaging studies in the diagnosis of patients with MASLD?

Imaging in MASLD diagnosis is reserved for patients for whom noninvasive testing (**Figure 2**) suggests advanced fibrosis. Ultrasonography (USG) can identify hepatic steatosis, radiographic signs of cirrhosis, and signs of portal hypertension (ascites, splenomegaly, or intra-abdominal varices) but cannot measure fibrosis and is therefore not routinely recommended. Elastography-based studies measure liver stiffness as a surrogate marker of liver fibrosis and include VCTE, acoustic radiation force impulse elastography (ARFI), and MRE. The elastography component of these studies measures the physical quality of the liver (stiffness) and does not give actual images of the liver, but it can be incorporated into imaging modalities such as ultrasound (for example, in ARFI) and MR (for example, MRE) and read by radiologists. However, use of these studies is limited by cost, expertise, and availability (1).

Point-of-care VCTE tests, such as the Fibroscan, can be performed during the clinical visit and provide both a liver stiffness measure and a controlled attenuation parameter reflecting steatosis (26). Therefore, the Fibroscan can confirm steatosis and assess fibrosis in patients with suspected MASLD. A liver stiffness measurement that is concerning for advanced fibrosis should be followed by USG to look for signs of portal hypertension and to screen for HCC. Increased subcutaneous adiposity, extrahepatic cholestasis, hepatic venous congestion, and acute inflammation can mimic fibrosis on elastography, leading to overestimates of fibrosis stage (27). The newer "XL" Fibroscan probe is more sensitive in persons with obesity (28) and should be considered in this setting if the standard probe is unable to yield valid measurements. Other sensitive tests for fibrosis include MRE and ARFI elastography.

What is the role of liver biopsy?

Less costly noninvasive tests have decreased the need for liver biopsy to demonstrate steatosis or fibrosis (29, 30). However, liver biopsy is sometimes required if another liver disease is suspected, the noninvasive test results are concerning for advanced fibrosis, or there is uncertainty due to inconsistent findings among clinical features, laboratory tests, and imaging (1).

When should clinicians consider consultation with a specialist for diagnosis?

Clinicians should consider referring patients to a liver specialist if the cause of the patient's liver disease is uncertain

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after initial evaluation, if there are several potential coexisting causes of liver disease, if liver enzymes do not improve with weight loss, or if there is indeterminate or high risk for stage 2 or greater fibrosis and/or signs of cirrhosis. Patients with low risk for fibrosis on noninvasive tests can be followed by a primary care clinician to monitor for improvement with weight loss. A retrospective study of more than 2000 patients with T2D and a high-risk FIB-4 score showed that patients referred to a hepatology clinic had a lower overall mortality risk than those who were not referred; improved outcomes were believed to be due to increased recognition of cirrhosis and its complications (31).

Diagnosis... MASLD is often detected incidentally (for example, due to hepatic steatosis found on imaging or during a work-up for elevated liver enzymes) or through screening of high-risk populations. Diagnosis is presumptive in those with prediabetes or T2D. Initial risk stratification typically includes a noninvasive test, such as the FIB-4 Index or the ELF test, and elastography followed by imaging when indicated to assess for advanced fibrosis. Clinicians should consider referring patients to a specialist if the cause is uncertain, if there are several potential coexisting causes, if liver enzymes do not improve with weight loss, or if stage 2 or greater fibrosis (including cirrhosis) is present.

CLINICAL BOTTOM LINE

Management and Treatment

What is the prognosis of MASLD, and what are the goals of management and treatment?

Most patients with MASLD do not have steatohepatitis but are at higher risk for cardiovascular disease because of their underlying metabolic risk (32). Nonetheless, MASH develops in about 20% to 30% of adults with MASLD, and about 20% of those with MASH progress to cirrhosis over several years. About 45% of those with cirrhosis will develop decompensation over the next 10 years, and 7% will develop HCC over 6.5 years (2). Resolution of MASH, regression of fibrosis, and decreased risk for progression can be achieved with sustained weight loss. Therefore, the goals of management in patients with MASLD are to 1) improve MASLD and prevent or reverse any fibrosis by addressing the underlying metabolic dysfunction, 2) screen for complications of liver disease, and 3) implement risk reduction strategies to improve cardiovascular and hepatic outcomes.

What are the roles of lifestyle change and weight loss in improving MASLD?

MASLD is linked to metabolic dysfunction, which can in turn be etiologically linked to overweight and obesity. Thus, addressing the underlying metabolic dysfunction through weight loss often results in improvement or resolution of MASH or MASLD and fibrosis. Studies suggest that weight loss of 3% to 5% can result in resolution of MASLD without necroinflammation; more substantial weight loss of 7% to 10% can result in resolution of MASH, and weight loss greater than 10% can reverse fibrosis (33, 34).

A prospective cohort study of 261 patients with liver biopsies performed before and after weight loss via lifestyle modifications showed improvement in histologic features of MASH. The highest rates of MASH resolution and fibrosis regression occurred in patients with weight loss of 10% or greater (34).

A 2021 meta-analysis of 43 studies (single-group, nonrandomized comparative, or randomized trials of weight loss

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interventions) involving 2809 participants showed significant improvements in MASH even with modest weight loss, but in participants with weight loss of 10% or greater, 90% had MASH resolution and 45% had reversal of fibrosis (33).

Diets abundant in saturated fats, refined carbohydrates, sugar-sweetened beverages, and fructose have been linked to obesity and to MASLD, MASH, and advanced fibrosis (35, 36). The American Association for the Study of Liver Diseases (AASLD) guidelines recommend a diet that leads to a caloric deficit and, when possible, one limited in carbohydrates and saturated fats but rich in fiber and unsaturated fats (1).

The Mediterranean diet is frequently recommended due to its beneficial effect on cardiovascular health and on reducing liver fat and because it is high in fiber and unsaturated fat but limited in carbohydrates and saturated fat (1, 37). However, its benefits have been contested by small randomized clinical trials (RCTs) (37) and may not be universally applicable across diverse cultures. Meta-analysis of observational studies also suggests that consuming more than 3 cups of coffee daily may reduce MASLD and liver fibrosis (38); however, patients should be advised to avoid adding sweeteners to their coffee.

Exercise offers both cardiovascular and hepatic benefits and should be routinely recommended and tailored to the patient. The AASLD guidelines recommend that patients be advised to increase their activity level to the extent possible (1). Observational studies and small RCTs suggest a synergistic effect of dietary and exercise interventions on MASLD (39–42).

Although MASLD, MASH, and fibrosis can resolve with sustained weight loss through lifestyle modification, maintaining long-term weight loss is challenging. A small proportion of patients (≤10%) successfully achieve this goal through structured interventions after 1 year, and fewer than half of these patients maintain the weight loss for 5 years after the intervention (43).

The AASLD guidelines recommend complete abstinence from alcohol in patients with clinically significant hepatic fibrosis (1). For patients without clinically significant hepatic fibrosis, minimizing alcohol use is a reasonable approach.

What is the role of pharmacologic therapies in improving MASLD?

Although only 1 pharmacologic agent has been approved by the U.S. Food and Drug Administration (FDA) for treatment of MASLD, several other pharmacologic therapies shown to promote weight loss and improve insulin sensitivity show promise (44).

Resmetirom

Resmetirom, an oral, liver-directed, thyroid hormone receptor β-selective agonist, is the only pharmacologic agent that is FDA-approved for treatment of MASH with stage 2 to 3 fibrosis.

In the phase 3 RCT of 966 patients with MASH, MASH resolved without worsening of fibrosis after 52 weeks in 25.9% in the 80-mg daily resmetirom group, 29.9% in the 100-mg resmetirom daily group, and 9.7% in the placebo group (P < 0.001). Fibrosis improved by at least 1 stage with no worsening of MASH in 24.2%, 25.9%, and 14.2%, respectively (P < 0.001). Diarrhea and nausea were more frequent with resmetirom than with placebo, but resmetirom was well tolerated overall (44).

The optimal duration of treatment is uncertain, and as of October 2024, resmetirom was available only through specialty pharmacies. This and its high cost will likely limit access. Given its mechanism of action, careful surveillance for early endocrine disease related to thyroid, gonadal, or bone disease may be needed. It is hoped that an ongoing RCT will provide data on long-term safety and efficacy.

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Weight loss and T2D medications

MASLD is strongly associated with obesity, insulin resistance, and T2D. Evidence suggests benefit on MASLD with some but not all insulin-sensitizing agents. Although studies have not shown improvement in liver histology with metformin (1), glucagon-like peptide-1 (GLP-1) analogues approved for treatment of both T2D and obesity, such as liraglutide and semaglutide, show promise (45, 46) (**Table 4**; **Appendix Table**, available at Annals.org).

In an RCT of 52 patients, liraglutide resulted in significantly greater resolution of MASH (39% vs. 9% with placebo) and significantly reduced progression to fibrosis (9% vs. 36% with placebo) (45).

In a phase 2b trial of 320 patients with biopsy-proven MASH with fibrosis but not cirrhosis (65% with T2D), patients were randomly assigned to 72-week treatment with 0.1, 0.2, or 0.4 mg of semaglutide or placebo. Semaglutide resulted in significantly greater histologic resolution of MASH (59% vs. 17% with placebo) but not improvement of fibrosis (46). However, semaglutide significantly slowed progression of liver fibrosis after 72 weeks of treatment compared with placebo (46).

In both of these trials, patients in all groups received counseling on nutrition and exercise.

Tirzepatide, a dual insulin receptor agonist that operates on both GLP-1 and glucose-dependent insulinotropic receptors, is another FDA-approved medication for treatment of T2D and obesity that seems to be effective in MASLD.

In an RCT that compared different doses of tirzepatide with placebo in 190 patients with biopsy-proven MASH and stage 2 or 3 fibrosis, the tirzepatide groups were more likely to have resolution of MASH without worsening of fibrosis (44% to 62% vs. 10%; $P < 0.001$*) (47).*

Given the challenge of sustaining weight loss, use of effective weight loss agents is reasonable for patients with other indications. The choice of medication should be tailored to comorbidities, patient preferences, and adverse effects. GLP-1 agonists, in particular, are preferred in patients with T2D who are at high cardiovascular risk (48) (see **Table 4**, the **Appendix Table**, and recent In the Clinic articles on obesity [21] and T2D [49]).

Thiazolidinediones (such as pioglitazone) are peroxisome proliferator-activated receptor agonists that are approved as third-line treatment for T2D and also show promise in the treatment of MASLD (50).

A meta-analysis of 8 RCTs of thiazolidinedione treatment in patients with MASH included 5 studies with pioglitazone. This meta-analysis confirmed that, compared with placebo, treatment with pioglitazone resulted in significantly higher likelihood of MASH resolution (odds ratio [OR], 3.65; $P < 0.001$*) and liver fibrosis improvement (OR, 1.77;* $P = 0.009$*) (50).*

A more recent meta-analysis of 4 double-blind RCTs on the effect of pioglitazone in patients with prediabetes or T2D and MASLD reported improvement in steatosis and resolution of steatohepatitis (OR, 1.78; $P = 0.03$*) but not fibrosis (51). Potential adverse effects of pioglitazone are increased risk for dose-dependent weight gain (1% to 2% at 15 mg/d and 3% to 5% at 45 mg/d) (52). The improvements in steatosis and steatohepatitis were not seen with rosiglitazone.*

Vitamin E

Although the exact mechanisms of vitamin E in MASH are unknown, clinical trial evidence suggests that it may improve MASLD (53). In the 2-year PIVENS trial, participants randomly assigned to 800 U/d showed greater histologic improvement of NASH compared with placebo, although there was no statistically significant improvement in fibrosis score (53).

However, long-term vitamin E use has risks. One large RCT of prostate cancer prevention found that oral vitamin E dietary supplementation significantly increased risk for prostate cancer (54). Other studies suggest that high levels of vitamin E may be associated with adverse

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Table 4. **Major Medications Available in the United States for T2D With Potential Benefit in Patients With T2D and MASLD**

Drug Class (Examples)	*Indication*	*HbA_{1c} Efficacy*	*Weight Loss*	*Other Benefits*	*Initial Dose*	*Maximum Dose*	*Usual Dose*	*Data in MASLD*
SGLT2-Is* (canagliflozin, empagliflozin, dapagliflozin, ertugliflozin)	Patients with ASCVD, HF, CKD, high risk for ASCVD, or overweight or obesity based on BMI†	Intermediate or high	Intermediate	Canagliflozin: ↓CV death, nonfatal MI, nonfatal stroke, HF hospitalization, end-stage kidney disease Empagliflozin: ↓CV death, HF hospitalization, death, end-stage kidney disease Dapagliflozin: ↓CV death, HF hospitalization	Canagliflozin: 100 mg/d Empagliflozin: 10 mg/d Dapagliflozin: 5 mg/d Ertugliflozin: 5 mg/d	Canagliflozin: 300 mg/d Empagliflozin: 25 mg/d Dapagliflozin: 10 mg/d Ertugliflozin: 15 mg/d	Canagliflozin: 100-300 mg/d Empagliflozin: 10-25 mg/d Dapagliflozin: 5-10 mg/d Ertugliflozin: 5-15 mg/d	Although more data are needed, the American Association of Clinical Endocrinology recommends consideration of the potential benefits of SGLT2-Is in patients with T2D and MASLD
GLP-1RAs*‡ (semaglutide, dulaglutide, liraglutide, exenatide, exenatide ER, lixisenatide)	Patients with ASCVD, HF, CKD, high risk for ASCVD, or overweight or obesity based on BMI†	High or very high	Semaglutide: Very high Dulaglutide: High Liraglutide: High Exenatide: Intermediate Exenatide ER: Intermediate Lixisenatide: Intermediate	Semaglutide: ↓CV death, nonfatal MI, nonfatal stroke, nephropathy Dulaglutide: ↓CV death, nonfatal MI, nonfatal stroke, nephropathy Liraglutide: ↓CV death, nonfatal MI, nonfatal stroke	Semaglutide: 0.25 mg/wk Dulaglutide: 0.75 mg/wk Liraglutide: 0.6 mg/d Exenatide: 5 mcg twice daily (≤60 min before meals) Exenatide ER: 2 mg once per week Lixisenatide: 10 mcg/d	Semaglutide: 1 mg/wk Dulaglutide: 1.5 mg/wk Liraglutide: 1.8 mg/d Exenatide: 10 mcg twice daily Exenatide ER: 2 mg once per week Lixisenatide: 20 mcg/d	Semaglutide: 0.5 mg/wk Dulaglutide: 0.75–1.5 mg/wk Liraglutide: 1.2 mg/d Exenatide: 5–10 mcg/d Exenatide ER: 2 mg once per week Lixisenatide: 20 mcg/d	Small randomized placebo-controlled trial of liraglutide showed greater MASH resolution and decreased fibrosis progression compared with placebo at 48 wk RCT of semaglutide also showed greater MASH resolution and decreased fibrosis progression at 72 wk, but not significantly more fibrosis regression
GLP-1/GIP receptor agonist*‡ (injection) (tirzepatide)	Patients with overweight or obesity based on BMI and without ASCVD, HF, CKD, or high risk for ASCVD	Very high	Very high	–	2.5 mg weekly for 4 wk, then 5 mg weekly; increase by 2.5 mg/wk every 4 wk	15 mg/wk	–	RCT comparing tirzepatide with insulin in patients with T2D and MASLD showed greater reduction in hepatic steatosis in the tirzepatide group
Thiazolidinediones (pioglitazone)	–	High	Neutral to mild weight gain	–	15–30 mg/d	45 mg/d	15–45 mg/d	Meta-analysis of 8 RCTs with thiazolidinediones showed more MASH resolution and fibrosis reversal for patients receiving pioglitazone but not rosiglitazone

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CKD = chronic kidney disease; CV = cardiovascular; DPP-4I = dipeptidyl peptidase-4 inhibitor; ER = extended-release; GIP = glucose-dependent insulinotropic polypeptide; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA_{1c} = hemoglobin A_{1c}; HF = heart failure; MASH = metabolic dysfunction–associated steatohepatitis; MASLD = metabolic dysfunction–associated steatotic liver disease; MI = myocardial infarction; RCT = randomized controlled trial; SGLT2-I = sodium–glucose cotransporter-2 inhibitor; T2D = type 2 diabetes mellitus.

** Not recommended in pregnant persons.*

† Effects of GLP-1RAs and SGLT2-Is in patients with ASCVD, HF, CKD, and high risk for ASCVD differ within each class. See "Other Benefits" for details.

‡ GLP-1RAs and DPP-4Is should not be combined.

cardiovascular outcomes, including risk for hemorrhagic stroke (55). Therefore, the role of vitamin E is uncertain, and potential risks should be considered and reviewed with the patient before treatment initiation.

What is the role of lipid management?

Approximately two thirds of patients with MASLD have dyslipidemia and T2D (2), and given that cardiovascular events are the leading cause of mortality in patients with MASLD, statins are often indicated for cardiovascular risk reduction. Statins have been shown to be safe in patients with MASLD, including those with advanced liver disease and compensated cirrhosis. However,

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despite extensive data showing safety, statins are often underused (56). The AASLD, American Association of Clinical Endocrinology (AACE), and ADA 2024 guidelines recommend statins for both compensated and decompensated cirrhosis (1, 7, 48); however, guidelines recommend that statin therapy should be used with caution and with close monitoring in patients with decompensated cirrhosis, for whom safety and efficacy data are more limited (1).

Some RCTs have shown reductions in liver enzymes with statin therapy in patients with MASLD, but there are no histologic data on resolution of MASH or reversal of fibrosis. Omega-3 fatty acids and ezetimibe have not shown benefit in the treatment of MASLD, but studies are limited (57, 58).

What is the role of metabolic surgery in MASLD?

Bariatric or metabolic surgery is an emerging therapy that could be considered in patients with MASH and obesity if the patient is not able to achieve sustained weight loss through lifestyle modifications and medical therapy. According to recent guidelines from the American Society for Metabolic and Bariatric Surgery (ASMBS) and the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO), bariatric surgery is recommended for patients with a BMI of 35 kg/m^2 or higher, regardless of comorbidities, and for those with a BMI of 30 kg/m^2 or higher and T2D or the inability to achieve substantial weight loss or improvement of comorbidities with weight loss (21). MASLD is recognized by ASMBS and IFSO as a valid indication for bariatric surgery in patients with a BMI of 30 kg/m^2 or higher who cannot achieve substantial weight loss, but the surgery is often not covered by insurers (59). The ADA recommends considering bariatric surgery in people with diabetes with a BMI of 30.0 kg/m^2 or higher (or ≥27.5 kg/m^2 for Asian Americans) (7).

Although minimally invasive endoscopic bariatric and metabolic surgery procedures are emerging as therapies for MASLD, long-term safety data are needed (60, 61).

A multicenter RCT of 288 patients with MASH from Italy who were randomly assigned to 1) lifestyle modification plus best medical care, 2) Roux-en-Y gastric bypass (RYGB), or 3) sleeve gastrectomy found that MASH resolution without worsening fibrosis (primary end point) was significantly higher in the RYGB (56%) and sleeve gastrectomy (57%) groups than in the lifestyle modification plus best medical care group (15%) (P < 0.0001). Severe adverse events occurred in 10 (6%) participants who had surgery but resolved with medical or endoscopic management and did not require reoperation (62).

A meta-analysis of 18 studies with 863 patients that examined the effect of endoscopic bariatric and metabolic therapies (EBMT) on the primary outcome of liver fibrosis and secondary outcomes of liver biochemistry, liver steatosis, and liver histology and insulin sensitivity before and after EBMT showed significant improvements in liver fibrosis, hepatic steatosis, and MASH (61). Average weight loss at the 6-month follow-up was 14.5% of the initial weight. However, the overall quality of the evidence for primary outcomes was low to very low, and more rigorous data are needed.

In patients with decompensated cirrhosis or clinically significant portal hypertension, bariatric surgery is associated with increased mortality and should be considered only under certain circumstances, such as with liver transplant in experienced centers (1).

What vaccinations should patients with MASLD receive?

Secondary prevention includes vaccination against hepatitis A and B as patients with underlying liver disease have a higher mortality risk with acute hepatitis A or B (63, 64).

How should patients with MASLD be monitored?

Patients with MASLD and no significant fibrosis (based on a low-risk FIB-4 score [<1.3] or VCTE [Fibroscan] <7 kPa) can be followed by their primary care physician with a repeated FIB-4 every 2 to 3 years (1). Patients with indeterminate to high risk for fibrosis on FIB-4 or elastography should be referred to a specialist. Those with advanced fibrosis should be seen at least every 6 months to monitor for signs of liver decompensation (jaundice, ascites, hepatic encephalopathy), for laboratory evaluation (complete blood count, INR, hepatic panel, kidney function, α-fetoprotein [AFP]), and to undergo USG for HCC screening. Laboratory signs of worsening liver function or increased portal hypertension include thrombocytopenia, increased INR, and increased bilirubin. Increased AFP raises concern about HCC. Variceal screening should be done with endoscopy at baseline, with repeated endoscopy if indicated by the baseline findings (1).

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What are additional management considerations in patients with progression to cirrhosis?

Patients with cirrhosis should be screened and managed similarly to those with cirrhosis due to other causes (1), and referral to a liver specialist is reasonable. Patients with cirrhosis should have laboratory evaluations at least every 6 months to calculate the Model for End-stage Liver Disease (MELD) 3.0 score. The MELD 3.0 score uses sex; INR; and serum creatinine, bilirubin, sodium, and albumin levels to predict liver mortality. Patients with cirrhosis require monitoring for clinical decompensation and screening for varices and HCC. Patients who develop clinical decompensation (ascites, hepatic encephalopathy, variceal hemorrhage, jaundice) or HCC or have a MELD 3.0 score of 15 or above should be referred to a liver specialist for evaluation for liver transplant (1).

Screening for varices with endoscopy and for HCC with liver imaging every 6 months allows for early diagnosis and intervention. Unfortunately, patients with cirrhosis resulting from MASH have lower screening rates for HCC than patients with cirrhosis from other causes and are thus diagnosed at more advanced and less treatable stages (65).

In a study of 756 patients that compared MASLD- and hepatitis C–related HCC, patients with MASLD-related HCC were diagnosed at more advanced stages (above stage A: 54% vs. 43%), more often had an infiltrative tumor pattern (21% vs. 4%), and had lower 3-year survival rates (48% vs. 61%) than were patients with hepatitis C–related HCC. In the same study, patients with MASLD-related HCC were also less frequently diagnosed (47% vs. 63%) as part of a surveillance protocol than patients with hepatitis C–related HCC (65).

When should clinicians consider consultation with a gastroenterologist or another specialist?

Consultation with a gastroenterologist should be considered in patients with any of the following: 1) indeterminate or high risk for advanced fibrosis on noninvasive testing (to discuss whether a liver biopsy is indicated); 2) significant fibrosis (stage ≥2) on elastography and inability to achieve sustained weight loss (to discuss further treatment for MASH); 3) potentially concomitant liver diseases or diagnostic uncertainty (to discuss whether further workup, including a liver biopsy, is indicated); 4) any radiologic, physical, or laboratory findings that raise suspicion of cirrhosis; or 5) any clinical signs of liver decompensation (for management of the symptoms and to evaluate for liver transplant).

Management and Treatment... Sustained weight loss and treatment of underlying metabolic derangements are the cornerstones of MASLD therapy. Weight loss improves hepatic steatosis, MASH, and hepatic fibrosis in a dose-dependent manner. If behavioral weight loss interventions are ineffective, pharmacotherapy, particularly GLP-1 agonists, and bariatric surgery can be considered in patients with approved indications. Patients with fibrosis from MASH should be referred to specialists to see whether they are candidates for resmetirom therapy. Clinically compensated patients with MASH cirrhosis should be screened for varices at diagnosis and should be assessed for liver function and HCC every 6 months. Patients with decompensated cirrhosis should be referred for liver transplant.

CLINICAL BOTTOM LINE

Practice Improvement

What do professional organizations recommend for diagnosis and management of MASLD?

The AASLD, the ADA, and the AACE have updated guidelines on diagnosis and management of MASLD. The guideline recommendations are reflected in this article.

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In the Clinic
Tool Kit

Metabolic Dysfunction–Associated Steatotic Liver Disease

Patient Information

www.niddk.nih.gov/health-information/liver-disease/nafld-nash
www.niddk.nih.gov/health-information/informacion-de-la-salud/enfermedades-higado/esteatohepatitis-no-alcoholica

Information on prevention, symptoms, and treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in English and Spanish from the National Institute of Diabetes and Digestive and Kidney Diseases.

https://familydoctor.org/condition/nonalcoholic-fatty-liver-disease
https://es.familydoctor.org/condicion/enfermedad-del-higado-graso-no-alcoholico-es

Information on metabolic dysfunction–associated steatotic liver disease in English and Spanish from the American Academy of Family Physicians.

Information for Health Professionals

www.aasld.org/practice-guidelines/clinical-assessment-and-management-metabolic-dysfunction-associated-steatotic

Practice guidelines on clinical assessment and management of metabolic dysfunction–associated steatotic liver disease from the American Association for the Study of Liver Diseases.

www.endocrinepractice.org/article/S1530-891X(22)00090-8/fulltext

Clinical practice guideline on diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings from the American Association of Clinical Endocrinology.

https://diabetesjournals.org/care/article/47/Supplement_1/S52/153956/4-Comprehensive-Medical-Evaluation-and-Assessment

Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Care in Diabetes–2024*, from the American Diabetes Association.

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WHAT YOU SHOULD KNOW ABOUT METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

What Is Metabolic Dysfunction–Associated Steatotic Liver Disease?

Metabolic dysfunction–associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), is a condition where you have too much fat in your liver and at least 1 of the following risk factors:

- Diabetes or insulin resistance (meaning that your body has difficulty handling blood sugar)
- Obesity or excess fat in your waist area
- High cholesterol
- High blood pressure

If there is too much fat and it has been there long enough, your liver could be damaged and not work as well as it should. In severe cases, cirrhosis or liver failure and liver cancer can develop over time. Alcohol intake can make the condition worse.

What Are the Risk Factors?

You may be at higher risk if you have the risk factors listed above.

What Are the Symptoms?

Most people who have MASLD do not have any symptoms. If you have had the disease for a long time, you could show such symptoms as:

- Very itchy skin
- Jaundice (yellowing of the skin and eyes)

How Is It Diagnosed?

- Your doctor will ask you about your medical history, perform a physical examination, and feel your abdomen to see whether your liver is larger than normal.
- You will get a blood test.
- You might have imaging tests, such as a special type of ultrasound that helps your doctor see how much fat and scarring is in your liver.
- A liver biopsy is rarely needed.

How Is It Treated?

- The best way to treat MASLD is by losing weight and controlling your blood sugar if you have diabetes. This can be accomplished by improving your diet and exercising 30 minutes a day on most days of the week. Eating a diet that is low in calories, carbohydrates, and saturated fats but high in fiber and unsaturated fats is recommended.
- Avoid alcohol, as alcohol intake can increase liver fat and worsen liver damage.
- Some medicines may help, including some that help you lose weight or control your blood sugar. Ask your doctor if medicine is right for you.
- Be sure to follow up with your doctor regularly.
- In rare cases where the damage to your liver is severe, you may need a liver transplant, where a surgeon removes your liver and replaces it with liver tissue from another person.



Questions for My Doctor

- What is causing my fatty liver?
- Should I take medicine to treat it?
- Is it safe for me to exercise? How should I start?
- What is the best diet to follow?
- Can I cure my fatty liver?
- Am I at risk for cirrhosis or liver failure?
- Will I eventually need a liver transplant?
- Should I see a specialist?

For More Information

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National Institute of Diabetes and Digestive and Kidney Diseases
www.niddk.nih.gov/health-information/liver-disease/nafld-nash

American College of Gastroenterology
https://gi.org/topics/steatotic-liver-disease-masld

Patient Information

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Appendix Table. **Anti–obesity Medications Approved by the U.S. Food and Drug Administration for Long-Term Use***

Medication	*Mechanism*	*Dose*	*Monthly Cost, $†*	*Weight Loss Efficacy‡*	*Demonstrated Benefits*	*Other Notes*
Orlistat	Inhibits intestinal lipase	60 mg TID (OTC); 120 mg TID (prescription)	45–55 (OTC); ×280 (prescription)	Modest; ~5%–6% loss of initial weight (54)	↓CVD risk factors; lowering of LDL cholesterol level independent of weight loss	Prescribe with multivitamin infusion to prevent deficiency (vitamins D, E, A, K); caution in patients with malabsorption or nephrolithiasis and those using medications that require reliable absorption (e.g., L-thyroxine, warfarin)
Bupropion–naltrexone	Bupropion: Inhibits neuronal uptake of norepinephrine and dopamine Naltrexone: Inhibits negative feedback loop on bupropion	Start at 90/8 mg/d; increase to 360/32 mg/d	100–515	Modest; ~6% loss of initial weight (55)	↓CVD risk factors; may have additional benefit in nicotine dependence and alcohol misuse	Contraindicated if seizure disorder, end-stage renal disease, current eating disorder or opioid use, or high-risk alcohol use
Phentermine–topiramate ER	Phentermine: Sympathomimetic Topiramate: CNS activity and dysgeusia	Start at 3.75/23 mg/d; increase to 7.5/46 or 15/92 mg/d	100–160	High; ~8%–10% loss of initial weight (57)	↓CVD risk factors; topiramate may have additional benefit for migraine	Teratogenic; contraindicated in nephrolithiasis, uncontrolled hypertension, tachycardia, concurrent stimulant use, serious CVD, and closed-angle glaucoma
Liraglutide§	Glucagon-like peptide-1 receptor agonist	Start at 0.6 mg/d; increase to 3.0 mg/d	1350–1400	High; ~8% loss of initial weight (58)	↓CVD risk factors; improves glycemic control independent of weight loss	GI adverse effects; pancreatitis; contraindicated if history of medullary thyroid cancer or pancreatitis or family history of MEN 2; caution in chronic kidney disease and GI motility disorders
Semaglutide§	Glucagon-like peptide-1 receptor agonist	Start at 0.25 mg/wk; increase to 2.4 mg/wk	1350–1400	High; ~15% loss of initial weight (51, 52)	↓CVD risk factors; improves glycemic control independent of weight loss; improved outcomes in HFpEF and in secondary prevention of CVD	GI adverse effects; pancreatitis; contraindicated if history of medullary thyroid cancer or pancreatitis or family history of MEN 2; caution in chronic kidney disease and GI motility disorders
Tirzepatide§	Dual glucagon-like peptide-1 and gastric inhibitory peptide agonist	Start at 2.5 mg/wk; increase to 10–15 mg/wk	1000	High; ~20%–22% loss of initial weight (63)	↓CVD risk factors; improves glycemic control independent of weight loss	GI adverse effects; pancreatitis; contraindicated if history of medullary thyroid cancer or pancreatitis or family history of MEN 2; caution in chronic kidney disease and GI motility disorders

CNS = central nervous system; CVD = cardiovascular disease; ER = extended-release; GI = gastrointestinal; HFpEF = heart failure with preserved ejection fraction; LDL = low-density lipoprotein; MASLD = metabolic dysfunction–associated steatotic liver disease; MEN 2 = multiple endocrine neoplasia type 2; OTC = over the counter; REMS = risk evaluation and mitigation strategy; TID = 3 times a day.

** This table is a modified version of Table 3 from the recent In the Clinic article on obesity (21). All medications are contraindicated in pregnancy or breastfeeding.*

† From www.goodrx.com. In the case of phentermine–topiramate and bupropion–naltrexone, the lowest cash price for each medicine is from one specific mail order pharmacy.

‡ When the drug is combined with lifestyle intervention (see text for source).

§ Data on the benefits of liraglutide, semaglutide, and tirzepatide in MASLD are summarized in Table 4. There are no good data on the other weight loss agents in the table.

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