Improving Diagnosis and Management of Metabolic Dysfunction-associated Steatotic Liver Disease

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Improving Diagnosis and Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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GENERAL OBJECTIVE:

To improve primary care physicians' knowledge and competence in diagnosing and managing Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD).

SPECIFIC OBJECTIVES:

At the end of this program, participants will be able to:

- Explain the natural history and progression of MASLD;
- Identify patients at risk of developing MASLD;
- Discuss diagnostic criteria for MASLD;
- Institute screening procedures for MASLD in patients with metabolic risk factors;
- Discuss a comprehensive management strategy for MASLD that incorporates lifestyle changes and the use of appropriate therapies such as GLP-1 receptor agonists and SGLT2 inhibitors.

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A New Name for an Established Condition

In 1980, researchers at the Mayo Clinic reported on a liver condition observed in twenty patients, most of whom were obese and/or presented with obesity-related diseases such as type 2 diabetes or cholelithiasis.[1] Although these patients reported moderate alcohol consumption, their liver tissues were characterized by fatty changes and functional abnormalities that histologically resembled alcoholic hepatitis. Fibrosis was noted in most of the specimens, and three individuals had cirrhosis. The researchers termed this condition "non-alcoholic steatohepatitis (NASH) of unknown cause." In the ensuing three decades, the association between metabolic risk factors and hepatic steatosis, inflammation, and fibrosis became solidified, and a new term, "non-alcoholic fatty liver disease (NAFLD)," was coined in 2007.[2] NAFLD encompassed a broad spectrum of histologies from steatosis to steatohepatitis and included subtypes such as NASH (disease with characteristic liver complications) and non-alcoholic fatty liver (NAFL; disease without liver complications).

"NASH" and "NAFLD" appeared as terms in various guidelines and research publications until 2023, when an international, multi-society panel of content experts and patient advocates released its consensus to change the nomenclature for fatty liver disease to "metabolic dysfunction-associated steatotic liver disease (MASLD)" to replace potentially stigmatizing language.[3] Going forward, MASLD will serve as the official term for this condition, which is increasing in prevalence and affects approximately 30% of adults globally.[4]

MASLD is associated with metabolic syndrome, and fatty liver deposits can confound management by promoting development of fibroses, cirrhosis, and hepatocellular carcinoma in some individuals. In addition to its' clinical ramifications, MASLD exerts a formidable economic impact. Although it is difficult to obtain exact totals, a 2016 analysis estimated that MASLD costs $103 billion ($1,613/patient) in annual direct medical costs plus $188 billion in societal costs in the US.[5] The increased global incidence of MASLD during the previous three decades mirrors the rise in obesity and its metabolic sequelae, suggesting more profound future clinical and economic burdens.[4,6]

Proactively diagnosing MASLD will lead to more effective management and improve the quality of life for patients with the condition. Many patients who experience metabolic syndrome symptoms will visit their primary care clinician for treatment. To address the management of MASLD in primary care, the New Jersey Academy of Family Physicians (NJAFP) assembled a panel of experts to improve patient outcomes by increasing primary care clinicians' knowledge, comprehension, and performance in diagnosing and managing this condition.

This publication reviews the current literature and guidelines and provides recommendations for diagnosis and treatment, enabling the primary care clinician to develop successful, personalized management plans for patients who present with symptoms of MASLD.

The Natural History of MASLD

MASLD is characterized by an excess of hepatic lipids (hepatic steatosis) that can cause inflammation (steatohepatitis) and progressive fibrosis.[7] Fibrosis and steatohepatitis are the primary predictors of disease progression, and some individuals with MASLD may develop liver-related morbidities, including cirrhosis, decompensation, and/or hepatocellular carcinoma.[8] The extent of liver fibrosis in patients with MASLD is linked to the development of liver-related outcomes and death.[8] Although disease progression reflects a complex interplay of diabetic and non-diabetic endocrinopathies, MASLD is most commonly associated with insulin resistance and obesity, conditions that are based on energy imblance.[7]

As the body's primary organ for metabolizing fatty acids, the liver plays a vital role in maintaining lipid homeostasis. Hepatocytes metabolize fatty acids from dietary and endogenous sources primarily by assembling triglycerides for storage and export to muscle and fat tissue. Triglycerides are neutral and suited for storage, and the liver maintains a balance by processing large quantities of fatty acids and storing a small proportion of triglycerides.[9] To compensate for a protracted dietary intake of fatty acids, excess calories are stored as triglycerides, packaged and exported from the liver to

AT A GLANCE

- Going forward, the term, "metabolic dysfunction-associated steatotic liver disease" (MASLD), replaces "non-alcoholic steatohepatitis (NASH)" and "non-alcoholic fatty liver disease (NAFLD)," as disease descriptors.
- Primary care clinicians play critical roles in identifying patients who have or who are at risk for MASLD and ensuring that they receive prompt and effective care and appropriate referrals when necessary.
- MASLD is closely linked with metabolic syndrome and is defined as the presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor (excess body weight, hyperglycemia, hypertension, hypertriglyceridemia, elevated HDL cholesterol) and no other discernible cause.
- The presentation of one insulin resistance-related cardiometabolic criterion should prompt the clinician to inquire further regarding liver health.
- All patients with hepatic steatosis or clinically-suspected MASLD based on obesity, metabolic risk factors, or unexplained elevated liver chemistries should undergo primary risk assessment using the FIB-4.
- Clinicians should manage persons with MASLD for obesity, metabolic syndrome, prediabetes, diabetes mellitus, dyslipidemia, hypertension, and CVD based on current standards of care.
- The first line of treatment for MASLD (and a modality that will continue throughout management) is a tailored, structured plan of lifestyle modifications, including a balanced diet and physical activity that aims to reduce body weight by 5-10%.
- Certain antihyperglycemic agents (GLP-1 RAs, pioglitazone) have been shown to reverse steatohepatitis in persons with obesity, prediabetes, or type 2 diabetes and may be appropriate as adjunct pharma cotherapies.
- Proactive management is critical to enhance quality of life and prevent future tissue damage, and clinicians and patients must partner in decision-making regarding MASLD management.
- Care pathways that include evidence-based therapies, patient education, support, and collaborations with an informed care team will improve outcomes for all patients with MASLD.

adipose tissues. Once these tissues reach their storage capacity, however, triglycerides accumulate within the hepatocytes. An excessive glycemic load, which often accompanies over-nutrition, drives insulin production, ultimately decreasing peripheral sensitivity in adipose and muscle tissue. Insulin resistance in adipose tissue promotes the release of fatty acids from the adipocytes and toward ectopic storage in the hepatocytes and other sites.[8] As the liver tries to compensate for inflammation, it forms areas of scar tissue or fibroses.[8] This cycle underpins fatty liver disease, and interventions aimed at controlling insulin resistance and body weight (discussed in subsequent sections) represent a central tenet of MASLD management.

Risk Factors and Symptoms of MASLD

In early stages of progression, MASLD may not present any symptoms, and the condition is often diagnosed in the context of other metabolic dysregulation. However, fatigue, malaise, or pain in the upper right abdomen may be early signals of liver-related issues.[10] As MASLD progresses, however, patients may exhibit a range of symptoms (Table 1).

TABLE 1. Symptoms of MASLD[10]

- Itchy skin
- Abdominal swelling (ascites)
- Shortness of breath
- Swelling of the legs
- Spidery blood vessels beneath the surface of the skin (telangiectasias or spider angioma)
- Enlarged spleen
- Red palms
- Jaundice

MASLD has been associated with various genetic[11] and non-genetic risk factors, which are often, but not always, associated with metabolic dysfunction.[8] Table 2 lists common non-genetic risk factors for the condition.

TABLE 2. Non-Genetic Risk Factors for MASLD[10]

- Family history of fatty liver disease or obesity
- Growth hormone deficiency
- High cholesterol
- High levels of triglycerides in the blood
- Metabolic syndrome
- Obesity, especially abdominal adiposity
- Polycystic ovary syndrome (PCOS)
- Obstructive sleep apnea
- Type 2 diabetes
- Hypothyroidism
- Hypopituitarism

The Role of the Primary Care Clinician

Primary care clinicians play critical roles in identifying patients who have or are at risk for developing MASLD and ensuring that they receive prompt and effective care.

Primary care physicians are well-positioned to recognize individuals who are at risk for MASLD and can act to prevent the development of cirrhosis and associated comorbidities.[12] Diagnosing the condition at an early stage can delay symptom onset and prevent complications and progression. Fatty liver disease can be conceptualized as the liver manifestation of metabolic syndrome. Primary care physicians routinely help their patients manage metabolic syndrome and its comorbidities, thus enabling them to recognize signs and symptoms that warrant further investigation. Additional roles of the clinician include:

- Identifying patients who may have MASLD and differentiating the condition from other liver abnormalities
- Assessing and determining referral needs
- Understanding cultural factors and patient preferences for treatment
- Discussing treatment options and adjunctive interventions
- Coordinating efforts with a care team (e.g., endocrinologist, hepatologist, dietitian) when warranted
- Keeping the patient actively engaged in disease management.

Given that many patients with MASLD may find it challenging to embark upon the lifestyle changes necessary to manage metabolic risk factors, the primary care clinician must recognize that they provide key support to help the individual receive proper treatment. In some cases, the clinician may represent the patient's sole resource when seeking help.

Because MASLD reflects findings that are affected by diet, lifestyle, and environmental influences, it can be thought of as a paradigm for primary care, as it interfaces with the core attributes of primary care medicine: continuity of care, comprehensiveness, first contact, community, and family. The nature of MASLD requires that patients be followed over time to assure a reduction of risks. Moreover, it warrants a comprehensive treatment strategy, and several interventions will be required to optimize outcomes.

MASLD often coincides with or precedes chronic conditions such as diabetes mellitus and CVD. Routine office visits provide the clinician with opportunities to identify those at risk. Thus, early intervention by the primary care clinician complements and supports population-based strategies and communal approaches to reduce the morbidity and mortality caused by MASLD and other metabolic dysregulation. Also, risk factors related to MASLD are influenced by familial genetic and environmental factors may be recognized more easily in the primary care setting.

Defining MASLD

MASLD is a chronic disorder, and early diagnosis and prompt management are critical to minimize potential disability and improve the patient's quality of life. Because MASLD is closely linked with metabolic syndrome, it is defined as the presence of hepatic steatosis in conjunction with **at least one cardiometabolic risk factor** (Table 3) and no other discernible cause (e.g., alcohol-related liver disease, drug-induced liver injury, HIV or HCV infection, celiac disease).[3] Steatosis grade is scored from 0-3 (see callout box); steatosis is considered present if identified in ≥5% of hepatocytes.[12]

Steatosis grade as determined histologically:

Hepatocyte Involvement:	Score:
< 5%	0
5% - 33%	1 (mild)
33% - 66%	2 (moderate)
> 66%	3 (severe)

TABLE 3. Cardiometabolic Criteria for MASLD[3]

Adult Criteria	Pediatric Criteria
BMI ≥25 kg/m² [23 Asia] **OR** Waist circumference >94 cm (M) 80 cm (F) **OR** Ethnicity-adjusted equivalent	BMI ≥85th percentile for age/sex [BMI z score ≥+1] **OR** Waist circumference >95th percentile **OR** Ethnicity-adjusted equivalent
Fasting serum glucose ≥5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose level ≥7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥5.7% [39 mmol/L] OR Type 2 diabetes **OR** Treatment for type 2 diabetes	Fasting serum glucose ≥5.6 mmol/L [≥100 mg/dL] **OR** Serum glucose ≥11.1 mmol/L [≥200 mg/dL] **OR** 2-hour post-load glucose level ≥7.8 mmol [140 mg/dL] **OR** HbA1c ≥5.7% [39 mmol/L] **OR** Already diagnosed/treated type 2 diabetes **OR** Treatment for type 2 diabetes
Blood pressure ≥130/85 mmHg **OR** Specific antihypertensive drug treatment	Blood pressure age < 13 yr, BP ≥95th percentile or ≥130/80 mmHg (whichever is lower); age ≥13 yr, 130/85 mmHg or specific antihypertensive drug treatment
Plasma triglycerides ≥1.70 mmol/L [150 mg/dL] **OR** Lipid-lowering treatment	Plasma triglycerides age < 10 yr, ≥1.15 mmol/L [≥100 mg/dL]; age ≥10 yr, ≥1.70 mmol/L [≥150 mg/dL] **OR** Lipid-lowering treatment
Plasma HDL-cholesterol ≤1.0 mmol/L [40 mg/dL] (M) and ≤1.3 mmol/L [50 mg/dL] (F) **OR** Lipid-lowering treatment	Plasma HDL-cholesterol ≤1.0 mmol/L [≤40 mg/dL] **OR** Lipid-lowering treatment

Screening for Liver Damage in Primary Care

While a biopsy remains the definitive means to assess the extent of liver damage, many non-invasive methods are used to identify and stage liver disease. Liver fibrosis scores are based on the METAVIR scoring system (Table 4), where stages F2-F4 represent clinically significant fibrosis. Hepatic fibrosis stage is a risk factor for overall and liver-related mortality, and several modalities and algorithms can help screen for patients at high risk. This section highlights options that are applicable to primary care practice.

Imaging. Where facilities allow, traditional imaging-based techniques, such as ultrasound, computed tomography, and MRI provide painless options to evaluate the extent of liver damage. When considering cost, ease of use in the primary care setting, and sensitivity, ultrasound is a practical modality to detect moderate to severe steatosis for screening purposes.[13,14] Vibration-controlled transient elastography (VCTE), an FDA-approved ultrasound-based method that measures liver stiffness, can be used to identify steatosis and advanced fibrosis in patients with MASLD.[15] Although not a confirmatory test per se, VCTE's sensitivity and specificity for establishing advanced fibrosis (stages F3-F4) make it a useful tool to help identify patients who warrant additional histologic assessment.[16]

TABLE 4. The METAVIR Scoring System for Liver Fibroses

Value	Characteristics
F0	No fibrosis
F1	Portal fibrosis without septa (e.g., minimal scarring or mild fibrosis
F2	Portal fibrosis with a few septa (e.g., intermediate level scarring; moderate fibrosis)
F3	Numerous septa without cirrhosis (extensive scarring; advanced fibrosis)
F4	Cirrhosis

Clinical Fibrosis Prediction Scores. Imaging can be complemented by several validated predictive indices for fibrosis that are calculated using indirect markers and body parameters, such as the AST-to-platelet ratio index (APRI), NAFLD Fibrosis Score (NFS), and fibrosis 4 (FIB-4; Figure 1).[17] Although the FIB-4 and APRI were originally designed to predict fibrosis in patients with HIV/HCV coinfection and chronic hepatitis C, respectively, they have been widely applied to MASLD patients as inexpensive methods to support clinical decision-making when staging liver disease (e.g., advanced fibrosis versus cirrhosis) in primary care. These tools can be used in conjunction with each other as needed. As discussed in the following section, the American Association for the Study of Liver Diseases (AASLD) and the American Diabetes Association (ADA) recommend using the FIB-4 as a starting point to stratify fibrosis risk, given its simplicity, cost-effectiveness, and specificity.[8,12,18]

AST-to-Platelet Ratio Index (APRI)

$$\text{APRI} = \frac{\frac{\text{AST level (IU/mL)}}{\text{AST (Upper limit of normal)*}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

* The upper limit of normal is established by the laboratory that performed the test. An APRI score of 0.7 indicates significant fibrosis, whereas a score >1.0 indicates cirrhosis.[19]

NAFLD Fibrosis Score (NFS)

$$\text{NFS} = -1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{IFG/diabetes (yes=1, no=0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet (x10}^9\text{/L)} - 0.66 \times \text{albumin (g/dL)}$$

An NFS value >0.676 indicates significant fibrosis (stages F3-F4), whereas a value of <-1.455 indicates the absence of significant fibrosis (stages F0-F2). A value between -1.455 and 0.675 indicates an indeterminate score.[20]

NAFLD Fibrosis 4 (FIB-4)

$$\text{FIB-4} = \frac{\text{Age (years) x AST level (U/L)}}{\text{Platelet Count (109/L) x } \sqrt{\text{ALT (U/L)}}}$$

FIB-4 scores roughly correspond to liver biopsy METAVIR fibrosis scores as follows: FIB-4 scores less than 1.45 correspond to an F0-F1 METAVIR score (no scarring/minimal scarring), whereas a FIB-4 score > 3.25 corresponds to an F3-F4 METAVIR score (e.g., extensive scarring without cirrhosis or cirrhosis).

Figure 1. Predictive Indices of Fibrosis that use Indirect Markers.[17]

The Enhanced Liver Fibrosis Test (ELF). The ELF is a commercial blood test that measures levels of markers of matrix turnover, including inhibitors of metalloproteinase-1, amino terminal propeptide of type III procollagen, and hyaluronic acid.[12,21] The output value from this test is used to estimate the rate of extracellular matrix metabolism in liver tissue, thus reflecting the severity of fibrosis.

Who Should be Screened for MASLD?

With the global rise in the prevalence of obesity, type 2 diabetes, and other metabolic sequelae, primary care clinicians can expect to see many patients who present with one or more cardiometabolic criteria that characterize MASLD. An estimated 12-20% of US adults with type 2 diabetes have clinically significant fibrosis (e.g., METAVIR stages F2-F4),[18] many of whom have not been previously diagnosed as such. The presentation of one insulin resistance-related cardiometabolic criterion should prompt the clinician to inquire further regarding liver health. Recognizing the importance of diagnosing MASLD early, many professional organizations, including the American Association for the Study of Liver Diseases (AASLD), the American Association of Clinical Endocrinology (AACE), and the American Diabetes Association (ADA) have issued recommendations for screening adults and children who are at risk for fibrosis. The non-invasive clinical prediction tests discussed previously facilitate risk stratification, enabling a practice to identify those patients who may require additional testing or referral.

Screening in Adults. Although the AACE/AASLD advises against screening the general population for MASLD, the organizations recommend that all patients with hepatic steatosis or clinically-suspected MASLD based on obesity, metabolic risk factors, or unexplained elevated liver chemistries should undergo primary risk assessment using the FIB-4.[8] In the primary care setting, this strategy rapidly assesses for advanced fibrosis and can be applied serially to track progression over time. Per the AACE/AASLD, individuals with a FIB-4 index <1.3 are at low risk of advanced fibrosis (F3-F4) and can generally be followed in primary care with periodic reassessment, whereas those with a score >1.3 should receive a secondary assessment using VCTE or ELF or referred for further risk stratification.

The AACE/AASLD notes further that plasma liver aminotransferase levels may be within normal range (e.g., less than 40 U/L) in many patients with MASLD seen in primary care; thus, these values should not be used alone to diagnose MASLD. Moreover, aminotransferase levels can be elevated by numerous secondary causes, including medications and vitamins, viral or autoimmune hepatitis, and endocrine disorders (e.g., hyper- or hypothyroidism, Cushing syndrome, hypogonadism), among other causes.

Table 5 summarizes evidence-based recommendations from these professional societies regarding screening and risk stratification for adults who have indications for MASLD.

Screening in Children. The AACE/AASLD has also issued recommendations for screening and diagnosing MASLD in children.[12] Clinicians are encouraged to use plasma aminotransferases to test children at high risk for MASLD and to use imaging (e.g., ultrasound or MRI-proton density fat fraction) or liver biopsy to diagnose the condition after excluding non-NAFLD causes of hepatic steatosis, such as Wilson syndrome, mitochondrial disease, and effects of medications. The AACE/AASLD notes, however, that "liver fibrosis prediction calculations and proprietary biomarkers currently available for the diagnosis of advanced fibrosis in adults should not be used in children as they either are inaccurate or require further validation." All of these recommendations carry a Strength of Evidence level of B as defined in Table 5.

TABLE 5. Recommendations for Screening Adults for MASLD §

American Association of Clinical Endocrinology (AACE) / American Association for the Study of Liver Diseases (AASLD) (2022)[12]

Recommendation	Strength of Evidence ‡
Clinicians should consider persons with obesity and/or features of metabolic syndrome, those with prediabetes or T2D, and those with hepatic steatosis on any imaging study and/or persistently elevated plasma aminotransferase levels (over 6 months) to be "high risk" and screen for NAFLD and advanced fibrosis.	**Grade B**
Clinicians should use liver fibrosis prediction calculations to assess the risk of NAFLD with liver fibrosis. The preferred noninvasive initial test is the FIB-4.	**Grade B**
Clinicians should consider persons in the "high-risk" groups who have an indeterminate or high FIB-4 score for further workup with an LSM (transient elastography) or ELF test, as available.	**Grade B**
To stage the risk of fibrosis in persons with NAFLD, clinicians should prefer the use of VCTE as best validated to identify advanced disease and predict liver-related outcomes. Alternative imaging approaches may be considered, including shear wave elastography (less well validated) and/or magnetic resonance elastography (most accurate but with a high cost and limited availability; best if ordered by liver specialist for selected cases).	**Grade B**
In persons with T2D, clinicians should consider screening for clinically significant fibrosis (stages F2-F4) using the FIB-4, even if they have normal liver enzyme levels.	**Grade B**
In persons with T1D, clinicians may consider screening for NAFLD with clinically significant fibrosis using the FIB-4 only if there are risk factors such as obesity, features of metabolic syndrome, elevated plasma aminotransferase levels (>30 U/L), or hepatic steatosis on imaging.	**Grade C; downgraded due to study heterogeneity and moderate to high probability of bias**
Clinicians should further risk stratify persons with T2D, or T1D with cardiometabolic risk factors and/or elevated plasma aminotransferase levels (>30 U/L) using the FIB-4, elastography, and/or ELF test.	**Grade B**
Persons with persistently elevated ALT or AST levels and/or with hepatic steatosis on imaging and indeterminate risk (FIB-4, 1.3-2.67; LSM, 8-12 kPa; or ELF test, 7.7-9.8) or high risk (FIB-4, >2.67; LSM, >12 kPa; or ELF test, >9.8) based on blood tests and/or imaging should be referred to a gastroenterologist or hepatologist for further assessment, which may include a liver biopsy.	**Grade B**
Clinicians should refer persons with clinical evidence of advanced liver disease (ascites, hepatic encephalopathy, esophageal varices, or evidence of hepatic synthetic dysfunction) to a gastroenterologist / hepatologist for further care.	**Grade B**

Table 5 continued on next page.

TABLE 5. Recommendations for Screening Adults for MASLD § *continued*

American Diabetes Association (2024)[18]

Recommendation	Evidence Grade*
Adults with type 2 diabetes or prediabetes, particularly those with obesity or cardiometabolic risk factors or established cardiovascular disease, should be screened/risk stratified for clinically significant liver fibrosis (defined as moderate fibrosis to cirrhosis) using FIB-4, even if they have normal liver enzymes.	B
Adults with diabetes or prediabetes with persistently elevated plasma aminotransferase levels for > 6 months and low FIB-4 should be evaluated for other causes of liver disease.	B
Adults with type 2 diabetes or prediabetes with an indeterminate or high FIB-4 should have additional risk stratification by liver stiffness measurement with transient elastography or ELF.	B
Adults with type 2 diabetes or prediabetes with indeterminate results or at high risk for significant liver fibrosis (i.e., by FIB-4, liver stiffness measurement, or ELF) should be referred to a gastroenterologist or hepatologist for further workup. Interprofessional care is recommended for long-term management.	B

§The term, "NAFLD," has been retained in this table because of its use in the original documents issued by the AACE/AASLD and ADA.

‡AACE / AASLD Strength of Evidence: B - Intermediate / high strength; C - Intermediate / weak strength.

*ADA Grade B: Supportive evidence from well-conducted cohort studies, including prospective cohort studies or registries or a meta-analysis of cohort studies OR a well-conducted case-control study.[22]

Abbreviations: ALT—alanine aminotransferase; AST—aspartate aminotransferase; LSM—liver stiffness measurement; T1D / T2D—type 1 / type 2 diabetes mellitus.

Managing MASLD

Managing MASLD begins by stratifying risk of liver cirrhosis and cardiovascular disease, followed by a tailored, multidisciplinary strategy that addresses the patient's metabolic risk factors. While patients with MASLD may present different combinations of cardiometabolic risk factors, these factors often cluster in predisposed individuals- identification of one risk factor implicated in MASLD should prompt the search for others.[23] While a detailed discussion of treating each risk factor is beyond the scope of this monograph, the AASLD notes that clinicians must manage persons with MASLD for obesity, metabolic syndrome, prediabetes, diabetes mellitus, dyslipidemia, hypertension, and CVD based on current standards of care (Evidence Strength: A; High/intermediate strength of evidence).[12]

MASLD cannot be managed fully in a single visit, and the clinician and patient must engage in shared, ongoing decision-making, revising management plans as needed to achieve goals. Because of the progressive nature of the condition, patients should be monitored regularly. Optimal management incorporates a holistic approach that combines medical, social, and emotional support. The following section will review several cornerstones of MASLD management in primary care, including lifestyle modifications, medications for liver disease and cardiometabolic conditions associated with MASLD, and immunizations. At the end of this section, Table 7 summarizes AACE/AASLD and ADA recommendations for managing MASLD through lifestyle changes and pharmacotherapy, along with the strength of their supporting evidence.

Lifestyle Modifications

Excess weight, physical inactivity, and carbohydrate-rich diets are implicated in the vast majority of cases of metabolic dysregulation. Therefore, the first line of treatment for MASLD (and a modality that will continue throughout management) is a tailored, structured plan of lifestyle modifications, including a balanced diet and physical activity. Citing evidence from numerous large-scale studies, the AACE/AASLD advocates that clinicians recommend lifestyle changes in persons with excess adiposity and MASLD, aiming for weight loss of at least 5% (but preferably 10% or more) over twelve months, as more weight loss is often associated with greater liver histologic and cardiometabolic benefit.[12,24] Furthermore, these organizations recommend that clinicians must recommend that overweight or obese persons with MASLD participate in a tailored, structured weight loss program when possible.

A Balanced Diet. Weight loss occurs when the amount of expended energy exceeds the caloric intake, and weight maintenance reflects a balance between intake and expenditure. For controlled weight loss, a healthy diet must create a daily deficit in energy (calories). Because each pound of adipose tissue stores approximately 3,500 calories,[25] a tailored diet that targets a deficit of 500 to 1,000 cal/day will promote the loss of 1-2 lbs / week.[26] Weight loss that exceeds this rate results in loss of water and muscle mass, thereby increasing health risks and encouraging weight regain.

Although caloric balance is the major determinant of weight loss, a healthy strategy requires more than simply cutting calories--nutritional balance and weight management are complementary goals to weight loss. Effective management represents a long-term lifestyle change through the adjustment of daily eating habits. Thus, any diet should be planned to achieve a gradual but progressive weight loss, and dietary adjustments should enfold into an overall lifestyle regimen that includes physical activity (see below for details).

There is no codified "best" dietary approach to manage MASLD, as individual patients will respond differently to specific directives. However, reducing macronutrient intake, especially saturated fats, is consistent across studies.[12] A low-calorie diet, with consideration given to the patient's food preferences, is the first step. According to evidence-based studies, the USDA reports that, in the absence of physical activity, any diet containing approximately 1,400 to 1,500 cal / day will result in weight loss, regardless of macronutrient composition.[27] Evidence-based studies suggest that calorie-restricted diets and low-fat diets can achieve long-term effects on body weight, although the intensity of the intervention plays a significant role.[28,29] Moreover, weight loss achieved through caloric deficit reduces hepatic steatosis regardless of dietary approach.[12] However, the number of kcal / day necessary for a patient to lose or maintain weight depends on the individual's usual caloric intake, and any caloric regimen must be tailored to the individual patient.

Commercially-produced fructose represents one source of calories that can be detrimental when managing MASLD. The increased consumption of fructose, which is commonly used (as high-fructose corn syrup) to sweeten colas and fruit beverages, is associated with postprandial hypertriglyceridemia and visceral adiposity.[30,31] In contrast to fructose found endogenously in fruits, commercial fructose consumption is associated with fibrosis severity in patients with MASLD.[30, 31] To this end, the American Gastroenterological Association recommends that adults with MASLD minimize fructose consumption along with saturated fatty acid intake.[32]

While there is no practice recommendation for a specific diet that patients with hepatic steatosis should follow, many studies have linked "Mediterranean" diets to improvements in cardiovascular risk parameters and reduction in hepatic fat content.[12] These diets are rich in whole foods (e.g., fruits, vegetables, fish, nuts, beans, olive oil) but low in processed foods / sugars and

saturated fats. Foods commonly included in a Mediterranean diet can lower blood pressure, protect against chronic conditions, reduce inflammation, and support weight loss regimens. While detailed dietary recommendations are beyond the scope of this monograph, general guidelines are available online.[33] For many individuals, the Mediterranean diet can be incorporated sustainably into daily life, thus promoting long-term adherence. Numerous professional societies have endorsed the Mediterranean diet for patients with MASLD,[12,32,34] and the Expert Panel endorses such diets as part of a healthy lifestyle that may positively impact MASLD symptoms and increase a sense of well-being in affected patients. When possible, the Panel suggests partnering with a clinical nutritionist or dietitian to work with the patient to tailor an appropriate diet. For further consultation, a registered dietitian can be located through the Academy of Nutrition and Dietetics (https://www.eatright.org/find-a-nutrition-expert).

Physical Activity. Physical activity increases muscle mass and metabolic rate, and an active lifestyle decreases risk factors for CVD, type 2 diabetes, dyslipidemia, and other Physical Activity. Physical activity increases muscle mass and metabolic rate, and an active lifestyle decreases risk factors for CVD, type 2 diabetes, dyslipidemia, and other comorbidities of overweight and obesity.[35-39] Moreover, physical activity is associated with a graded response in a number of different lipoprotein variables (e.g., decreases in total and very-low-density lipoprotein triglycerides, a decrease in the number of LDL particles, and an increase in HDL-C) with only minimal changes in body weight.[40] In addition, physical activity improves insulin sensitivity by mobilizing glycogen stores and creating a glucose storage space.[41] Regular exercise also increases levels of cytokines with anti-inflammatory and antioxidant properties.[42] Therefore, physical activity provides numerous impactful health benefits (e.g., cardiovascular fitness, muscle strength, improved insulin sensitivity, improved sleep, increased mobility in overweight persons) that can improve quality of life.[43]

When helping patients to establish a physical activity regimen, the clinician should stress that activity does not necessarily equate with traditional exercise and may include walking, sports, and common chores (e.g., gardening, waxing a car, pushing a stroller, raking leaves). Moreover, the primary care clinician should note that physical activity accumulates over the course of the day; the patient need not complete the day's allotment of activity in one session to achieve health benefits. For patients with metabolic syndrome, physical activity should be initiated slowly and increased gradually, and any patient who is starting an activity program should be evaluated for cardiovascular fitness prior to commencement.

For overall health, the American Heart Association (AHA) suggests 150 minutes per week of moderate-intensity aerobic activity or 75 minutes per week of vigorous aerobic activity (or a combination of both), preferably spread throughout the week.[44] The AHA also recommends adding moderate- to high-intensity muscle-strengthening activity (e.g., resistance or weight training) on at least two days per week. Furthermore, even light-intensity activity can offset some of the risks of being sedentary, and benefits will accrue with additional activity above the recommended amounts. Examples of moderately intense physical activity include (but are not limited to): walking or jogging, bicycling, golf, social dance, tennis, gardening, and low-impact aerobics. The clinician should stress that some activity is preferable to no activity; even three 10-minute periods of activity during the course of the day provides benefit. Any activity regimen should begin conservatively to promote compliance.

As with dietary intervention, a physical activity plan should be tailored to the individual, with the understanding that each patient will progress through an activity regimen at an individual rate. For patients who will get the majority of their physical activity through walking, pedometers or smartphone apps can measure activity level as a function of steps/day. It is recommended that the primary care clinician help the patient set a target number of steps per day (usually 5,000-10,000), depending on the patient's level of baseline activity and physical fitness. Resistance training may be added as an adjunct to (but not a replacement for) aerobic activity.

The Expert Panel recommends encouraging patients with MASLD to be active within appropriate contexts. Physically inactive patients should be encouraged to begin moderately; walking for ten minutes daily will produce measurable health benefits. However, a successful activity regimen will be tailored to the patient's needs and should utilize available resources—a recommendation for water exercise classes does not benefit the patient who lacks access to a facility in which these classes are conducted.

Pharmacotherapy

Managing MASLD is linked with managing metabolic dysregulation, liver disease, and body weight. Pharmacotherapy should be prescribed as an adjunct to (but not a substitute for) lifestyle modifications designed to reduce cardiometabolic and hepatic risk factors. This section will review classes of agents with efficacy in managing MASLD as supported by a strong evidence base.

Treating Liver Disease and Cardiometabolic Conditions Associated with MASLD. Treatment recommendations for MASLD usually serve joint goals of managing liver disease in the context of controlling body weight or associated cardiometabolic risk factors, such as type 2 diabetes. While there are multiple classes of FDA-approved antihyperglycemic agents and multiple agents indicated for weight loss, only a subset of these has been shown to be efficacious in the context of liver disease.

Two medication classes approved for glycemic control, pioglitazone and glucagon-like peptide 1 receptor agonists (GLP-1 RAs), have been shown to reverse steatohepatitis in persons with obesity, prediabetes, or type 2 diabetes.[12] A meta-analysis of eight randomized, controlled clinical trials (n=516) to evaluate thiazolidinediones (pioglitazone or rosiglitazone maleate) in individuals with biopsy-proven NASH suggests that pioglitazone use improves advanced fibrosis (from stages F3-F4 to stages F0-F2) in patients with or without diabetes.[45] Pioglitazone is a cost-effective medication, although thiazolidiendiones have been associated with dose-dependent weight gain that is more pronounced when combined with insulin secretagogues and insulin.[46] It should be noted that, in the context of glucose control, the ADA recommends thiazolidinediones and GLP-1 RAs as second-line agents, usually in conjunction with metformin. The ADA also notes that insulin is the preferred antihyperglycemic agent for managing glucose levels in adults with type 2 diabetes and decompensated cirrhosis.[18]

GLP-1 RAs act indirectly on hepatocytes through various mechanisms while promoting satiety and weight loss through direct effects on the central nervous system.[47] GLP-1 RAs have been studied in the context of liver disease in a wide variety of settings and cohorts, and, despite study heterogeneity, there is agreement that these agents normalize plasma aminotransferase levels and reduce liver fat content in individuals with MASLD.[48] As a class, GLP-1 RAs have been associated with robust clinical benefits, including weight loss, glycemic control, and cardiometabolic improvements, although individual agents vary in efficacy.

Three GLP-1 RAs—liraglutide, semaglutide, and tirzepatide--have recently received FDA approval as adjunct therapies to a reduced-calorie diet and increased physical activity for chronic weight management for adults (all agents) and for pediatric patients aged twelve years and older (liraglutide and semaglutide).[49-51] These agents are indicated for obese adults (BMI >30 kg / m^2) or for overweight adults (BMI >27 kg / m^2) who have at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes, or dyslipidemia, CVD, obstructive sleep apnea). Liraglutide and semaglutide are also indicated for pediatric patients aged 12 and older with body weight >60 kg and an initial BMI that corresponds to 30 kg/m2 for adults using international cut-offs. All three agents carry a black-box warning about the risk of thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans based on dose- and treatment duration-dependent C-cell tumor development in rodents at clinically

relevant exposures. As such, they are contraindicated in individuals who have a personal or family history of MTC or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Patients who are candidates for these agents should be counseled about the risks and symptoms of thyroid tumors.

Another class of antihyperglycemic agents, the sodium-glucose cotransporter 2 (SGLT2) inhibitors, inhibits renal glucose reabsorption, thereby increasing the amount of glucose excreted in the urine at a given plasma glucose concentration. Several randomized, controlled trials have indicated that individual agents improve hepatic insulin sensitivity or[52] reduce liver fat[53,54] in persons with type 2 diabetes. Although not approved for weight management, these agents could be potentially beneficial for managing MASLD, as the reduced lipid burden on the liver from glycosuria creates an energy deficit and weight loss.[55] Based on their cardiometabolic and renal protective effects and their ability to reduce hepatic steatosis, SGLT2 inhibitors may be considered as adjunctive pharmacotherapy for individuals with type 2 diabetes and MASLD.[12]

The AASLD/AACE notes that other medication classes approved for glycemic management, including metformin, acarbose, dipeptidylpeptidase IV inhibitors, and insulin, have not demonstrated benefit for hepatocyte necrosis or inflammation, although they may be initiated or continued as needed to treat hyperglycemia in persons with type 2 diabetes and MASLD.[12]

In March of 2024, the FDA approved resmetirom (*Rezdiffra*), indicated for adults with non-cirrhotic, nonalcoholic steatohepatitis with moderate to advanced liver fibrosis.[58] The drug works by activating a thyroid hormone receptor that helps reduce liver fat accumulation. Resmetirom was approved based on the results from a Phase 3 clinical trial, which showed that a significant proportion of patients achieved resolution of nonalcoholic steatohepatitis without worsening liver fibrosis and improved liver fibrosis by at least one stage compared to those receiving a placebo. The approval was granted under an accelerated pathway due to the unmet medical need for effective treatments. Common side effects of resmetirom include diarrhea and nausea. It is not recommended for patients with decompensated cirrhosis, and it may interact with other medications, particularly statins used for lowering cholesterol.[58] Additional information can be found at https://www.metabolismjournal.com/article/S0026-0495(24)00061-1/fulltext

Immunizations. Table 6 lists immunizations currently recommended by the Centers for Disease Control and Prevention for adults ages 19 or older with chronic liver disease.[56,57]

TABLE 6. Immunizations Recommended for Adults (Ages 19 or Older) with Chronic Liver Disease[56,57]

- COVID-19 vaccine
- Influenza vaccine
- Tetanus, diphtheria, and pertussis (Tdap) vaccine
- Measles, mumps, and rubella (MMR) vaccine
- Varicella vaccine
- Pneumococcal polysaccharide vaccine (PPSV23)
- Hepatitis A vaccine
- Hepatitis B vaccine
- Human papilloma virus (HPV) vaccine‡
- Zoster (RZV) vaccine§
- Respiratory syncytial virus (RSV) vaccine*

‡Ages 19-26 years: recommended; ages 27-45 years: based on shared decision-making

§Ages 50 or older

*Ages 60 or older: based on shared decision-making.

TABLE 7. Recommendations for Managing Adults with MASLD§

American Association of Clinical Endocrinology (AACE) / American Association for the Study of Liver Diseases (AASLD) (2022)[12]

Recommendation	Strength of Evidence
Clinicians must manage persons with NAFLD for obesity, metabolic syndrome, prediabetes, diabetes mellitus, dyslipidemia, hypertension, and CVD based on the current standards of care.	**Grade A**
Clinicians should recommend lifestyle changes in persons with excess adiposity and NAFLD with a goal of at least 5%, preferably >10%, weight loss, as more weight loss is often associated with greater liver histologic and cardiometabolic benefit, depending on individualized risk assessments. Clinicians must recommend participation in a structured weight loss program, when possible, tailored to the individual's lifestyle and personal preferences.	**Grade B**
Clinicians must recommend dietary modification in persons with NAFLD, including a reduction of macronutrient content to induce an energy deficit (with restriction of saturated fat, starch, and added sugar) and adoption of healthier eating patterns, such as the Mediterranean diet.	**Grade A**
In persons with NAFLD, clinicians must recommend physical activity that improves body composition and cardiometabolic health. Participation in a structured exercise program should be recommended, when possible, tailored to the individual's lifestyle and personal preferences.	**Grade A**
Pioglitazone and GLP-1 RAs are recommended for persons with T2D and biopsy-proven NASH.	**Grade A**
Clinicians must consider treating diabetes with pioglitazone and/or GLP-1 RAs when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and noninvasive tests.	**Grade A**
To offer cardiometabolic benefit in persons with T2D and NAFLD, clinicians must consider treatment with GLP-1 RAs, pioglitazone, or SGLT2 inhibitors; however, there is no evidence of benefit for treatment of steatohepatitis with SGLT2 inhibitors.	**Grade A**
Due to the lack of evidence of efficacy, metformin, acarbose, dipeptidyl peptidase IV inhibitors, and insulin are not recommended for the treatment of steatohepatitis (no benefit on hepatocyte necrosis or inflammation) but may be continued as needed for the treatment of hyperglycemia in persons with T2D and NAFLD or NASH.	**Grade B**
Vitamin E can be considered for the treatment of NASH in persons without T2D, but there is not enough evidence at this time to recommend for persons with T2D or advanced fibrosis.	**Grade B**
Other pharmacotherapies for persons with NASH cannot be recommended at the present time due to the lack of robust evidence of clinical benefit.	**Grade A**
Clinicians should recommend the use of obesity pharmacotherapy as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH with a goal of at least 5%, preferably >10 %, weight loss, as more weight loss is often associated with greater liver histologic and cardiometabolic benefit, when this is not effectively achieved by lifestyle modification alone.	**Grade B**

Table 7 continued on next page

TABLE 7. Recommendations for Managing Adults with MASLD§ *continued*

American Association of Clinical Endocrinology (AACE) / American Association for the Study of Liver Diseases (AASLD) (2022)[12]

Recommendation	Strength of Evidence
For chronic weight management in individuals with a BMI of >27 kg/m2 and NAFLD or NASH, clinicians should give preference to semaglutide 2.4 mg/week (best evidence) or liraglutide 3 mg / day.	**Grade B**
Clinicians must consider obesity pharmacotherapy (with preference to semaglutide 2.4 mg / week [best evidence] or liraglutide 3 mg/day) as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH to promote cardiometabolic health and treat or prevent T2D, CVD, and other end-stage manifestations of obesity.	**Grade A**

American Diabetes Association (2024)[18]

Recommendation	Evidence Grade *
Adults with type 2 diabetes or prediabetes, particularly with overweight or obesity, with NAFLD should be recommended lifestyle changes that promote weight loss, ideally within a structured nutrition plan and physical activity program for cardiometabolic benefits and histological improvement.	**B** (for cardiometabolic benefits); **C** (for histological improvement)
For adults with type 2 diabetes, particularly with overweight or obesity, with NAFLD, consider using a glucagon-like peptide 1 (GLP-1) receptor agonist with demonstrated benefits in NASH as an adjunctive therapy to lifestyle interventions for weight loss.	**B**
Pioglitazone or GLP-1 receptor agonists are the preferred agents for the treatment of hyperglycemia in adults with type 2 diabetes with biopsy- proven NASH or those at high risk with clinically significant liver fibrosis using non-invasive tests.	**A**
In adults with type 2 diabetes and NAFLD, use of glucose-lowering therapies other than pioglitazone or GLP-1 receptor agonists may be continued as clinically indicated, but these therapies lack evidence of benefit in NASH.	**B**
Insulin therapy is the preferred agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis.	**C**
Adults with type 2 diabetes and NAFLD are at increased cardiovascular risk; therefore, comprehensive management of cardiovascular risk factors is recommended.	**B**
Statin therapy is safe in adults with type 2 diabetes and compensated cirrhosis from NAFLD and should be initiated or continued for cardiovascular risk reduction as clinically indicated. Statin therapy should be used with caution and close monitoring in people with decompensated cirrhosis, given limited safety and efficacy data.	**B**
Consider metabolic surgery in appropriate candidates as an option to treat NASH in adults with type 2 diabetes and to improve cardiovascular outcomes.	**B**
Metabolic surgery should be used with caution in adults with type 2 diabetes with compensated cirrhosis from NAFLD and is not recommended in decompensated cirrhosis.	**B**

§The terms "NAFLD" and "NASH" have been retained because of their use in the original documents issued by the AACE/AASLD and ADA.

*ADA Evidence Grades:[22]

Grade A: Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including evidence from a well-conducted multicenter trial or from a meta-analysis that incorporated quality ratings in the analysis OR supportive evidence from well-conducted randomized controlled trials that are adequately powered, including evidence from a well-conducted trial at one or more institutions or from a meta-analysis that incorporated quality ratings in the analysis.

Grade B: Supportive evidence from well-conducted cohort studies, including prospective cohort studies or registries or a meta-analysis of cohort studies OR a well-conducted case-control study.

Grade C: Supportive evidence from poorly controlled or uncontrolled studies, including randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the result, observational studies with high potential for bias (such as case series with comparison with historical controls), or case series or case reports OR conflicting evidence with the weight of evidence supporting the recommendation.

Assembling a Cardiometabolic / MASLD Care Team and Referring to Specialists

MASLD is a chronic condition that requires that the clinician and the patient collaborate to develop and evolve a management plan. Because of the lifestyle changes that are warranted to maintain liver health, MASLD cannot be managed solely by the primary care clinician and the hepatologist. The Expert Panel notes that patients must be managed as people who cannot be reduced to a single organ, system, or condition. The primary care clinician must meet the patient where they are and work with a team to mesh the clinical aspects of management with the psychosocial adjustments that the patient must make to embark on their journey. Ideally, the primary care clinician should assembled a care team that includes an endocrinologist, hepatologist, nutritionist, and psychologist or social worker. Patients who are embarking on lifestyle changes may benefit from the guidance provided by a physical therapist, nutritionist, or cognitive behaviorist. If referring patients to a weight management center, the clinician should confirm that the center is board-certified for obesity management.

Per the ADA and AACE/AASLD, patients that should be referred to a gastroenterologist or hepatologist for further workup include:[12,18]

- Adults with type 2 diabetes or prediabetes with indeterminate results or at high risk for significant liver fibrosis (i.e., by FIB-4, liver stiffness measure ment, or ELF);
- Persons with persistently elevated ALT or AST levels and/or with hepatic steatosis on imaging and indeterminate risk (FIB-4, 1.3-2.67; LSM, 8-12 kPa; or ELF test, 7.7-9.8) or high risk (FIB-4, >2.67; LSM, >12 kPa; or ELF test, >9.8) based on blood tests and/or imaging;
- Persons with clinical evidence of advanced liver disease (e.g., ascites, hepatic encephalopathy, esophageal varices, or evidence of hepatic syn thetic dysfunction);
- Patients whose condition cannot be managed with pharmacotherapy and lifestyle interventions and for whom bariatric surgery may be considered.

For these individuals, inter-professional care is recommended for long-term management.

MASLD Resources for Clinicians and Patients

Table 8 lists resources that provide a broad range of liver disease and cardiometabolic-related information and can serve as launching points for clinicians and patients who seek information about diagnosing and managing MASLD.

TABLE 8. MASLD Resources for Clinicians and Patients

Source	Contact Information	Resources
The American Association for the Study of Liver Diseases (AASLD)	www.aasld.org	• MASLD decision tree for physicians • Webinars / educational resources • Informational resources on liver disease
The American Liver Foundation (ALF)	www.liverfoundation.org	• Patient infomration / educational resources • Caregiver resources • Clinical trials information
National Institute of Diabetes and Digestive Kidney Diseases (NIDDK)	www.niddk.nih.gov	• Multilingual resources • Patient information • Research updates
The Mayo Clinic	www.mayoclinic.org	• Patient information • Multilingual resources • Continuing medical education and clinician resources
American Diabetes Association	www.diabetes.org	• Patient informational material on topics including risk management, nutrition, fitness, and weight loss • Caregiver resources • Educational programs
Centers for Disease Control and Prevention (CDC)	https://www.cdc.gov/healthy-weight-growth/about/index.html	• Information for parents / care givers to help children achieve a healthy weight and growth
MyPlate	https://www.myplate.gov/	• Information for patients on how to eat healthy
Dietary Guidelines for Americans	https://www.dietaryguidelines.gov/	• 2020-2025 Dietary Guide lines from the US Depart ment of Agriculture

Conclusion

Going forward, the term, "metabolic dysfunction-associated steatotic liver disease" (MASLD), replaces "non-alcoholic steatohepatitis (NASH)" and "non-alcoholic fatty liver disease (NAFLD)," as disease descriptors. MASLD is defined as the presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor (excess body weight, hyperglycemia, hypertension, hypertriglyceridemia, elevated HDL cholesterol) and no other discernible cause. With the global rise in the prevalence of obesity, type 2 diabetes, and other metabolic sequelae, primary care clinicians can expect to see many patients who present with one or more cardiometabolic criteria that characterize MASLD. The condition can often be managed in primary care, and early diagnosis and prompt treatment improve quality of life and reduce the risk of permanent tissue damage. Primary care clinicians should carry out primary risk assessment for all patients with hepatic steatosis or clinically-suspected MASLD based on obesity, metabolic risk factors, or unexplained elevated liver chemistries. Management is based on current standards of care for the cardiometabolic risk factors present, and the identification of one risk factor should prompt the clinician to search for others. Long-term management centers around a tailored plan of diet and activity designed to reduce body weight by 5-10%. Certain antihyperglycemic agents (GLP-1 RAs, pioglitazone) have been shown to reverse steatohepatitis in persons with obesity, prediabetes, or type 2 diabetes and may be appropriate as adjunct pharmacotherapies.

Informed management of MASLD centers around a partnership between the patient and the clinician that incorporates biological and psychological aspects within a tailored, holistic framework. Care pathways that include evidence-based therapies, patient education, support, and collaborations with an informed care team will improve outcomes for all patients with MASLD. Through diagnosis, treatment, and appropriate referral, the primary care clinician plays a vital role in improving the quality of life for patients who present with MASLD.

CASE STUDIES

Case Study #1: Russell - Diagnosing MASLD

Russell, a 45-year-old African-American man, reports to the office because he has been feeling fatigued and "not himself" during the previous couple of months. He notes that he is concerned about heart issues, which run in his family. He reports that he does not smoke and drinks "a couple of beers per week," but his job is sedentary, and he does not do any routine exercise.

1. Russell's BMI is 28 kg/m2, and his blood pressure is 140/100 mm Hg. He reports that he used to take a statin for elevated cholesterol, although he quit doing it several years ago. You will order a lipid panel and a liver function test, but, given only the information at hand, should you screen Russell for clinically significant liver fibrosis?

a) Yes. Russell has at least two cardiometabolic risk factors for MASLD. He should undergo primary risk assessment based on these criteria.

b) No. Results from the liver function test, in particular the liver amino transferase level, should be evaluated before screening for MASLD.

Answer: a. The AACE and AASLD recommend that all patients with clinically-suspected MASLD based on obesity, metabolic risk factors, or unexplained elevated liver chemistries undergo primary risk assessment. However, plasma liver aminotransferase levels may be within normal range (e.g., less than 40 U/L) in many patients with MASLD seen in primary care. Moreover, aminotransferase levels can be elevated by numerous secondary causes, including medications and vitamins, viral or autoimmune hepatitis, and endocrine disorders (e.g., hyper- or hypothyroidism, Cushing syndrome, hypogonadism), among others.

2. Which of the following is a convenient and inexpensive prediction calculation to assess the risk of MASLD with liver fibrosis that is readily amenable to primary care practice?

a) Ultrasound

b) FIB-4

c) Transient elastography

d) Liver biopsy

Answer: b. The FIB-4 is a sensitive and specific test that uses liver panel values, providing an initial test to help stratify risk and determine whether additional tests are warranted.

3. Results from Russell's laboratory workup are as follows:

LDL-C: 128 mg/dL
Total Cholesterol: 198 mg/dL
Triglycerides: 180 mg/dL
HDL-C: 45 mg/dL
HbA1c: 8.6%

AST: 38 U/L
ALT: 40 U/L
Platelet counts: 200 (109/L)

These data indicate that Russell has additional cardiometabolic risk factors that put him at risk for MASLD. His FIB-4 score is 1.35, which places him at indeterminate risk for MASLD with liver fibrosis. Which of the following modalities are viable options for further workup to assess the extent of his liver fibrosis?

a) Ultrasound/Transient elastography (VCTE)
b) Enhanced liver fibrosis test (ELF)
c) Liver biopsy
d) All of the above

Answer: d. All of these are viable approaches.

4. A biopsy is the definitive means to assess the extent of liver damage. Is it necessary to refer Russell for a biopsy before beginning to manage his metabolic dysregulation?

a) Yes. Results from a biopsy will provide the information needed to guide management.
b) No. Although additional workup with elastography, ELF, or biopsy will further stratify Russell's fibrosis risk (or degree of fibrosis), managing his cardiometabolic risk factors should begin promptly.

Answer: b. MASLD is a chronic disorder, and early diagnosis and prompt management are critical to minimize potential disability and improve the patient's quality of life. Russell's management plan can be adjusted in light of additional information.

Case Study #2: Esperanza - Managing MASLD

Esperanza is a 69-year-old Hispanic female with an eleven-year history of type 2 diabetes mellitus who presents complaining of numbness in her feet and hands. Approximately one year ago, she was prescribed liraglutide but never filled the prescription due to cost. She has no glucose readings but notes thrice-nightly nocturia. She currently takes metformin at 1000 mg twice daily. She also has a history of hypertension, dyslipidemia, and depression.

Her exam is notable for blood pressure of 136/82 mmHg and abdominal obesity (BMI: 29.4 kg/m2). She takes lisinopril and rosuvastatin in addition to metformin. Esperanza works as a custodian and has lived with her daughter, son-in-law, and two grandchildren since her husband's death four years ago. She does not smoke and denies using alcohol or illicit drugs. A recent laboratory workup includes the following values:

A1c: 8.1%,
Fasting glucose: 198 mg/dL
LDL-C: 109 mg/dL
Triglycerides: 254 mg/dL
HDL-C: 27 mg/dL.

Esperanza reports a history of elevated A1c levels. She states that she visits a doctor every 6-12 months on average, but she provides little information regarding diet and activity levels outside of work.

1. Which of the following cardiometabolic factors increase Esperanza's risk for MASLD?

a) Diabetes
b) Hypertension
c) Dyslipidemia
d) Abdominal obesity
e) All of the above

Answer: e. All of these factors increase risk for MASLD, and they commonly cluster in at-risk individuals.

2. During your exam, you stress the importance of routine office visits to manage cardiometabolic and liver risk factors. Esperanza notes the difficulty in making routine visits every three months, as she works in the evenings and watches her grandchildren many days while her daughter works.

Based on Esperanza's symptoms and lab values, should you work with her to develop a lifestyle modification program at this point?

a) Yes. Lifestyle modifications and education to promote healthy diet, weight loss/control, and physical activity will be a cornerstone of her tailored intervention, regardless of disease severity or pharmaco therapy.
b) No. Lifestyle modifications are optional at this point, although she will likely need to adjust her medications.
c) No. Given Esperanza's A1c, she should begin insulin therapy immediately.

Answer: a. Lifestyle changes, including diet, physical activity, and social support designed to facilitate behavioral change, are the mainstay of management over the entire treatment continuum.

3. Weight loss will be a central goal of Esperanza's management plan. Ideally, what is a target weight loss for Esperanza to lower metabolic risk and help to manage liver steatosis?

a) 1-2%
b) 2-5%
c) 5-10%
d) 10-20%
e) 25%

Answer: c. 5-10% weight loss, achieved gradually and with planned effort, will reduce cardiometabolic risk and improve complications from MASLD.

4. You mention to Esperanza that she will need to incorporate lifestyle changes to manage her cardiometabolic risk. What are some concrete suggestions that you could offer in terms of dietary and activity changes that would incorporate into Esperanza's current life?

a) Incorporate walking into daily life (e.g., around the block, in place during TV commercials)
b) Consider subtle changes to meals/staples that she prepares for herself (e.g., eat nuts or grains instead of pre-packaged snacks while at work, use less sugar in coffee, limit the number of sugar-sweetened drinks available at the house)

c) Encourage eating raw whole foods or vegetables

d) All of the above

Answer: e. Any of these suggestions could work for Esperanza, with the recognition that a support system will be necessary to incorporate these changes. It will be important to listen to her feedback and to incorporate her suggestions for changes as well.

5. What else can you do to help Esperanza make these lifestyle changes?

a) Arrange for her to receive counseling from a Certified Diabetes Educator (CDE) on principles of self-management and with a dietitian to help achieve controlled weight loss

b) Suggest using community resources (e.g., church, community center) as needed

c) Consider group-based diabetes therapy/ participation in a support group

d) Stress to her and to her daughter (if possible) the important role that the family will play in this process

e) All of the above

Answer: e.

6. Esperanza's pharmacotherapy regimen should also be reconsidered, as her metformin alone is not achieving tight glycemic control. What other adjunct antihyperglycemic agents have been shown to reverse steatohepatitis in persons with obesity, prediabetes, or type 2 diabetes and may be appropriate as adjunct pharmacotherapies?

a) GLP-1 receptor agonists

b) Pioglitazone

c) SGLT2 inhibitors

d) All of the above

e) a or b could be appropriate

Answer: e. According to ADA and AASLD/AACE recommendations, pioglitazone or GLP-1 receptor agonists are the preferred agents for the treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven NASH or those at high risk with clinically significant liver fibrosis using non-invasive tests.

7. Esperanza's FIB-4 score is 2.75, suggesting a high risk for clinically significant fibrosis. Although you will continue to see Esperanza, should you also refer her to a partner hepatologist for further care?

a) No. With a proper combination of lifestyle and medication, she can be managed exclusively in primary care.

b) Yes. Adults with type 2 diabetes who are at high risk for significant liver fibrosis (by FIB-4, liver stiffness measurement, or ELF) should be referred to a gastroenterologist or hepatologist for further workup.

Answer: b. Per the ADA and AASLD/AACE recommendations, Esperanza's high risk for clinically significant fibrosis warrants referral. Inter-professional care is recommended for long-term management.

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