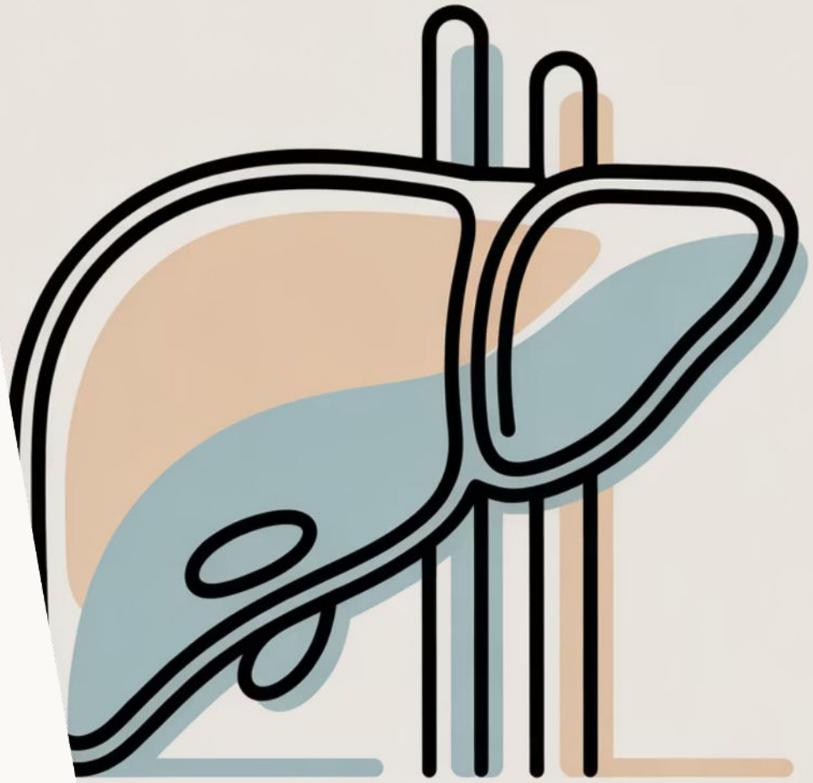
Beyond Fatty Liver: Primary Care Strategies for MASLD and MASH



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Disclosures

- Insulet (Diabetes)

AI Disclosure

Parts of this presentation (and/or its related materials) were generated using AI and are labeled as such, and the faculty have confirmed and validated this information.

Learning Objectives



Understand New Terminology

Master the updated diagnostic criteria and nomenclature for MASLD and MASH, understanding why the field moved beyond NAFLD terminology.



Apply Risk Stratification

Incorporate evidence-based screening tools including FIB-4 scoring and non-invasive fibrosis assessments into routine primary care practice.



Implement Interventions

Navigate lifestyle modifications and pharmacologic strategies to slow disease progression and reduce overall metabolic risk in affected patients.



Coordinate Specialty Care

Recognize appropriate timing for hepatology referral and establish effective care coordination between primary and specialty settings.

Why the Name Changed: From NAFLD to MASLD

Previous Terms

- Non-alcoholic fatty liver disease (NAFLD)
- Non-alcoholic fatty liver (NAFL)
- Non-alcoholic steatohepatitis (NASH)

Current Terms

- Metabolic dysfunction-associated steatotic liver disease (MASLD)
- Metabolic dysfunction-associated steatotic liver (MASL)
- Metabolic dysfunction-associated steatohepatitis (MASH)

The nomenclature shift represents a fundamental change in how we conceptualize this disease.

- Rather than defining the condition by what it is *not* (non-alcoholic), we now name it for what it *is*—a metabolic disorder. This transition moves from an **exclusionary diagnosis** to one that accurately **represents the root cause**: metabolic dysfunction rather than simply the absence of alcohol use.
- The new terminology also reduces potentially **stigmatizing language** and allows for **diagnostic overlap** between metabolic-associated steatotic disease and alcohol-associated liver disease, reflecting the complex reality of clinical practice where patients may have both metabolic and alcohol-related contributions to their liver disease.

Citation: Metabolic dysfunction–associated steatotic liver disease: Update and impact of new nomenclature on the American Association for the Study of Liver Diseases practice guidance on nonalcoholic fatty liver disease. https://journals.lww.com/hep/fulltext/2024/05000/metabolic_dysfunction_associated_steatotic_liver.23.aspx

The Clinical Spectrum and Risks of MASLD

MASLD serves as an umbrella term encompassing both MASL and MASH. Understanding the prevalence and progression risk is essential for appropriate screening and counseling.

01

Steatotic Changes (MASL)

Fatty accumulation in the liver **without** significant inflammation.

Affects 25-30% of the general population and 30-75% of people with type 2 diabetes (T2D).

02

Steatohepatitis (MASH)

Approximately 1 in 3 patients with MASL progress to develop **inflammatory** changes characteristic of MASH.

03

Cirrhosis

About 1 in 25 patients with MASH develop cirrhotic **scarring** of the liver, leading to increased risk of liver cancer, hepatic decompensation, and liver-related mortality.

AASLD guidance: Cardiovascular disease (CVD) and non-hepatic malignancies represent the most common causes of mortality in patients with MASLD *without* advanced fibrosis. However, death from liver disease predominates in patients *with* advanced fibrosis. This underscores why fibrosis staging is so critical to management decisions.

Citations:

1. The VA's "Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)" https://www.veteranshealthlibrary.va.gov/142,41692_VA#vhlMainContent
2. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx

Risk Factors for Developing MASLD

The bidirectional relationship between MASLD and metabolic disease means that identifying and managing MASLD can have ripple effects across multiple organ systems.

Metabolic Risk Factors for MASLD

- Overweight and obesity
- Abdominal/visceral adiposity
- T2D
- Prediabetes
- Hypertension
- Hyperlipidemia

MASLD Increases Risks for

- T2D
- CVD
- Chronic kidney disease (CKD)
- Hepatocellular CA
- Non-hepatic cancers

MASLD Associated with Pre-Existing Endocrine Conditions

- Hypothyroidism
- Hypogonadism
- Growth hormone deficiency
- Polycystic ovary syndrome (PCOS)

*Causality has not been established

Genetic Risk: Having a first-degree relative with NASH cirrhosis conveys a 12-fold increased risk of developing advanced fibrosis. Family history matters.

Citations:

1. The VA's "Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)" https://www.veteranshealthlibrary.va.gov/142,41692_VA#vhlMainContent
2. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx

Natural History: How MASLD Progresses

Fibrosis represents the primary driver of adverse outcomes in MASLD, though the clinical course is multifactorial and influenced by comorbidities, environmental exposures, and genetic factors. Understanding typical progression rates helps inform screening intervals and counseling.

MASL Progression

Steatosis without inflammation advances at an average rate of **1 fibrosis stage per 14 years** based on meta-analysis data.

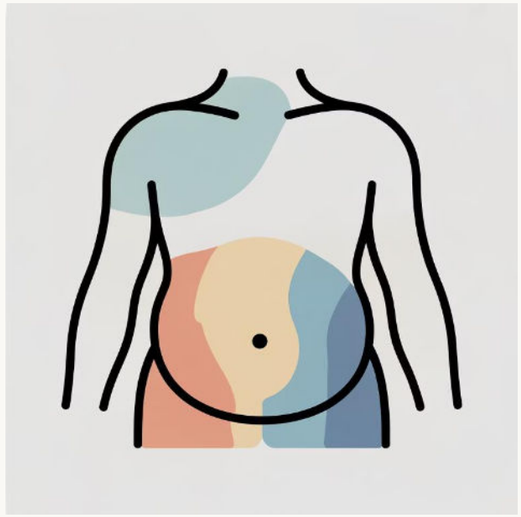
MASH Progression

With inflammatory changes present, disease advances more rapidly at approximately **1 fibrosis stage per 7 years**—twice the rate of MASL.

These rates represent population averages. Individual patients may progress faster or slower depending on the presence and control of metabolic risk factors, genetic predisposition, and response to interventions.

Citation: AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease.
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Obesity and MASLD: More Than Just BMI



The relationship between obesity and MASLD is complex and nuanced. Both the presence and severity of obesity influence not just whether MASLD develops, but how rapidly it progresses.

Critically, **fat distribution matters as much as total body weight**. The risk hierarchy runs as follows:

- Gynoid fat distribution (hip/thigh) = Lower risk
- Abdominal subcutaneous fat = Intermediate risk
- Visceral fat = Highest risk

Central adiposity drives hepatic disease through multiple mechanisms.

Visceral fat —> state of metabolic stress and dysfunction —> promotes inflammation and impairing insulin signaling. —> increased release of free fatty acids, which accumulate in the liver —> trigger inflammatory cascades.

The result: heightened risk of insulin resistance, cardiovascular disease, and hepatic fibrosis—all irrespective of BMI alone.

Citation: AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease.
https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx



Type 2 Diabetes: The Most Impactful Risk Factor

According to AASLD, T2D represents "the most impactful risk factor for the development of MASLD, fibrosis progression, and hepatocellular carcinoma." This relationship is bidirectional and clinically significant.

Diabetes → MASLD

Longer diabetes duration increases MASLD risk.

Debate continues regarding whether glycemic control directly impacts MASLD development and progression.

MASLD → Diabetes

MASLD decreases insulin sensitivity, creating 2-5x increased risk of developing T2D.

Screen all MASLD patients for diabetes.

Type 1 Diabetes (T1D) Note: MASLD does occur in T1D, though less frequently than in type 2. Risk increases when other metabolic factors are present—obesity, hypertension, hyperlipidemia.

Citation: AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx

Hypertension and Obstructive Sleep Apnea

Hypertension (HTN)

HTN is associated with MASLD

HTN incidence increases as disease progresses from early steatosis through cirrhosis.

Important caveat: Causality and directionality have not been definitively established. We cannot yet say whether hypertension causes MASLD, MASLD causes hypertension, or both share common upstream mechanisms.

Obstructive Sleep Apnea (OSA)

OSA is independently associated with MASLD through multiple mechanisms.

Intermittent hypoxia creates mitochondrial dysfunction, dysregulates glucose and lipid metabolism, worsens insulin resistance, and increases hepatic lipogenesis.

Screen patients with MASLD for OSA

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Hyperlipidemia and MASLD

MASLD is associated with 2x likelihood of hyperlipidemia(HLD)

Relationship is bidirectional —> Resolution of MASLD improves lipid levels, while improved lipid management may slow hepatic disease progression.

Importantly, cirrhosis increases cardiovascular disease risk *regardless of lipid control*, emphasizing that MASLD management extends beyond simply treating numbers on a lipid panel.



First-Line Therapy

Moderate to high-intensity statins based on lipid levels and ASCVD risk scores.

Statins are safe across the MASLD spectrum, including compensated cirrhosis.



Decompensated Cirrhosis

Statins can still be used but require more caution given higher rates of statin-associated adverse effects in this population.



Add-On Therapies

If goals aren't met with statins alone, consider combination therapy with ezetimibe, PCSK-9 inhibitors, inclisiran, bempedoic acid, fibrates, omega-3 fatty acids, or icosapent ethyl as clinically indicated.

Dual Benefit: Pioglitazone used for glycemic control may also provide lipid benefits in appropriate patients.

Citation: AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx



Cardiovascular Disease and MASLD

CVD represents a leading cause of death in patients with MASLD, though the extent to which MASLD serves as a primary driver versus marker of shared metabolic dysfunction remains unclear.

What *is* clear: optimizing management of cardiovascular risk factors is essential for all patients with MASLD. This includes:

- Aggressive treatment of comorbid hypertension
- Optimal management of dyslipidemia
- Tight glycemic control in those with diabetes
- Active promotion of smoking cessation

These interventions reduce cardiovascular mortality while potentially slowing hepatic disease progression—a win-win approach to care.

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https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx

Chronic Kidney Disease and MASLD



MASLD is associated with a 2-fold increased risk of CKD.

MASH correlates with increased risk of diabetic microvascular complications, including diabetic kidney disease (DKD).

As with many MASLD associations, causality has not been definitively established. The relationship may represent shared metabolic pathology rather than direct causation.

Clinical implication: Monitor renal function regularly in patients with MASLD, particularly those with MASH and diabetes. Early detection of declining kidney function allows for timely intervention.

Citation: AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease.
https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx

How NOT to Screen for MASLD

Liver Function Tests (LFTs)

Do NOT use LFTs as a screening tool for MASLD.

LFTs can be completely normal in MASLD, and elevated LFTs are not specific to MASLD—many other conditions cause transaminase elevation.

However, if you encounter intermittently or chronically elevated LFTs without obvious cause, MASLD should be included in your differential diagnosis and evaluated appropriately.

Liver Ultrasound (US)

Do NOT use liver US for screening or diagnosis of MASLD.

Ultrasound has insufficient sensitivity for detecting less severe steatosis, particularly in patients with obesity. It produces false negatives for MASH and fibrosis.

Additionally, ultrasound assessment of steatosis severity is subjective and operator-dependent, making it unreliable for both diagnosis and monitoring.

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Who Should Be Screened for MASLD

Target your screening efforts to high-risk populations where early identification can meaningfully impact outcomes:

Type 2 Diabetes

All patients with type 2 diabetes should be screened given the strong bidirectional relationship and high prevalence of MASLD in this population.

Prediabetes

The American Diabetes Association recommends screening this intermediate-risk group.

Family History

First-degree relatives of patients with MASLD cirrhosis face significantly elevated risk (12-fold) and warrant screening per AASLD.

Medically-Complicated Obesity

Patients with obesity or overweight plus elevated waist circumference who have at least one metabolic-associated comorbidity.

Incidental Fatty Liver

Patients with steatosis discovered on imaging performed for other reasons, particularly if metabolic risk factors are present.

Citations:

1. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx
2. Younossi, Zobair M. et al. Global Consensus Recommendations for Metabolic Dysfunction-Associated Steatotic Liver Disease and Steatohepatitis. Gastroenterology, Volume 169, Issue 5, 1017 - 1032.e2. https://www.gastrojournal.org/article/S0016-5085%2528%252825%252900632-8/fulltext
3. Kenneth Cusi, et al; Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) in People With Diabetes: The Need for Screening and Early Intervention. A Consensus Report of the American Diabetes Association. Diabetes Care 20 June 2025; 48 (7): 1057–1082. https://doi.org/10.2337/dci24-0094

The FIB-4 Index: Your Primary Screening Tool



Non-invasive tests (NITs) have strong negative predictive value for excluding advanced fibrosis. The Fibrosis-4 (FIB-4) index serves as an accessible, validated, first-line screening tool that requires only routine laboratory values and can be calculated at the point of care.

Low Risk

FIB-4 <1.3

Low probability of advanced fibrosis. These patients can be managed in primary care with periodic monitoring.

Intermediate Risk

FIB-4 1.3-2.67

Uncertain fibrosis risk. Proceed to secondary risk assessment with VCTE or Enhanced Liver Fibrosis (ELF) testing.

High Risk

FIB-4 >2.67

High probability of advanced fibrosis. Refer to gastroenterology or hepatology for further evaluation and management.

Accessible at: https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis

Next Steps After Initial FIB-4 Screening

1

Low Risk (FIB-4 <1.3)

Repeat FIB-4 screening every 2-3 years for routine monitoring. **Exception:** If patient has 2 or more metabolic risk factors (especially prediabetes or type 2 diabetes), increase frequency to every 1-2 years.

2

Intermediate Risk (FIB-4 1.3-2.67)

Proceed to secondary risk assessment using vibration-controlled transient elastography (VCTE) or Enhanced Liver Fibrosis (ELF) blood test to clarify fibrosis stage.

3

Secondary Assessment Results

If VCTE or ELF shows low risk: Return to periodic FIB-4 monitoring as above. If VCTE or ELF shows intermediate or advanced fibrosis risk: Refer to gastroenterology or hepatology.

4

High Risk (FIB-4 >2.67)

Direct referral to gastroenterology or hepatology without requiring secondary testing. These patients need specialty evaluation and management.

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Primary Care Role and Referral Thresholds

The primary care-specialist partnership is crucial for optimal MASLD management. Primary care physicians serve as the first line of detection and the ongoing managers of metabolic comorbidities, while specialists provide advanced fibrosis assessment and management of complex cases.



Primary Care Management

Screen for MASLD in at-risk populations and identify patients at risk for or with advanced fibrosis using validated tools like FIB-4 screening.

Provide initial management for cases with MASLD at low risk for advanced fibrosis (FIB-4 <1.3).



When to Refer

Refer patients at intermediate or high risk for advanced fibrosis: intermediate risk (FIB-4 1.3-2.67) or high risk (FIB-4 >2.67).

Also refer when more advanced evaluations like magnetic resonance elastography (MRE) are needed because non-invasive tests are indeterminate or don't match clinical suspicion.

Citations:

1. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx
2. Diagnosis-Non-Alcoholic Fatty Liver. https://www.hepatitis.va.gov/HEPATITIS/nafl/diagnosis.asp



The Role of Liver Biopsy

Academically, liver biopsy remains the gold standard for definitively diagnosing MASH and staging fibrosis. However, in **clinical practice**, biopsy is reserved for specific situations where non-invasive testing is insufficient.

Consider liver biopsy when:

- Diagnosis remains uncertain after non-invasive evaluation
- NITs conflict with clinical presentation, imaging findings, or laboratory values
- Competing or comorbid hepatic diagnoses require differentiation (such as autoimmune hepatitis, drug-induced liver injury, or iron overload)
- LFTs remain persistently elevated for 6 months or longer without clear explanation

For most patients, the combination of clinical assessment, metabolic profiling, and non-invasive fibrosis testing provides sufficient information to guide management without requiring biopsy.

Citations:

1. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_G...
2. Diagnosis-Non-Alcoholic Fatty Liver. https://www.hepatitis.va.gov/HEPATITIS/nafl/diagnosis.asp

Universal Treatment Principles for All MASLD Patients

Lifestyle Intervention

Implement comprehensive lifestyle modifications addressing nutrition, physical activity, and weight management.

Lifestyle remains the cornerstone of MASLD therapy across all disease stages.

Assess Alcohol Use

Systematically evaluate and document alcohol consumption at every visit.

Even **moderate** alcohol use can accelerate MASLD progression, particularly in the setting of obesity or diabetes.

Manage Comorbidities

Aggressively treat metabolic comorbidities and reduce cardiovascular risk, including tobacco use.

Preferentially select **medications that may also benefit MASLD** when multiple options exist for treating T2D or HLD.

These three pillars apply to **every patient with MASLD**, regardless of fibrosis stage. They form the foundation upon which additional targeted therapies are built.

Citation: AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease.
https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx

Lifestyle and MASLD: The Metabolic Foundation

The pathophysiology of MASLD is fundamentally metabolic. Insulin resistance is present in the majority of cases, leading to increased release of free fatty acids from adipocytes during fasting. This lipolysis worsens as disease progresses from MASLD to MASH.

Dietary factors that increase MASLD risk:

- Excessive refined dietary carbohydrate intake
- Higher saturated versus unsaturated fat consumption
- Ultra-processed food consumption

Energy balance—the relationship between caloric intake and physical activity—plays a central role, modified by genetic factors that influence individual susceptibility and progression.



Cardiovascular Risk Reduction: Promote smoking cessation in all patients with MASLD to decrease cardiovascular disease risk, which represents a leading cause of mortality in this population.

Citation: AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease.
https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx

Weight Loss: Setting Realistic Goals

For patients with overweight or obesity, weight loss represents one of the most effective interventions for improving MASLD. However, the approach must be sustainable and patient-centered.



Improves Steatosis

Even modest weight loss of 3-5% body weight meaningfully reduces hepatic fat content



Improves MASH and Fibrosis

Weight loss exceeding 10% can lead to resolution of inflammatory changes and regression of fibrosis

Establish a long-term, multidisciplinary care approach. Obesity and overweight are chronic diseases requiring chronic management—similar to hypertension or hyperlipidemia. One-time counseling sessions are insufficient.

Structured, ongoing nutritional support is strongly recommended. Consider building a multidisciplinary team that includes registered dietitians or nutritionists, behavioral health specialists, and the patient's personal support system to improve adherence and long-term outcomes.

Citation: AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx

Nutritional Composition: Quality Matters

Regardless of whether weight loss is the goal, adjustments in nutritional composition benefit most patients with MASLD. The quality of calories consumed matters as much as quantity.

Patterns to Limit

- Excess total calories
- Excess saturated fats
- Refined carbohydrates
- Sugar-sweetened beverages
- Added fructose and sucrose
- Ultra-processed foods

Patterns to Amplify

- Low refined carbohydrates
- Low saturated fat
- High fiber content
- High unsaturated fats
- Whole, minimally processed foods

Citations:

1. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx
2. Kenneth Cusi, et al; Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) in People With Diabetes: The Need for Screening and Early Intervention. A Consensus Report of the American Diabetes Association. Diabetes Care 20 June 2025; 48 (7): 1057–1082. https://doi.org/10.2337/dci24-0094

Nutritional Composition: Quality Matters

Reframe the Conversation: Positive framing improves adherence and reduces feelings of deprivation.

Swap From

- Saturated fats
- Refined carbohydrates
- Sugar-sweetened beverages

Swap To

- Unsaturated fats & add more whole grains, vegetables, legumes
- Whole grains & other complex carbohydrates
- Water or unsweetened drinks

Citations:

1. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx
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Specific Dietary Plan?

Many popular diets like DASH and Mediterranean have shown similar results for reducing steatosis, but the **role in steatohepatitis and fibrosis is unclear**. While a specific diet plan may be helpful for some patients, guideline-directed therapy focuses is on nutritional patterns patterns that are individualized to patients' preferences and needs.

Mediterranean diet:

- Generally recommended in practice as it provides cardiovascular protection and has demonstrated benefit for reducing steatosis.
- Recommended by ADA for patients with DM or MASH/MASLD.
- Sustainable for many patients.
- Can be restrictive and may not align with all cultural food traditions.
- Adapt recommendations to each patient's cultural context and preferences whenever possible.

DASH Diet:

- Recommended by ADA for patients with DM or MASH/MASLD.
- Sodium intake <2,300mg/day, low in saturated and *trans* fat.
- High in potassium, calcium, and magnesium.

Portfolio Diet:

- Reduces LDL by 28.6% (approximately equivalent to low-intensity statin).
- Very low saturated fat.
- High in plant sterols, soy protein, viscous fibers, and almonds.

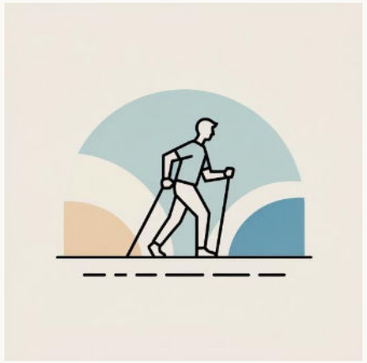
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Physical Activity: Encourage Maximum Movement

The exact amount and intensity of exercise needed for MASLD benefit varies across guidelines, but the message is consistent: ***more physical activity is better***.

Important Exception: Individuals with cirrhosis require specialized physical activity recommendations. Consult with their hepatology team before prescribing exercise regimens in advanced liver disease.



"Patients should be encouraged to exercise as much as possible"
per AASLD

Evidence-based recommendation:
Moderate-intensity physical activity 5 times per week totaling 150 minutes per week. This approach is supported by:

American College of Lifestyle Medicine

American College of Sports Medicine

American Diabetes Association

Global Consensus on MASLD

Alternative approaches showing benefit:

- Increasing physical activity by 60 minutes per week from baseline
- Engaging in vigorous-intensity physical activity.

Citations:

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Alcohol and MASLD: Defining Safe Limits

Alcohol contributes to progression of steatotic liver disease, though the relationship is dose-dependent and modified by other risk factors. Assess alcohol intake systematically in all patients with MASLD.

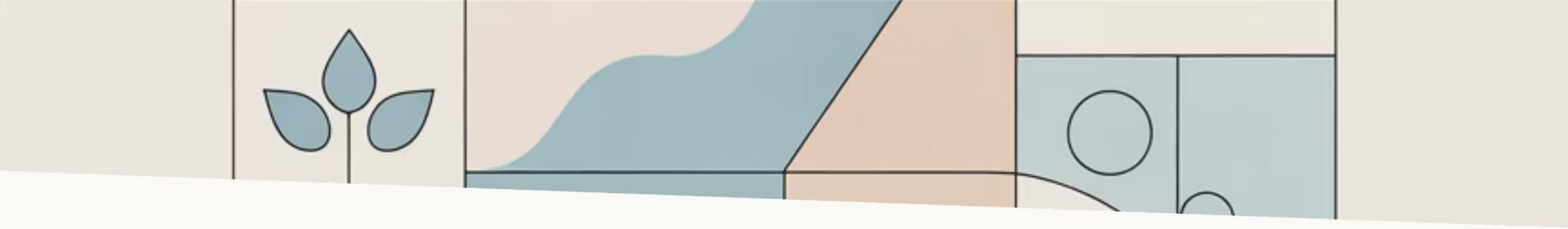
Classification	Women (grams)	Women (ounces)	Men (grams)	Men (ounces)
Mild	≤20g	≤0.7oz	≤30g	≤1oz
Moderate	>20-<40g	>0.7-<1.4oz	>30-<60g	>1-<2.1oz
Heavy	≥40g	≥1.4oz	≥60g	≥2.1oz

Evidence summary:

- Mild alcohol consumption shows conflicting evidence regarding effects on MASLD.
- Moderate alcohol use increases probability of advanced fibrosis, with the effect magnified by concomitant obesity or type 2 diabetes.
- Heavy alcohol use should be avoided entirely—it clearly accelerates liver injury, fibrosis progression, cirrhosis, hepatocellular carcinoma, and death from liver disease.

The combination of alcohol use and obesity synergistically increases risk of liver injury, cirrhosis, HCC, and liver-related mortality beyond what either factor would cause alone.

Citation: AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease.
https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx



Lifestyle Interventions: Summary Framework

Weight Management

Target 3-5% weight loss for steatosis improvement, >10% for MASH and fibrosis benefit. Use multidisciplinary team approach for sustainability.

Nutritional Quality

Reduce refined carbohydrates, saturated fats, and ultra-processed foods. Increase fiber, unsaturated fats, and whole foods. Consider Mediterranean dietary pattern.

Physical Activity

Aim for 150 minutes weekly of moderate-intensity exercise for most patients. Encourage maximum movement tolerated.

Alcohol Reduction

Assess intake systematically. Avoid heavy use entirely. Counsel that moderate use may accelerate progression, especially with obesity or diabetes.

Citations:

1. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx
2. Younossi, Zobair M. et al. Global Consensus Recommendations for Metabolic Dysfunction-Associated Steatotic Liver Disease and Steatohepatitis. Gastroenterology, Volume 169, Issue 5, 1017 - 1032.e2. https://www.gastrojournal.org/article/S0016-5085%2528%252825%252900632-8/fulltext
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Medications That May Benefit MASLD

When treating comorbid conditions, consider selecting agents that may provide additional benefit for MASLD. This allows you to address multiple conditions simultaneously.

GLP-1 Receptor Agonists

GLP-1 agonists improve glycemic control while reducing hepatic steatosis and promoting weight loss.

Semaglutide now has FDA approval for MASH with F2-F3 fibrosis (more on this later).

Pioglitazone

This insulin sensitizer may improve hepatic histology in NASH.

Consider in appropriate patients with T2D, weighing risks vs benefits.

Vitamin E

High-dose vitamin E (800 IU daily) may benefit select patients without diabetes with biopsy-proven MASH, weighing risks versus benefits.

Not first-line but may be considered.

Statins

Safe across the MASLD spectrum including compensated cirrhosis.

Provide cardiovascular benefit and do not worsen liver disease—use them when indicated for hyperlipidemia.

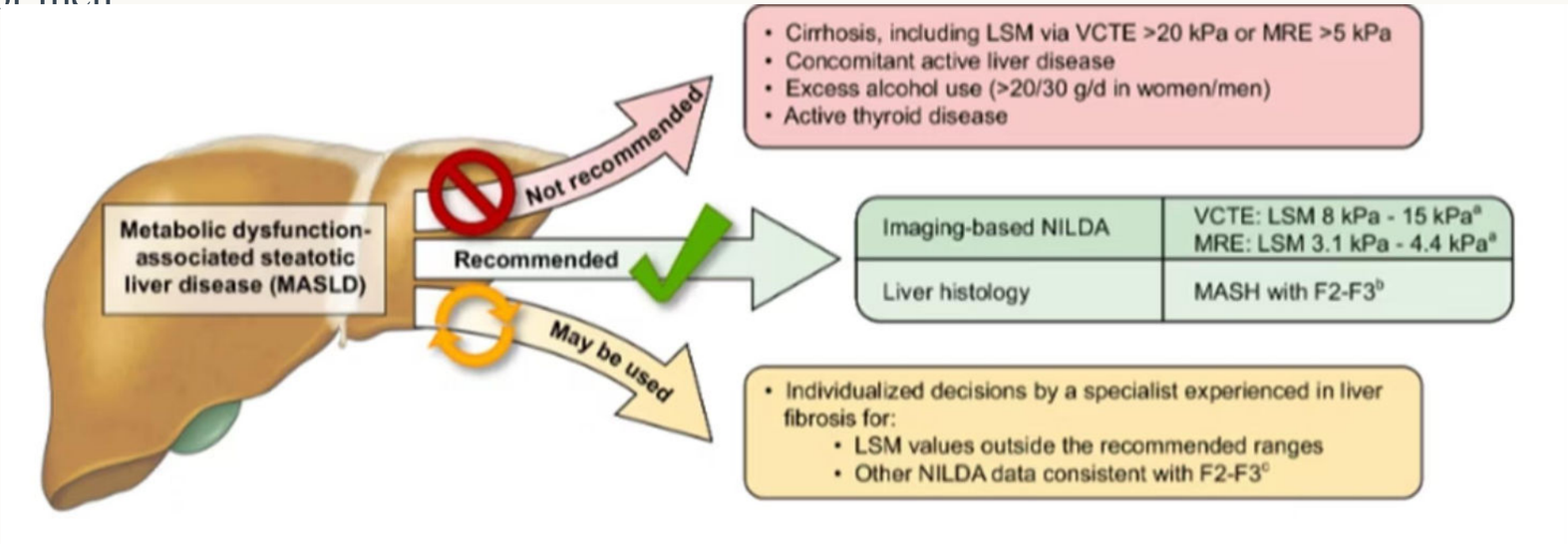
Citation: AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease.
https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx

Resmetirom (Rezdriffa): First FDA-Approved MASH Therapy

In March 2024, resmetirom became the **first medication approved specifically for MASH** with moderate to advanced liver fibrosis (stages F2-F3). This represents a landmark development in targeted MASH therapy.

Importantly, the FDA-approved label does not require liver biopsy to confirm fibrotic MASH diagnosis.

Patient selection criteria: Evidence of steatosis and fibrosis determined by NITs among persons with cardiometabolic risk factors, after excluding other causes of steatosis. Specifically exclude those with alcohol consumption exceeding 20g/day for women or 30g/day for men



Citation: Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance.
https://journals.lww.com/hep/fulltext/2025/01000/resmetirom_therapy_for_metabolic.28.aspx

Resmetirom: Concomitant Therapy Considerations

Resmetirom doesn't work in isolation. Lifestyle intervention and management of metabolic comorbidities remain essential foundations of care.

Statin Interactions

Resmetirom may influence statin metabolism when taken concurrently. Adjust statin doses as follows:

- Rosuvastatin: maximum 20 mg/day
- Simvastatin: maximum 20 mg/day
- Atorvastatin: maximum 40 mg/day
- Pravastatin: maximum 40 mg/day

Note: Resmetirom reduces LDL cholesterol, but long-term CV effects remain unknown. Reassess lipid panel after any dose adjustment.

CYP2C8 Inhibitor Interactions

Resmetirom is a substrate for cytochrome P450 enzyme 2C8. When used with CYP2C8 inhibitors (such as clopidogrel), reduce resmetirom dose:

- Patients ≥100 kg: 80 mg/day
- Patients <100 kg: 60 mg/day

Combination Therapy: AASLD notes that in the absence of other approved therapies, pioglitazone and vitamin E could be considered in appropriate patients, though these were not studied in combination with resmetirom.

Citation: Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance.
https://journals.lww.com/hep/fulltext/2025/01000/resmetirom_therapy_for_metabolic.28.aspx

Resmetirom: Adverse Effects and Monitoring

Gastrointestinal Effects

Most common treatment-emergent adverse events are diarrhea and nausea.

Typical onset occurs within 12 weeks of initiation, often within the first 4 weeks.

These are generally mild and manageable with supportive care.

Gallstone Disease

Increased incidence of symptomatic gallstone disease observed.

However, presence of gallstones or history of biliary colic are not contraindications to treatment.

Counsel patients about this risk.

Hepatotoxicity Risk

One case of severe hepatotoxicity reported in trials.

Monitor LFTs before treatment, then at 3, 6, and 12 months.

Discontinue if specific thresholds are met (see below).

AASLD discontinuation criteria: AST or ALT >5× upper limit of normal, or alkaline phosphatase >2× upper limit of normal on two occasions; or total bilirubin >2.5 mg/dL plus elevated transaminases or alkaline phosphatase; or INR >1.5 plus elevated transaminases or alkaline phosphatase.

Citation: Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance.
https://journals.lww.com/hep/fulltext/2025/01000/resmetirom_therapy_for_metabolic.28.aspx

Semaglutide (Wegovy): Newly Approved for MASH

In August 2025, semaglutide received **FDA approval for MASH** with moderate to advanced fibrosis (stages F2-F3). This represents the second medication specifically approved for MASH treatment.

Appropriate candidates for semaglutide in MASH: Patients with MASH and stage 2-3 fibrosis identified using non-invasive tests such as vibration-controlled transient elastography (VCTE), magnetic resonance elastography (MRE), or Enhanced Liver Fibrosis (ELF) blood test.

Liver biopsy is impractical and unnecessary for most patients. For those with NITs showing advanced fibrosis, AASLD recommends confirming with another NITs or using cross-sectional imaging to exclude nodular liver contour and signs of portal hypertension, or checking for thrombocytopenia (platelet count <150,000/mm³).

Continuity of Care: Patients already taking semaglutide for other indications (diabetes, obesity) who also have advanced fibrosis can continue treatment with careful monitoring.

Citation: Semaglutide therapy for metabolic dysfunction-associated steatohepatitis: November 2025 updates to AASLD Practice Guidance.
https://journals.lww.com/hep/abstract/9900/semaglutide_therapy_for_metabolic.1465.aspx

Semaglutide: Monitoring and Adverse Effects

Monitoring Requirements

Liver function tests: routine monitoring only, no special surveillance required beyond standard care.

Thyroid function: non-significant changes observed in trials. No change in thyroid monitoring recommendations.

Other endocrine changes: Increases sex hormone-binding globulin (SHBG), which raises total testosterone and estradiol. Clinical significance unknown.

Concomitant therapy: Lifestyle modifications remain the cornerstone of treatment. Combination therapy with resmetirom has not yet been studied.

Common Adverse Events

Most frequent: nausea, diarrhea, constipation, vomiting. Generally mild and transient. Patient education and gradual dose titration improve tolerance.

Rare but serious risks:

- Acute kidney injury (from dehydration)
- Symptomatic gallbladder disease
- Pancreatitis
- Thyroid C-cell tumors
- Retinopathy progression
- Lean mass loss

Citation: Semaglutide therapy for metabolic dysfunction-associated steatohepatitis: November 2025 updates to AASLD Practice Guidance.
https://journals.lww.com/hep/abstract/9900/semaglutide_therapy_for_metabolic.1465.aspx

Monitoring Treatment Response

While exact thresholds for improvement remain under investigation, several markers correlate with histological benefit and can guide ongoing management.

ALT Reduction

ALT reduction relates to improvement in liver histology. Normalization of ALT can predict NASH resolution. This represents an accessible, low-cost monitoring tool available in all primary care settings.

Non-Invasive Test Improvement

Improvement in FIB-4, Enhanced Liver Fibrosis (ELF), vibration-controlled transient elastography (VCTE), and other biomarkers associates with histological improvement. These provide more specific information about fibrosis regression.

Per AASLD: "Improvement in ALT or reduction in liver fat content by imaging in response to an intervention can be used as a surrogate for histological improvement in disease activity."

Further research is needed to establish specific monitoring strategies, optimal thresholds, and appropriate frequency of reassessment.

Citation: AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease.
https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx

Call to Action: Integrating MASLD Care into Practice



Screen Systematically

Implement routine MASLD screening for all patients with T2D, medically-complicated obesity, prediabetes, metabolic comorbidities, first-degree relative with MASLD, and incidental fatty liver on imaging.

Use FIB-4 as your first-line tool—it's accessible, validated, and actionable.



Stratify Risk Thoughtfully

Use the FIB-4 stratification system to identify who needs specialty referral and who can be managed in primary care.

Remember: FIB-4 <1.3 = primary care management with periodic monitoring; FIB-4 1.3-2.67 = proceed to secondary testing; FIB-4 >2.67 = refer to hepatology.

Call to Action: Integrating MASLD Care into Practice



Treat the Whole Patient

Address MASLD as part of comprehensive cardiometabolic care.

Optimize control of metabolic comorbidities including diabetes and hyperlipidemia using agents that may provide hepatic benefit when possible.

Promote evidence-based lifestyle interventions across the spectrum of MASLD—weight management, nutritional quality, physical activity, alcohol reduction, and smoking cessation.



Partner with Specialists

Build strong referral relationships with gastroenterology and hepatology, dieticians, and behavioral health specialists.

They provide advanced fibrosis assessment, specialized therapies, nutritional counseling, and health behavioral intervention; you provide ongoing management of metabolic comorbidities and long-term follow-up. Together, you optimize outcomes.

Call to Action: Primary care clinicians are uniquely positioned to identify MASLD early, initiate evidence-based interventions, and coordinate long-term management. With systematic screening, thoughtful risk stratification, and comprehensive cardiometabolic care, we can meaningfully impact outcomes for millions of patients living with this increasingly common condition.

Key Takeaways: MASLD Management Essentials

New Nomenclature Matters

MASLD/MASH terminology reflects metabolic etiology and reduces stigma.

Understanding this shift improves communication with patients and specialists.

Fibrosis Drives Outcomes

Advanced fibrosis determines prognosis.

Use FIB-4 to stratify risk and guide tx intensity.

Those with F2-F3 fibrosis benefit from targeted therapies.

Lifestyle is Foundational

Weight management, nutritional quality, physical activity, alcohol reduction, and smoking cessation remain cornerstones across all stages.

Medications augment, not replace, lifestyle intervention.

New Therapies Available

Resmetirom and semaglutide offer targeted treatment for MASH with F2-F3 fibrosis.
Consider in appropriate patients as part of comprehensive management strategy.

Resources for Continued Learning

AASLD Practice Guidance

Comprehensive clinical guidance on assessment and management of NAFLD/MASLD, regularly updated with latest evidence.

Access Guidelines

ADA Consensus Report

Diabetes-focused guidance on MASLD screening and intervention for people with diabetes.

Read Report

FIB-4 Calculator

Free online calculator for point-of-care fibrosis risk assessment using routine laboratory values.

Calculate FIB-4

Global Consensus Recommendations

International expert consensus on metabolic dysfunction-associated steatotic liver disease and steatohepatitis.

View Recommendations

Questions?

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