

ABOUT THE AUTHORS

Giada Sebastiani, MD

Giada Sebastiani is Professor of Medicine in the Division of Gastroenterology and Hepatology at McGill University. She received a medical degree and specialized in internal medicine at the University of Padua, Italy. She had research training at Harvard Medical School (US), University College of London (UK), University of Bordeaux (France). Her work focuses on steatotic liver disease (MASLD), liver fibrosis and non-invasive diagnostic tools in liver disease. She is author of 170 articles in peer-reviewed journals (including Nature Reviews Gastroenterology & Hepatology, Lancet Gastroenterology and Hepatology, Lancet Digital Health, Gastroenterology, Hepatology, Journal of Hepatology, Clinical Infectious Diseases; h-index=46, citations>9,500), 13 book chapters, 275 conference publications. Dr Sebastiani is the 2024 President Elect of the Canadian Association for the Study of the Liver. She is co-founder of the Canadian NASH Network and panel member in the Consensus on Models of Care in MASLD of the International Liver Foundation. She is the sole North American representative in the guidelines of the European AIDS Clinical Society as panel member of the Liver Group. Dr Sebastiani was awarded the prestigious Senior Clinical Research Salary Award from Fonds Recherche Sante Quebec. Her research program is funded by the Canadian Institute for Health Research, the Fonds Recherche Sante Quebec, the CIHR Canadian HIV Trials Network, Crohn's Colitis Canada.



Affiliations

Chronic Viral Illness Service, McGill University Health Centre, Montreal, Quebec, Canada
Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal, Quebec, Canada

Felice Cinque, MD

Dr. Felice Cinque is a clinician-scientist currently enrolled in the last year of internal medicine residency and the first year of the PhD program in clinical research at the University of Milan. He completed a research fellowship at McGill University in the Division of Gastroenterology and Hepatology and Infectious Diseases in 2023. His work focuses on chronic liver disease, MASLD in vulnerable populations such as people living with HIV and people with diabetes, with a focus on patient-centered care. He is also an advocate for the inclusion of the LGBTQ+ community in medicine and research.



Affiliations

Chronic Viral Illness Service, McGill University Health Centre, Montreal, Quebec, Canada
Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal, Quebec, Canada
SC-Medicina Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Department of Pathophysiology and Transplantation, University of Milan, Italy

NAVIGATING THE MAZE: A MINI-GUIDE FOR THE MANAGEMENT AND THERAPY OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Abstract

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), formerly known as Nonalcoholic Fatty Liver Disease (NAFLD), poses a significant global health challenge with a prevalence of 30% worldwide. Alarming projections anticipate a substantial increase in MASLD cases, highlighting the urgent need for preparedness and effective policies. The pathophysiology of MASLD involves a complex interplay of metabolic, genetic and lifestyle factors. Although liver biopsy remains the gold standard for the diagnosis of MASLD, non-invasive methods such as abdominal ultrasound, transient elastography with controlled attenuation parameter, shear wave elastography, and non-invasive serum fibrosis scores have been developed and validated. Effective risk stratification in primary care with non-invasive fibrosis scores, such as fibrosis 4 (FIB-4) index and NAFLD fibrosis score (NFS), optimizes healthcare resource utilization, ensuring appropriate referrals for high-risk patients while minimizing unnecessary referrals. Lifestyle intervention, including diet and physical activity, remains the primary therapy for MASLD. Notably, with the FDA approval of resmetirom, the first authorized medication for fibrotic metabolic dysfunction-associated steatohepatitis (MASH), and several antifibrotic agents under investigation, the therapeutic landscape for MASLD is rapidly evolving. Despite its increasing prevalence, morbidity and mortality, MASLD is frequently underdiagnosed in primary care. In this review, we aim to provide primary care physicians an update on the diagnosis, management and treatment of MASLD.

Introduction

With a 30% prevalence in Canada and globally, metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), is the most common liver disease worldwide.¹ Projection studies depict a concerning scenario, with Canadian data foreseeing a 20% MASLD case increase and up to a 95% rise in MASLD-related decompensated cirrhosis and hepatocellular carcinoma (HCC) incidence.² Is the world ready for the MASLD surge? This question led to the development of the MASLD Policy Preparedness Index. Surprisingly, no country scored above 50 out of 100, with Canada, which has no national MASLD management policy, ranking particularly low at 18.25 out of 100.³

Fighting this liver disease begins with establishing the most appropriate name and definition. Therefore, in June 2023, a multi-society Delphi consensus renamed NAFLD to MASLD, offering a positive definition highlighting the pathophysiologic link to metabolic disease and avoiding stigmatizing terms like "fatty".⁴ MASLD is defined as evidence of fat in more than 5% of hepatocytes, with at least one cardiometabolic risk factor, without significant alcohol intake or other causes of steatotic liver disease, the new term covering all hepatic steatosis aetiologies (Figure 1). The Delphi consensus process also introduced a new category, Metabolic Dysfunction and Alcohol Associated Liver Disease (MetALD), aiming to generate knowledge for a prevalent patient group with hepatic steatosis, with co-existing metabolic conditions and alcohol consumption exceeding the MASLD threshold (average daily 20 g-50 g for females, 30-60 g for males).⁴ The clinical and histological spectrum of MASLD ranges from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), a necroinflammatory condition that eventually progresses to liver fibrosis – the hallmark event in the natural history of any liver disease leading to cirrhosis, liver failure and HCC.⁵ MASLD extends beyond the liver, impacting extrahepatic organs and posing a well-established risk for all-cause mortality, especially cardiovascular disease-related mortality – the primary cause of death in MASLD.⁶ In addition, patients with MASLD often experience mental, emotional and social challenges, resulting in impaired quality of life and a significant burden on healthcare resources.⁷

Despite the increasing prevalence of MASLD, with associated morbidity and mortality, real-world evidence shows underdiagnosis of MASLD in the primary care setting. This may be due to the lack of guidelines for screening for MASLD in primary care, the uncertainties associated with currently available diagnostic tests and pharmacotherapy.⁸ The aim of this review is to provide an update on the pathophysiology, diagnosis, management, and treatment of MASLD for primary care physicians.

Pathophysiology and Risk Factors

MASLD pathogenesis is an intricate interplay of metabolic, genetic and lifestyle factors.⁹ Insulin resistance is crucial

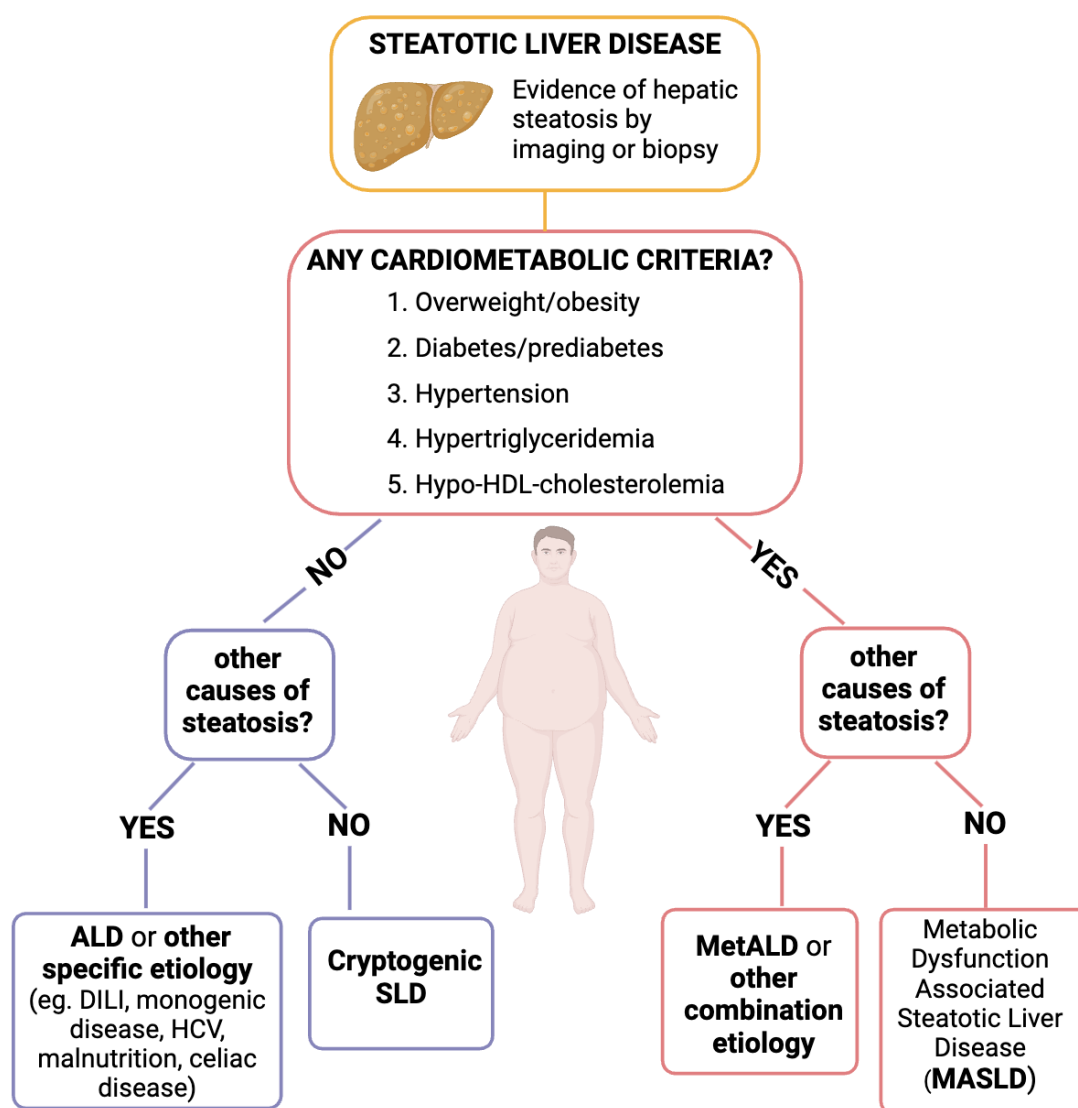


Figure 1. MASLD diagnostic criteria; courtesy of Giada Sebastiani, MD, Felice Cinque, MD

Cardiometabolic criteria: 1. Overweight defined as BMI ≥ 25 kg/m² [23 Asia] OR WC > 94 cm (M) 80 cm (F) OR ethnicity adjusted equivalent; 2. Diabetes/prediabetes defined as fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] OR 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥ 140 mg/dL] OR HbA1c $\geq 5.7\%$ [39 mmol/L] OR T2DM OR treatment for T2DM; 3. Hypertension defined as blood pressure $\geq 130/85$ mmHg OR specific antihypertensive drug treatment; 4. Hypertriglyceridemia defined as plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] OR lipid lowering treatment; 5. hypo-HDL-cholesterolemia (plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) OR lipid lowering treatment).

Abbreviations: ALD = alcohol-associated/related liver disease; BMI = body mass index; BP, blood pressure; CMRF = cardiometabolic risk factors; DILI = drug induced liver disease; MetALD = metabolic dysfunction and alcohol associated steatotic liver disease; SLD = steatotic liver disease; WC = waist circumference.

in MASLD, enhancing hepatic *de novo* lipogenesis and inhibiting adipose tissue lipolysis, causing liver steatosis.¹⁰ It also promotes the production and release of adipokines and inflammatory cytokines, actively contributing to liver inflammation.¹⁰ Visceral adipose tissue dysfunction, characterized by hypersecretion of adipokines and reduced levels of adiponectin, is also implicated in the pathogenesis of MASLD, as it increases oxidative stress and lipotoxicity.¹¹ Furthermore, alterations in gut microbiota are associated with MASLD, as increased intestinal permeability promotes increased fatty acid

absorption and activates inflammatory pathways leading to liver inflammation.¹²

Notably, according to the multiple-hit hypothesis, MASLD development results from the convergence of various risk factors rather than a single causative agent.⁹ First, as perfectly encoded in the new terminology, classic metabolic risk factors are associated with increased MASLD risk. Indeed, in patients with T2DM or obesity, MASLD prevalence rises to 50% and 90%, respectively.¹ Second, a genetic predisposition, particularly the I148M

polymorphism of PNPLA3 affecting triglyceride lipolysis in lipid droplets, variations in TM6SF2 influencing cholesterol metabolism, and alterations in MBOAT7, a key player in phospholipid metabolism, have been identified.¹³ Third, lifestyle habits such as physical inactivity and an unhealthy diet rich in refined carbohydrates, fructose-containing beverages, saturated fats, and processed red meats, significantly contribute to MASLD onset and

progression.¹⁴ **Table 1** provides a list of risk factors for identifying patients at risk for MASLD and liver fibrosis.

Diagnostic Tools for MASLD, MASH and Related Fibrosis

Liver biopsy, the gold standard for diagnosing all three key features of MASLD (hepatic steatosis, steatohepatitis, and fibrosis), is currently the sole approved tool for diagnosing

Risk factor	Criteria
Dysglycaemia or type 2 diabetes	• Prediabetes: HbA1c 39-47 mmol/mol (5.7-6.4%) or fasting plasma glucose 5.6-6.9 mmol/L (100-125 mg/dl) or 2-h plasma glucose during OGTT 7.8-11 mmol/L (140-199 mg/dl) or • Type 2 diabetes: HbA1c >=48 mmol/mol (>=6.5%) or fasting plasma glucose >=7.0 mmol/L (>=126 mg/dl) or 2-h plasma glucose during OGTT >=11.1 mmol/L (>=200 mg/dl) or • Treatment for type 2 diabetes
Overweight/ Obesity	Body mass index • >=25 kg/m2 (>=23 kg/m2 in people of Asian ethnicity) Waist circumference • >=94 cm in men and >=80 cm in women (Europeans) • >=90 cm in men and >=80 cm in women (South Asians and Chinese) • >=85 cm in men and >=90 cm in women (Japanese)
Dyslipidaemia	• High tryglicerides: >=1.7 mmol/L (>=150 mg/dl) or • Low HDL-cholesterol: <=1.0 mmol/L (<=39 mg/dl) in men and <=1.3 mmol/L (<=50 mg/dl) in women or • Lipid lowering treatment
Hypertension	• >=130/85 mmHg or treatment for hypertension
Obstructive sleep apnoea	
Polycystic ovary syndrome	
Other Comorbid Conditions	• HIV infection • Inflammatory bowel disease
Older age	Age >50 years old
Family history of MASLD	
Hispanic population	
Menopausal status	

Table 1. Risk factors for MASLD and liver fibrosis; *courtesy of Giada Sebastiani, MD, Felice Cinque, MD*
Abbreviations: **HbA1c** = glycated haemoglobin; **HIV** = Human Immunodeficiency Virus; **HDL** = high-density lipoprotein; **OGTT** = oral glucose tolerance test

MASH.¹⁵ However, it is costly, invasive, and susceptible to high sampling and inter-operator variability. Hence, several non-invasive tests have been developed demonstrating high accuracy in assessing steatosis and fibrosis, but not steatohepatitis. They can be classified in (i) imaging assessing liver's anatomy (abdominal ultrasound); (ii) methods to assess physical properties of the liver, such as stiffness and attenuation, namely controlled attenuation Parameter (CAP); transient elastography (TE); shear wave elastography (SWE); (iii) blood-based tests, such as Fibrosis-4 (FIB-4), NAFLD fibrosis score (NFS); and Enhanced Liver Fibrosis (ELF).

Due to its accessibility and cost-effectiveness, abdominal ultrasound remains the most widely used tool for first-line steatosis detection, yielding 85% sensitivity (80%-89%) and 94% specificity (87%-97%), respectively.¹⁵ Steatotic liver exhibits increased brightness and echogenicity on ultrasound compared to normal liver tissue and the right kidney (hepatorenal contrast). However, ultrasound can only detect steatosis above 20%, is susceptible to inter-operator variability, and is challenging in obese patients.

CAP, a point-of-care technique on the Fibroscan device, quantitatively assesses liver fat by measuring the attenuation of ultrasound signals through the liver.

Although no universally agreed-upon thresholds exist, values above 275 dB/m demonstrate over 90% sensitivity in detecting steatosis.¹⁵

TE by Fibroscan employs a low-frequency vibration to generate shear waves in liver tissue measuring their velocity to determine liver stiffness, which represents a quantitative measure of liver tissue rigidity and serves as a surrogate for liver fibrosis. Widely used and validated, thresholds of 8 kPa to rule out and 12-15 kPa to rule in advanced fibrosis are currently recommended.¹⁵

SWE is a tool similar to TE that employs focused ultrasound beams to generate shear waves within the liver tissue. Meta-analyses indicate comparable performance to TE in measuring liver stiffness. Despite this, it sees less frequent use in hepatology clinics, and there is limited data available for MASLD patients.

Several serum markers and scores have been developed to assess liver fibrosis, with FIB-4 (based on AST, ALT, age, and platelets) and NFS (based on age, BMI, AST/ALT ratio, platelets, hyperglycemia, and albumin) being the most validated. FIB-4 < 1.3 and NFS < -1.455 rule out advanced fibrosis, while FIB-4 > 2.67 and NFS > 0.676 rule in advanced fibrosis.¹⁵ These scores, quickly calculated from simple

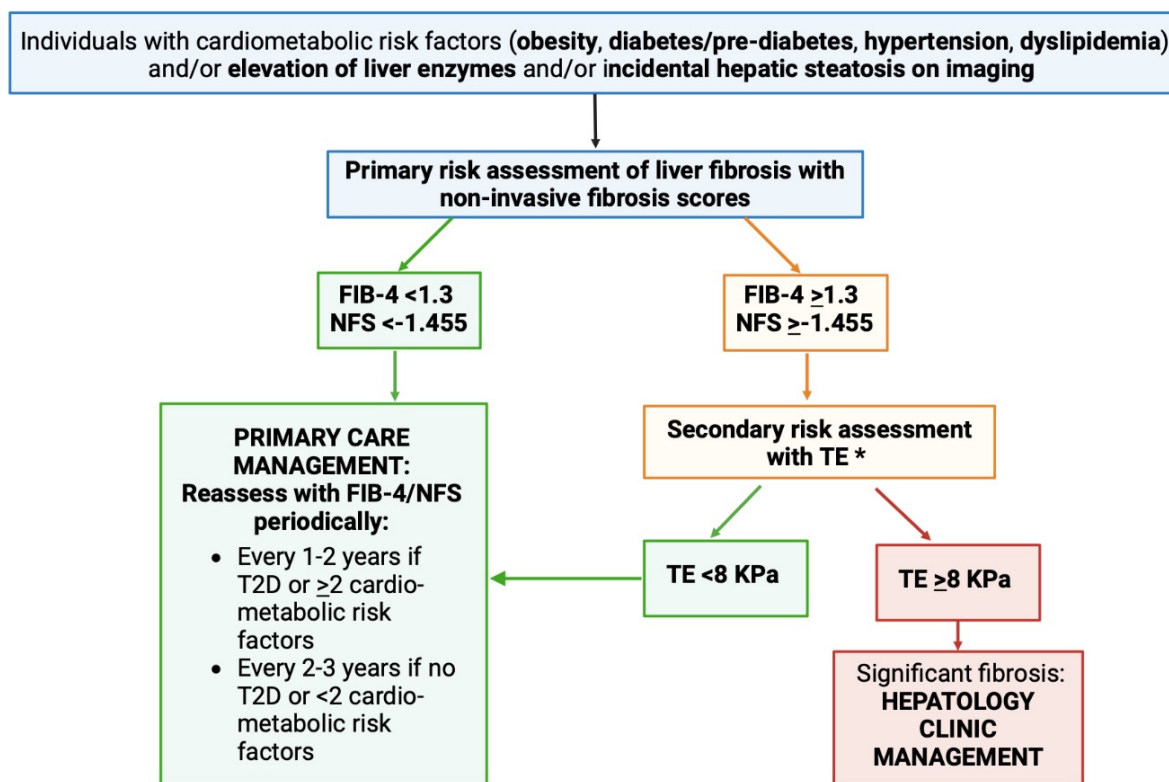


Figure 2. Algorithm for liver fibrosis assessment of patients at risk for or with established MASLD in primary care; courtesy of Giada Sebastiani, MD, Felice Cinque, MD

* The Enhanced Liver Fibrosis (ELF) test, with a cut-off of less than 7.7, can be used as a second-line test in lieu of transient elastography to rule out significant liver fibrosis, particularly in rural or remote areas with limited access to transient elastography.

Abbreviations: CAP = controlled attenuation parameter; FIB-4 = fibrosis score; MASLD = metabolic dysfunction associated steatotic liver disease; TE = transient elastography.

variables readily available in primary care, are easily repeatable. However, approximately one-third of patients receive an undetermined result, falling between the upper and lower cut-off values, necessitating additional tests to confirm liver fibrosis. Consequently, they play a role primarily in population screening, aiding physicians in identifying patients within primary care who need referral to hepatology clinics.¹⁵ Patented serum fibrosis biomarkers have also been developed, such as ELF, which is a combination of three biomarkers (hyaluronic acid, tissue inhibitor of metalloproteinases 1, and amino-terminal propeptide of type III collagen) and is recommended in current guidelines as a second-tier test to assess advanced fibrosis.⁵

Screening and Management of MASLD and Related Fibrosis in Primary Care

In primary care, individuals with T2DM or other cardiometabolic risk factors, and/or elevated transaminases, and/or incidental hepatic steatosis on imaging are highly suspicious for MASLD and at risk for developing liver fibrosis, which is the major prognostic factor predicting hepatic and extrahepatic complications, including all-cause mortality, in MASLD.¹⁶ Therefore, these patients require initial testing to rule out advanced liver fibrosis with non-invasive scores, with FIB-4 considered the best performing simple score according to major guidelines (Figure 2).⁵ This approach optimizes resource use by identifying high-risk patients needing hepatology care and avoiding unnecessary referrals for those with simple steatosis, manageable by primary care physicians. Two points need to be emphasized. First, T2DM is the greatest risk factor for liver fibrosis, with MASLD and T2DM creating a perfect storm that increases the risk of cirrhosis and HCC. Indeed, international hepatology and diabetology guidelines recommend screening people with T2DM for MASLD-related liver fibrosis.^{5,17} Second, nearly 80% of MASLD patients have normal transaminase levels, including 20% of those with MASH and 15% with advanced fibrosis.⁵ While elevated liver enzymes are a red flag for MASLD and liver fibrosis, reliance on transaminase levels alone is inadequate, and at-risk patients should be screened for liver fibrosis even if their transaminase levels are normal. Current guidelines suggest that FIB-4 or other non-invasive scores should be used periodically to monitor patients at risk for liver fibrosis. Given the high negative predictive value of FIB-4 in ruling out advanced fibrosis, patients with a negative result ($\text{FIB-4} < 1.3$) can be followed up in primary care and undergo a repeat risk assessment every two to three years. Patients with T2DM or two or more cardio-metabolic risk factors should undergo FIB-4 reassessment more closely, at least every one to two years, given the higher risk of MASLD progression. Individuals with an indeterminate ($1.3 < \text{FIB-4} < 2.67$) or positive ($\text{FIB-4} > 2.67$) result require secondary risk assessment to confirm advanced fibrosis

with TE or ELF testing, depending on availability. MASLD patients with confirmed advanced fibrosis should be referred to hepatology care.

Implementing this stepwise screening strategy is crucial for the early detection and management of MASH and related fibrosis, allowing timely intervention on hepatic and extrahepatic complications.⁵

Current and Emerging Therapies for MASLD

While treatment options for MASLD are rapidly advancing with the FDA approval of Resmetirom, the first authorized medication for MASH, lifestyle intervention remains the cornerstone of treatment. The goal of lifestyle intervention, whether through diet, physical activity or ideally a combination of both, is to achieve a 7%-10% weight loss for overweight/obese patients and 3%-5% for lean patients.⁵ The Mediterranean diet has the strongest evidence for MASH regression, but any calorie restriction strategy like the ketogenic, DASH or low-carb diets, or intermittent fasting can be recommended to improve MASLD outcomes.¹⁸ Regardless of weight loss, diet quality is crucial. Patients with MASLD are advised to avoid refined carbohydrates, sugar-sweetened beverages, alcohol, and red meat. Instead, they should prioritize high fibres, unsaturated fats and vitamins from fruits; vegetables; legumes; nuts; olive oil; white meats; low-fat dairy; coffee; and small, controlled portions of dark chocolate.¹⁴ Regarding physical activity, patients should aim for at least 150-300 minutes of moderate intensity aerobic exercise or 75-150 minutes of vigorous intensity aerobic exercise weekly, divided into three to five sessions.¹⁹ Adding two days per week of muscle-strengthening activity provides additional benefits. Patients should start with small amounts of exercise, gradually increasing frequency and intensity, and minimize sedentary behaviour.¹⁹ Bariatric surgery is a proven option for morbidly obese patients with MASLD, as evidence suggests that it not only improves MASH, but also cardiovascular outcomes.⁵ Effectively managing metabolic comorbidities with appropriate pharmacotherapy for hypertension, dyslipidemia, and T2DM, is crucial in MASLD, contributing to mortality reduction.⁵ For patients with MASLD at risk of adverse outcomes, including those with MASH, significant fibrosis $\geq \text{F2}$, or high risk of rapid disease progression (e.g., with T2D, metabolic syndrome, persistently increased transaminases, high necroinflammation), MASH-targeting drugs may be considered.⁵ Following promising results from the phase 3 MAESTRO-NASH trial²⁰, resmetirom - an oral, liver-targeted, selective thyroid hormone receptor agonist - became the first FDA-approved drug for treating MASH with F2-F3 fibrosis. Additionally, current guidelines recommend vitamin E and pioglitazone, approved for other metabolic conditions, as effective treatments for MASH in the appropriate clinical settings.⁵ Vitamin E 800 UI daily is recommended as a short-term therapeutic

option for non-diabetic MASH patients. Pioglitazone, approved for T2DM treatment, showed promising results on MASH and cardiovascular outcomes and might be recommended in individuals with T2DM and fibrotic MASH. Interestingly, other antidiabetic drugs, namely the glucagon-like peptide-1 receptor agonists semaglutide and tirzepatide, have shown promising effects on MASLD in phase 3 trials. Current guidelines suggest considering semaglutide for treating obesity and T2DM in patients with MASH, although its anti-fibrotic effects have not yet been proven.⁵

Conclusion

MASLD is a significant global health challenge and needs to be addressed appropriately in the primary care setting. Individuals with cardio-metabolic factors, and in particular T2DM, transaminases elevation or incidental hepatic steatosis on imaging should undergo initial non-invasive assessment for liver fibrosis (FIB-4, NFS). This will help identify patients with suspected advanced fibrosis for further testing and referral to the hepatology clinic. The FDA-approval of resmetirom and ongoing research into new therapies offer hope for the future of MASLD management, although lifestyle interventions remain essential.

Correspondence:

Giada Sebastiani, MD

Email: giada.sebastiani@mcgill.ca

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