Review

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD): A State-of-the-Art Review

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is the latest term for steatotic liver disease associated with metabolic syndrome. MASLD is the most common cause of chronic liver disease and is the leading cause of liver-related morbidity and mortality. It is important that all stakeholders be involved in tackling the public health threat of obesity and obesity-related diseases, including MASLD. A simple and clear assessment and referral pathway using non-invasive tests is essential to ensure that patients with severe MASLD are identified and referred to specialist care, while patients with less severe disease remain in primary care, where they are best managed. While lifestyle intervention is the cornerstone of the management of patients with MASLD, cardiovascular disease risk must be properly assessed and managed because cardiovascular disease is the leading cause of mortality. No pharmacological agent has been approved for the treatment of MASLD, but novel anti-hyperglycemic drugs appear to have benefit. Medications used for the treatment of diabetes and other metabolic conditions may need to be adjusted as liver disease progresses to cirrhosis, especially decompensated cirrhosis. Based on non-invasive tests, the concepts of compensated advanced chronic liver disease and clinically significant portal hypertension provide a practical approach to stratifying patients according to the risk of liver-related complications and can help manage such patients. Finally, prevention and management of sarcopenia should be considered in the management of patients with MASLD.

Key words: Non-alcoholic fatty liver disease, Liver cirrhosis, Portal hypertension

INTRODUCTION

There have been significant developments in the field of non-alcoholic fatty liver disease (NAFLD) in recent years including (1) a change in its nomenclature, (2) a recommendation for screening to identify more severe liver disease among patients with type 2 diabetes mellitus (T2DM), (3) the concept of compensated advanced chronic liver disease (cACLD) and clinically significant portal hypertension (CSPH) diagnosed using non-invasive tests, and (4) recognition of the importance of sarcopenia. This review aims to provide an update on these areas and to highlight some important

considerations in terms of lifestyle intervention, cardiovascular disease (CVD) risk reduction, and use of anti-hyperglycemic drugs and other medications for management of metabolic comorbidities, especially in patients with cirrhosis.

NEW NOMENCLATURE

In 1980, Ludwig et al.[1] reported a liver condition mimicking alcoholic hepatitis that can progress to cirrhosis in persons who did not consume a significant amount of alcohol. The patients were moderately obese, and many had obesity-related diseases, such as

diabetes mellitus. The term non-alcoholic steatohepatitis was coined for this liver condition.[1] In 2007, Farrell et al.[2] in the Asian-Pacific Working Party for NAFLD proposed the operational definition of NAFLD, which could be diagnosed based on ultrasonography findings, and following exclusion of significant alcohol intake, drugs that can cause hepatic steatosis, and other causes of chronic liver disease. This was followed by a position statement by the European Association for the Study of Liver (EASL) in 2010, which acknowledged that, despite its historic diagnosis by exclusion of other causes of chronic liver disease, the strong association of NAFLD with metabolic syndrome and its co-occurrence with other chronic liver diseases strongly argued for a change in nomenclature.[3] The term NAFLD continued to be used in major international guidelines,[4-6] but there were signs of an imminent change. For example, EASL used the term primary NAFLD, which was defined as NAFLD-associated with metabolic risk factors, in its 2016 guidelines,[5] while the Asian-Pacific Working Party proposed a "positive" definition for NAFLD in its 2017 guidelines.[6]

In 2020, Eslam et al.[7,8] proposed the new term 'metabolic dys-function-associated fatty liver disease (MAFLD),' which could be diagnosed in adults with hepatic steatosis detected by imaging techniques, blood biomarkers, or liver histology, when overweight or obese, or in the presence of T2DM or at least two metabolic risk abnormalities. This was endorsed by the Asian Pacific Association for the Study of the Liver (APASL),[9] multiple national societies including the Malaysian Society of Gastroenterology and Hepatology,[10,11] and various stakeholders globally.[12] In June 2023, a multi-society Delphi consensus statement on a new fatty liver disease nomenclature was published, introducing the term metabolic dys-function-associated steatotic liver disease (MASLD) and effectively retiring the term NAFLD.[13] The terms MAFLD and MASLD have more in common than not and are more appropriate for the condition (Table 1).

EPIDEMIOLOGY, NATURAL HISTORY, AND BURDEN OF DISEASE

MASLD has been estimated to affect 30% of the adult population

Table 1. The terms MAFLD and MASLD have more in common than not and have achieved the objective of a more appropriate name for the condition[8,13]

	MAFLD	MASLD
Positive diagnostic criteria (i.e., defines what the disease is rather than what it is not)	Yes	Yes
Attributes the condition to its etiology	Yes	Yes
Criteria	Hepatic steatosis detected either by imaging techniques, blood biomarkers/scores, or liver history, plus (1) Overweight or obese (2) Type 2 diabetes mellitus or (3) Presence of ≥2 metabolic risk abnormalities Metabolic risk abnormalities include: (1) Waist circumference ≥102/88 cm in Caucasian men and women (or ≥90/80 cm in Asian men and women) (2) Blood pressure ≥130/85 mmHg or specific drug treatment (3) Plasma triglycerides ≥150 mg/dL (≥1.70 mmol/L) or specific drug treatment (4) Plasma HDL cholesterol <40 mg/dL (<1.0 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or specific drug treatment (5) Prediabetes (i.e., fasting glucose levels 100–125 mg/dL [5.6–6.9 mmol/L], or 2-hour post-load glucose levels 140–199 mg/dL [7.8–11.0 mmol], or HbA1c 5.7%–6.4%) (6) HOMA-IR ≥2.5 (7) Plasma hs-CRP level >2 mg/L	Hepatic steatosis detected by imaging or biopsy, plus at least 1 of 5: (1) BMI ≥25 kg/m² (≥23 kg/m² in Asian) or waist circumference >94 cm in men, >80 cm in women, or ethnicity adjusted (2) Fasting serum glucose ≥100 mg/dL (≥5.6 mmol/L) or 2-hour post-load glucose level ≥140 mg/dL (≥7.8 mmol/L) or HbA1c ≥5.7% or on specific drug treatment (3) Blood pressure ≥130/85 mmHg or specific drug treatment (4) Plasma triglycerides ≥150 mg/dL (≥1.70 mmol/L) or specific drug treatment (5) Plasma HDL cholesterol <40 mg/dL (<1.0 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or specific drug treatment
Presence of other concomitant liver diseases	Other concomitant liver diseases retain their own term	Falls under a separate group (i.e., MetALD* or other combination etiology)

*MetALD, i.e., weekly intake 140–350 g for female, 210–420 g for male (average daily 20–50 g for female, 30–60 g for male).
MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; HDL, high-density lipoprotein; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostatic model for assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; BMI, body mass index; MetALD, MASLD and increased alcohol intake.

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worldwide, with its prevalence increasing from 22% to 37% from 1991 to 2019.[14,15] The increasing prevalence of MASLD parallels the increasing prevalence of obesity and obesity-related diseases. Metabolic dysfunction-associated steatohepatitis (MASH) is the more severe form of MASLD, is defined histologically by the presence of lobular inflammation and hepatocyte ballooning, and is associated with a greater risk of fibrosis progression.[16] MASH has been found in 63% of patients with MASLD undergoing liver biopsy in an Asian multi-center cohort.[17] Among patients with MASLD without an indication for liver biopsy, the prevalence of MASH is 7%.[18] While CVD is the leading cause of mortality in patients with MASLD, those with more severe liver fibrosis are at increased risk of liver-related mortality, with the risk increasing exponentially with fibrosis stage.[19] A prospective study on a cohort of patients with MASLD and baseline liver biopsy found the rate of cardiovascular event to be 2.03 per 100 person-years while the rate of liver-related event was 0.43 per 100 person-years. Liver-related events occurred only in patients with advanced liver fibrosis (cumulative incidence 9.1% in patients with advanced liver fibrosis vs. 0% in patients without advanced liver fibrosis), with rates of a liver-related event of 1.47 and 3.85 per 100 person-years among patients with F3 and F4 fibrosis, respectively (F3 is bridging fibrosis on liver biopsy, while F4 is cirrhosis; fibrosis stage ≥ F3 is considered advanced liver fibrosis).[20]

Steatotic liver disease (SLD) contributes significantly to the burden of chronic liver disease. While 62% of patients seen in our liver clinic had MASLD, 47% of patients with other chronic liver diseases had significant hepatic steatosis. Overall, 85% of all patients seen in our liver clinic had significant hepatic steatosis.[21] A majority of patients admitted to our ward for cirrhosis and its complications had cryptogenic cirrhosis, which is due to MASLD in most cases.[22] Similarly, cryptogenic cirrhosis as the etiology of hepatocellular carcinoma (HCC) cases seen in our center has more than doubled from 16% to 34% (not including 7% with established diagnosis of MASH) between the time periods of 2006–2009 and 2011–2014.[23] In the United States, MASH has become one of the leading causes of adult liver transplantation and among patients with HCC undergoing liver transplantation.[24,25] The burden of MASLD and its complications, including HCC, is projected to continue to increase in the coming years.[26,27]

PATIENTS WITH T2DM: AN IMPORTANT TARGET GROUP FOR DETECTION OF ADVANCED LIVER FIBROSIS

MASLD is prevalent in the general population, with a small yet significant proportion of people having advanced liver fibrosis. For example, in a population-based study in Hong Kong, 27% of participants were found to have MASLD, while 4% had advanced liver fibrosis.[28] As the disease is generally asymptomatic until decompensation takes place, many people present for the first time with complications of cirrhosis. A simple and clear assessment and referral pathway is needed to ensure that patients with severe liver disease are referred to specialist care, while those with less severe disease remain in primary care, where they are best managed. In this context, patients with T2DM represent an important target group for detection of advanced liver fibrosis.[11,29] The majority of patients with T2DM has SLD, and a substantial proportion of them has advanced liver fibrosis.[30] T2DM has been recognized as an independent risk factor for MASH and for advanced liver fibrosis.[17] Recent guidelines recommend using simple fibrosis score (e.g., fibrosis-4 index [FIB4]) as an initial test to screen for advanced liver fibrosis.[11,31,32] The FIB4 has very good negative predictive value for advanced liver fibrosis, but its positive predictive value is suboptimal.[33] Therefore, patients with elevated FIB4 should undergo a second test (e.g., liver stiffness measurement [LSM]) for further risk stratification (see section on 'Compensated advanced chronic liver disease and clinically significant portal hypertension' below). The cut-off to prompt referral to specialist care may depend on available resources and local practice in terms of the defined roles of primary and specialist care providers (Fig. 1).[11,34]

LIFESTYLE INTERVENTION IS THE CORNERSTONE IN THE MANAGEMENT OF MASLD

Calorie restriction and increased physical activity with resulting weight loss can lead to significant improvements in MASLD. A study on patients with biopsy-proven MASH demonstrated that this could result in resolution of MASH and improvement in liver fibrosis in up to 90% and 45% of patients, respectively.[35] Another
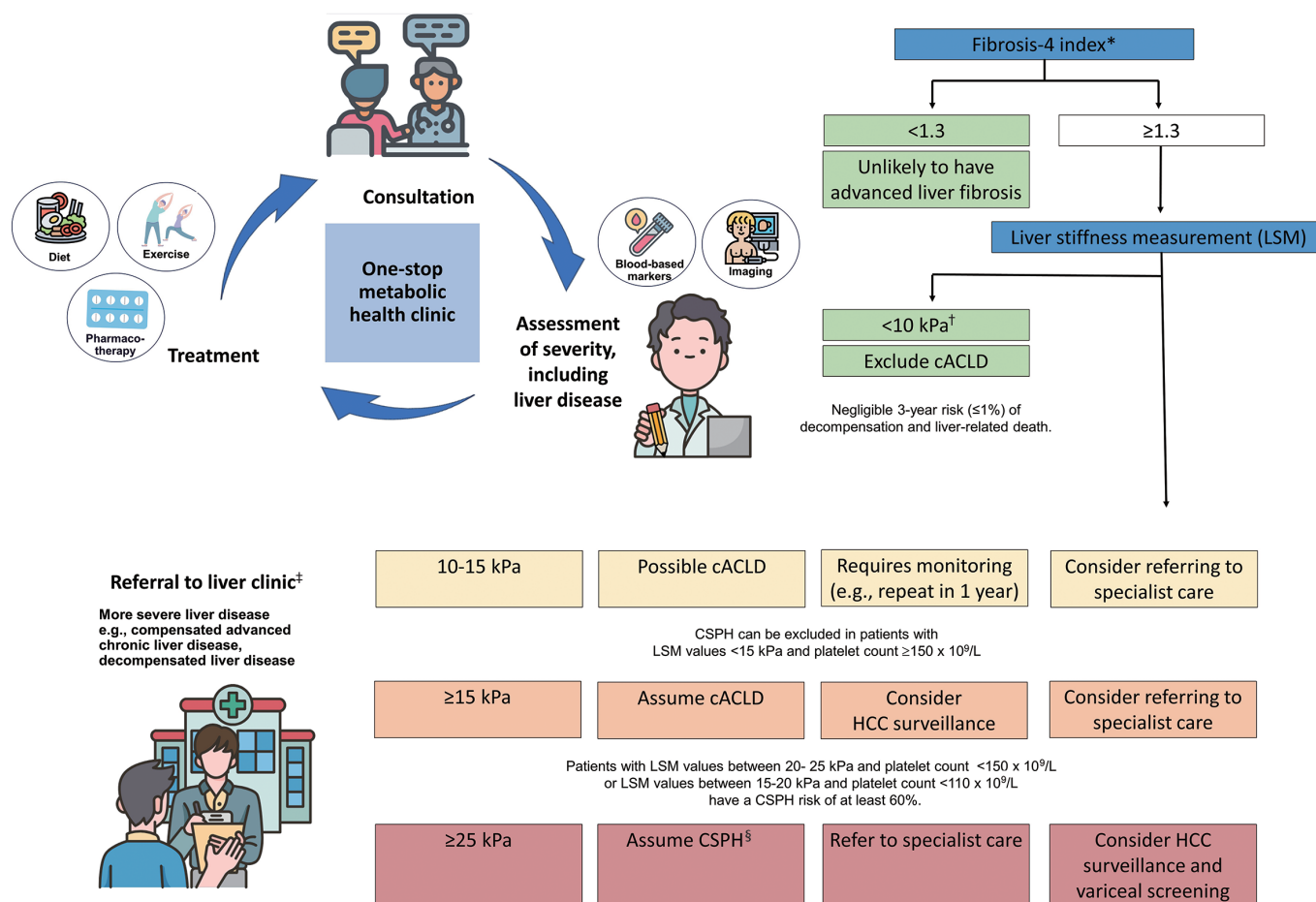
Figure 1. A simple and clear assessment and referral pathway is essential in streamlining the management of patients with metabolic dysfunction-associated steatotic liver disease, and this depends on available resources and local practice in terms of the defined role between primary and specialist care providers.[11,92] *For patients ≥65 years old, fibrosis-4 index cut-off 2.0 (instead of 1.3) may be used to improve specificity[34]; †Sensitivity and negative predictive value >90%; ‡Patients should be considered for referral to specialist care if they have persistently elevated serum aminotransferase level and/or if the cause of elevated serum aminotransferase level is uncertain; §Specificity and positive predictive value >90%. cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma.

study showed that lifestyle intervention could result in resolution of SLD in up to 97% of patients.[36] The APASL guidelines recommend gradual weight loss (up to 1 kg/wk) through a hypocaloric diet (with 500 to 1,000 kcal deficit) and physical activity (30 min/day of moderate intensity exercise for at least 5 day/week or a total of at least 150 min/wk, or at least 20 min/day of vigorous intensity exercise for at least 3 day/wk or a total of at least 75 min/wk) in the management of MASLD. Lifestyle intervention should be emphasized at all levels of patient care with the goal of improvements in both MASLD and the cardiometabolic and overall health of the individual patient. Weight loss can lead to improvements in blood pressure and glycemic and lipid profiles and reduction in CVD risk, among other benefits.[37] There is currently no U.S. Food and Drug Admin-

istration (FDA)-approved pharmacological therapy for MASH. However, some commercially available medications may be helpful, including pioglitazone,[38,39] glucagon-like peptide-1 receptor agonist (GLP1 RA), and sodium glucose co-transporter-2 (SGLT2) inhibitor (see section on 'MASLD and anti-hyperglycemic drugs').

CARDIOVASCULAR DISEASE RISK REDUCTION

As mentioned above, CVD is the leading cause of death in patients with MASLD.[40] A recent 2022 American Heart Association (AHA) Scientific Statement recognizes that MASLD is an often-unappreciated independent risk factor for atherosclerotic cardiovascular

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Table 2. Cardiovascular disease risk factors and treatment targets in patients with metabolic dysfunction-associated steatotic liver disease[40,43-50]

Risk factor	Optimal target	Preferred pharmacotherapeutic agent	Comments
LDL cholesterol	Moderate or intermediate risk* (diabetes alone): <100 mg/dL (<2.6 mmol/L) Higher risk (diabetes+multiple other ASCVD risk factors): <70 mg/dL (<1.8 mmol/L) High risk (established ASCVD): <55 mg/dL (<1.4 mmol/L)[†]	1st line: Statin at an appropriate dose/intensity for risk category Moderate intensity: ≥30% decrease from baseline e.g., simvastatin 20–40 mg,[43,44] atorvastatin 10–20 mg, rosuvastatin 5–10 mg, pravastatin 40–80 mg, lovastatin 40 mg, pitavastatin 2–4 mg High intensity: ≥50% decrease from baseline, e.g., rosuvastatin 20–40 mg, atorvastatin 40–80 mg 2nd line: Ezetimibe or PCSK9i can be added if the target is not achieved on maximal tolerated statin dose.	Safe and may be used if serum aminotransferase level is <3× upper limit of normal. All patients at moderate or high risk must start statin regardless of baseline LDL cholesterol level.
Triglycerides[44]	<150 mg/dL (<1.7 mmol/L)	Intensify lifestyle modification and optimize glycemic control	Fibrates do not improve cardiovascular outcomes.
BP	Treat if BP ≥140/90 mmHg in all patients Treat if BP ≥130/80 mmHg in diabetes or ASCVD risk ≥10% Aim for BP 120–129/70–79 mmHg	RAS blockade preferred if albuminuria present or patient has IHD or heart failure.	For elderly patients (≥65 years) who are nursing home residents with high burden of comorbidity and limited life expectancy, treatment decision should be based on patient preference and team-based assessment of risk vs. benefit.
BMI and waist circumference	Ethnicity- and gender-specific targets BMI: <23 kg/m² for Asians and <25 kg/m² for Caucasians Waist circumference: Asian, <80 cm (<85 cm in Korea)[48] for female, <90 cm for male; Caucasian, <80 cm for female, <94 cm for male Weight loss ≥5%	Lifestyle modification. Adjunctive GLP1 RA with proven cardiovascular benefit if BMI ≥27 kg/m² with comorbidities or BMI ≥30 kg/m² without comorbidities	Weight loss ≥5% can lower HbA1c and BP and improve lipid profile. Use of GLP1 RA has cardiorenal benefits in patients with diabetes. Bariatric surgery results in sustained weight loss, improves liver histology, and reduces cardiovascular events.
HbA1c	<6.5%[‡50]	SGLT2 inhibitor preferred in patients with CVD/heart failure/CKD. GLP1 RA preferred in patients with CVD/albuminuria.	Pioglitazone improves liver histology in MASLD, lowers glucose, and improves cardiovascular outcomes, but demonstrates safety concerns e.g., heart failure and side effects such as weight gain/edema. SGLT2 inhibitor improves liver fat content and may improve histology in MASLD. GLP1 RA improves liver fat content and histology in MASLD.

*CVD risk calculated using the American College of Cardiology/American Heart Association ASCVD risk calculator (Risk Estimator Plus), a tool to estimate 10-year risk of a first ASCVD event based on the Pooled Cohort Equations (available online at tools.acc.org/ASCVD-Risk-Estimator-Plus): <5%, low risk; 5% to <7.5%, borderline risk; 7.5% to <20%, moderate/intermediate risk; and ≥20%, high risk; [†]American Diabetes Association (ADA) 2023 guidelines recommend a target LDL <55 mg/dL (<1.4 mmol/L) in patients with diabetes and established ASCVD; however, the American Heart Association 2018 guidelines recommend a target LDL <70 mg/dL (<1.8 mmol/L) in this group of patients; [‡]HbA1c target should be individualized as recommended by the ADA.
LDL, low-density lipoprotein; ASCVD, atherosclerotic cardiovascular disease; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; BP, blood pressure; RAS, renin-angiotensin system; IHD, ischemic heart disease; BMI, body mass index; GLP1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycosylated hemoglobin; SGLT2, sodium glucose co-transporter-2; CVD, cardiovascular disease; CKD, chronic kidney disease; MASLD, metabolic dysfunction-associated steatotic liver disease.

disease (ASCVD).[41] Increased risk of cardiovascular events in patients with MASLD is partially mediated by the strong associations with T2DM and abdominal adiposity. Other proposed mechanisms include increased insulin resistance, pro-inflammatory mediators, pro-atherogenic dyslipidemia, oxidative stress, and hepatokines.[42] Weight loss is considered a clinically important target with a positive impact on both MASLD and CVD risk factors (i.e., blood pressure, glucose, and lipid levels).[43] In addition to lifestyle interventions (i.e., diet, physical activity, weight management, and smoking cessation),

a wide range of proven pharmacological agents is available for CVD risk reduction.[44] Treatment targets of CVD risk factors and the recommended pharmacological agents are outlined in Table 2.[40,43-50]

Statins are the first-line therapy to reduce CVD risk by lowering low-density lipoprotein (LDL) cholesterol and reducing high-risk atherosclerotic plaques.[45] Statins have been under-utilized in patients with MASLD due to concern of drug-induced liver injury, although they are safe and recommended for both primary and secondary prevention of CVD with robust evidence of reduction in

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all-cause mortality and cancer mortality in MASLD.[42,44,45,51,52] Experimental and epidemiological data indicate that statins could potentially prevent development or progression of HCC, a known complication of MASLD.[40,42] Broadly speaking, the decision on statin therapy should be based on (1) whether therapy is for primary or secondary prevention of ASCVD and (2) estimation of the patient's CVD risk. While several risk estimators have been developed, the AHA recommends the use of the Pooled Cohort Equations, which calculate 10-year CVD risk.[44,45] The AHA algorithms provide guidance on not only when to initiate statins, but also the tailoring of intensity (i.e., type and dose) of statin therapy for various at-risk populations. Achieving optimal outcomes based on efficacy data requires (1) aiming for a target LDL cholesterol level or a percentage reduction in LDL cholesterol level from baseline and (2) using a minimum pre-defined dose of a statin with proven improvement in cardiovascular outcome.[44,45] The combination of LDL and triglyceride-rich very LDL is more atherogenic than either fraction alone.[45] Therefore, it is recommended that triglyceride level be maintained < 150 mg/dL (< 1.7 mmol/L). Statin therapy can lower both LDL and triglyceride levels; however, the use of fibrates in combination with statins to reduce CVD risk is not recommended.[44] Combination treatment of ezetimibe with statin can further decrease LDL and triglyceride levels compared to statin monotherapy and has stronger cardiovascular protective effects in high-risk patients with T2DM.[53,54]

Lowering blood pressure is also vital to reduce CVD risk. The preferred agents with proven cardiovascular benefits are drugs that block the renin-angiotensin system.[44,46] Reducing glycosylated hemoglobin (HbA1c) alone can modestly reduce cardiovascular risk in patients with T2DM, although its benefits are more evident for microvascular complications.[44] While HbA1c targets should be individualized, especially in the elderly and those with advanced comorbidities where risk of hypoglycemia is greater, a general target advocated by the American Diabetes Association is HbA1c < 7% without significant hypoglycemia. Current guidelines recommend the use of SGLT2 inhibitor and GLP1 RA that can reduce cardiorenal risk in patients with T2DM and established or high-risk ASCVD, heart failure, and/or chronic kidney disease.[44] While SGLT2 inhibitors are approved for use in those without diabetes but with ischemic heart disease or heart failure, GLP1 RAs are currently only FDA approved for use in patients with diabetes or obesity. Aspirin is essential for secondary prevention of ASCVD and may be considered for primary prevention in those at high risk of ASCVD.[44] Aspirin has even been implicated in improved liver histology in patients with MASLD.[42] However, the risk of gastrointestinal bleeding should be discussed as part of a shared decision-making process in the primary prevention group, especially those > 70 years old who are at higher risk of bleeding or anemia due to renal disease and complications of liver disease (e.g., portal hypertension).[44]

MASLD AND ANTI-HYPERGLYCEMIC DRUGS

To date, there are no FDA-approved drugs for the treatment of MASLD and MASH.[55,56] Among people with T2DM and MASH, current treatment recommendations are focused on the amelioration of (1) cardiometabolic risk factors (glycemia, blood pressure, lipids, and body weight) and (2) steatohepatitis, especially if there is clinically significant fibrosis (stage ≥ F2).[55,57,58] Although a liver biopsy is the gold standard to diagnose and stage the severity of liver fibrosis, it is invasive and may not be acceptable or feasible to certain people. Hence, pharmacological therapy can be considered based on (1) elevated FIB4 > 1.3, (2) elevated serum aminotransferase level, (3) imaging such as transient elastography and magnetic resonance elastography, and/or (4) plasma biomarkers for liver fibrosis such as the enhanced liver fibrosis test.[55,58,59]

Among people with T2DM, prediabetes, or obesity, pioglitazone and GLP1 RAs are the two anti-hyperglycemic drugs that have proven efficacy and safety to reverse MASH.[55,58] Pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist, reduces insulin resistance by improving lipid storage/redistribution and glucose utilization.[57] It was the first anti-hyperglycemic drug to show efficacy in an early randomized clinical trial (RCT) involving 55 people with prediabetes/T2DM and biopsy-proven MASH.[60] In a single-center study involving 101 people with prediabetes/T2DM and biopsy-proven MASH, after a mean follow-up of 36 months, 58% of those treated with pioglitazone 45 mg daily had a reduction of at least two points in NAFLD Activity Score, while 51% reported resolution of MASH (treatment difference: 41% and 32% vs. placebo, respectively).[38] Despite a modest weight gain, pioglitazone was as-

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sociated with sustained improvements in liver fibrosis score, insulin resistance, and hepatic triglyceride contents.[38] In a meta-analysis of eight RCTs involving 516 people with biopsy-proven MASH, pioglitazone was associated with 1.6 to 3.2 odds of improved liver fibrosis and MASH resolution.[61] However, pioglitazone may be associated with adverse effects including heart failure, fracture, and bladder cancer.[55]

Given the robust benefits in glycemia, body weight, and other cardiometabolic risk factors, GLP1 RAs have emerged as the key pillars for managing people with T2DM and/or obesity.[62] In a phase 2 RCT involving 52 people with body mass index (BMI) ≥ 25 kg/m^2 and biopsy-proven MASH, injectable liraglutide (1.8 mg daily) was significantly associated with a relative risk of 4.3 for resolution of MASH compared with placebo.[63] Another phase 2 RCT compared the efficacy and safety of injectable semaglutide at 0.1, 0.2, and 0.4 mg daily (equivalent to 2.4 mg weekly) among 320 people with BMI ≥ 25 kg/m^2 and biopsy-proven MASH.[64] The mean percentage of total body weight loss was 13% in the 0.4 mg group, compared with 1% in the placebo group.[64] Resolution of MASH was reported in 40% in the 0.1 mg group, 36% in the 0.2 mg group, and 59% in the 0.4 mg group compared with 17% in the placebo group ($P < 0.001$ for semaglutide 0.4 mg vs. placebo).[64] Among people with T2DM and/or obesity, a novel GLP1/glucose-dependent insulinotropic polypeptide receptor agonists (i.e., tirzepatide)[65] showed superior metabolic efficacy with improved serum aminotransferase level and liver fibrosis score,[66] although more evidence of the changes in liver histological features is needed.[67]

SGLT2 inhibitors, which have proven cardiorenal benefits,[62] can be used as adjunctive pharmacological therapy among people with T2DM and MASLD. This is due to improvements in cardiometabolic risk factors and inflammation with reduced hepatic triglyceride contents and serum aminotransferase level.[56,68-70] Although there are significant benefits in improving hepatic steatosis assessed by magnetic resonance imaging techniques and non-invasive biomarkers, histological evaluations of liver biopsy after treatment with SGLT2 inhibitors are yet to be reported.[56] Given the lack of efficacy data, metformin, dipeptidyl peptidase-4 inhibitors, alpha-glucosidase inhibitors, and insulin are not recommended for the treatment of MASLD. However, these anti-hyperglycemic drugs can be tailored for hyperglycemia among people with T2DM and MASLD. A summary of the effects of anti-hyperglycemic drugs on MASLD can be found in Table 3.[55,56,62]

MANAGEMENT OF DIABETES AND OTHER METABOLIC COMORBIDITIES IN CIRRHOSIS

The management of T2DM patients with liver cirrhosis has become an increasingly common scenario with the global increase of obesity, diabetes, and MASLD.[71,72] There is a clear unmet need in this area, as patients in this population have been rarely studied. Data on glucose monitoring and targets, as well as the use of anti-hyperglycemic drugs in liver cirrhosis, remain sparse. Although diabetes can be diagnosed by conventional criteria of fasting plasma glucose (FPG), 2-hour post prandial glucose after a 75 g oral glucose tolerance test (OGTT), or HbA1c, the accuracy of these methods in liver cirrhosis differs.[73,74] The OGTT outperforms the FPG and HbA1c in terms of accuracy in diagnosing new onset diabetes in

Table 3. Effects of anti-hyperglycemic drugs on metabolic dysfunction-associated steatotic liver disease[55,56,62]

	Liver parameters				Cardiorenal-metabolic parameters	
	Serum aminotransferase	Liver fat	Liver fibrosis	MASH resolution	Body weight	Cardiorenal benefits
Pioglitazone	↓	↓	↓	Yes	↑	↔
GLP1 RAs	↓	↓	↓	Yes	↓	Yes
GLP1/GIP RAs	↓	↓	Unknown	Unknown	↓	Unknown
SGLT2 inhibitors	↓	↓	Unknown	Unknown	↓	Yes
Insulin	↓	↓	Unknown	Unknown	↑	↔
Metformin	↔	↔	↔	↔	↔	↔
DPP-4 inhibitors	↔	↔	↔	↔	↔	↔

MASH, metabolic dysfunction-associated steatohepatitis; GLP1 RA, glucagon-like peptide-1 receptor agonist; GIP RA, glucose-dependent insulinotropic polypeptide receptor agonist; SGLT2, sodium glucose co-transporter-2; DPP-4, dipeptidyl peptidase-4.

liver cirrhosis.[74] The standard measure of glucose control using HbA1c needs to be used with caution in liver cirrhosis.[72] HbA1c does not correlate well with continuous glucose monitoring in patients with decompensated cirrhosis due to changes in erythrocyte turnover, hemolysis caused by splenomegaly, impaired erythropoiesis due to bone marrow suppression, and repeated blood transfusions.[75] Other parameters such as fructosamine or glycated albumin may also be less accurate because of hypoalbuminemia. The use of serial monitoring of capillary blood glucose or continuous glucose monitoring methods or flash glucose monitoring are better options to accurately assess glucose control in the setting of decompensated cirrhosis.[75-77]

The presence of diabetes and poor glucose control is linked to higher risk of decompensation (e.g., hepatic encephalopathy, spontaneous bacterial peritonitis, and variceal bleeding), development of HCC, and reduced survival in patients with liver cirrhosis.[78,79] In those with compensated cirrhosis, glycemic targets should be the same as in those without cirrhosis. In decompensated cirrhosis, complications and survival are primarily liver-related; therefore, glycemic targets can be less stringent to prevent hypoglycemia or other undesirable complications from anti-hyperglycemic drugs. To date,

there is no evidence for exact measures of glucose targets, but the general consensus is that this needs to be individualized. Commonly used anti-hyperglycemic drugs and their benefits, risks, and safety in liver cirrhosis are summarized in Table 4.[61,72,80-86] Most anti-hyperglycemic drugs are contraindicated or need to be used with caution in decompensated cirrhosis. Insulin is the primary treatment of choice in decompensated cirrhosis; however, since insulin is metabolized by hepatic insulinase, the dose may need to be reduced and analogue insulins are preferred to avoid hypoglycemia.[72,84-86] Decreased insulin clearance, hyperinsulinemia due to portal circulation stunting in addition to decreased glycogen storage and inadequate gluconeogenesis increases the risk of hypoglycemia. A pre-meal glucose of 100 to 200 mg/dL (5.5 to 11.0 mmol/L) is considered acceptable for those on insulin therapy.[72]

As patients with liver cirrhosis develop ascites, their blood pressure often drops. Mineralocorticoid receptor antagonists remain a mainstay of therapy, and loop diuretics may be added if required. Impaired liver function may lead to elevated concentrations of some beta blockers and calcium channel blockers, so doses may need to be reduced.[87-89] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are usually avoided in decompensated

Table 4. Anti-hyperglycemic drugs and considerations in patients with liver cirrhosis[56,61,72,80-86]

Agent	Main site of elimination	Benefits	Major concerns	Compensated cirrhosis, Child-Pugh A	Decompensated cirrhosis, Child-Pugh B	Decompensated cirrhosis, Child-Pugh C
Metformin	Kidney (dose according to renal function)	Possibly reduce HCC risk	Metabolic acidosis	Safe	Contraindicated	Contraindicated
Sulphonylureas (only second and third generations)	Kidney/protein-bound	-	Hypoglycemia	Safe	Contraindicated	Contraindicated
Glinides*	Liver	-	Hypoglycemia	Caution	Caution	Contraindicated
DPP-4 inhibitors[†]	Kidney	No hypoglycemia risk	Lack of efficacy	Safe	Safe	Contraindicated
SGLT2-inhibitors	Liver (small amount by the kidney)	No hypoglycemia risk, benefit in MASLD	Dehydration, hypotension	Safe	Safe	Contraindicated
GLP1 RAs (human GLP1-based), e.g., liraglutide, dulaglutide, and semaglutide	Degraded by DPP-4 enzyme	No hypoglycemia risk, benefit in MASLD	Excessive weight loss/malnutrition	Safe	Safe	Contraindicated
GLP1 RAs (exendin based), e.g., lixisenatide and exenatide	Kidney	No hypoglycemia risk	Excessive weight loss/malnutrition	Safe	Contraindicated	Contraindicated
Acarbose	Gastrointestinal tract	No hypoglycemia risk	Lack of efficacy	Safe	Safe	Contraindicated
Pioglitazone	Liver	Benefits NASH without cirrhosis	Fluid retention	Caution	Contraindicated	Contraindicated
Insulin (insulin analogues preferred)	Liver	Safe in all degrees of liver cirrhosis	Hypoglycemia	Safe	Safe	Safe

*Repaglinide and [†]Vildagliptin are contraindicated in cirrhosis.
HCC, hepatocellular carcinoma; DPP-4, dipeptidyl peptidase-4; SGLT2, sodium glucose co-transporter-2; MASLD, metabolic dysfunction-associated steatotic liver disease; GLP1 RA, glucagon-like peptide-1 receptor agonist; NASH, non-alcoholic steatohepatitis.

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cirrhosis as they may further reduce effective arterial volume and renal perfusion.[90] Statins are safe in compensated cirrhosis but generally not recommended in decompensated cirrhosis as it is unlikely that there will be benefit from statin at this stage, and there is risk of accumulation of high serum level due to impaired metabolism.[91]

COMPENSATED ADVANCED CHRONIC LIVER DISEASE AND CLINICALLY SIGNIFICANT PORTAL HYPERTENSION

With increasing utility of both liver biopsy and LSM using vibration-controlled transient elastography (LSM-VCTE), more patients are being diagnosed with advanced liver fibrosis and early cirrhosis. These patients have severe liver disease but are asymptomatic. The term cACLD has been used to describe this group of patients.[92] Even though these patients do not manifest clinical decompensation of liver disease, they are at risk of liver-related events, such as index decompensation (ascites or variceal bleed) and HCC.[92] It is important to identify these patients so that timely intervention can be administered to attenuate or even reverse disease progression and reduce liver-related events. Patients with LSM-VCTE < 10 kPa are unlikely to have cACLD, with a negligible risk of adverse clinical outcomes, while those with LSM-VCTE > 15 kPa can be assumed to have cACLD (Fig. 1).[34,92,93]

Patients with more advanced liver fibrosis can develop CSPH, albeit without any symptomatic manifestation. (1) One such sequalae of CSPH is gastroesophageal varices that require obliteration and initiation of non-selective beta-blocker (NSBB) (i.e., varices needing treatment [VNT]) to prevent bleeding and index decompensation. CSPH is confidently ruled out (> 90% sensitivity and negative predictive value) if LSM-VCTE is ≤ 15 kPa and platelet count is ≥ 150 × 10⁹/L; in patients with MASLD, cACLD, and BMI < 30 kg/m², LSM-VCTE ≥ 25 kPa is sufficient to identify CSPH (specificity and positive predictive value > 90%).[92] Based on the landmark ANTICIPATE study, patients with LSM values between 20 and 25 kPa and platelet count < 150 × 10⁹/L or LSM-VCTE values between 15 and 20 kPa and platelet count < 110 × 10⁹/L have a CSPH risk of at least 60%.[94] However, when the similar cut-off value of LSM-VCTE used in CSPH was applied to patients with BMI ≥ 30 kg/m², the specificity and positive predictive values were

only 62.8%,[94] which implies an overestimation of CSPH in these patients. Hence, a new model (ANTICIPATE-NASH model) to predict CSPH with better accuracy for MASLD patients with BMI ≥ 30 kg/m² (which incorporates BMI, LSM-VCTE, and platelet count) has been proposed but requires further validation.[94]

The current recommendation is that MASLD patients with cACLD do not require variceal screening via endoscopy if LSM-VCTE is < 20 kPa and platelet count is > 150 × 10⁹/L,[92] where the risk of missing VNT is not more than 5%. LSM-VCTE and platelet count should be monitored annually to initiate variceal surveillance if LSM-VCTE increases to ≥ 20 kPa or platelet count decreases below 150 × 10⁹/L.[92] An effective strategy to prevent decompensation in patients with CSPH is to initiate treatment with NSBBs (e.g., propranolol, nadolol, or carvedilol). Studies have shown that patients with CSPH and on NSBB have a significantly lower risk of index decompensation,[95,96] and this effect is more profound with carvedilol, as it has intrinsic anti-alpha adrenergic vasodilatory effects that provide a greater portal-pressure-reducing effect.[92,96] Furthermore, patients who are on NSBB for prevention of decompensation do not need a screening endoscopy for detection of varices since the result will not change management.[92,97]

Liver cirrhosis is a known risk factor for HCC. Surveillance with 6-monthly ultrasound examination of the liver with or without serum alpha-fetoprotein level is recommended by all major guidelines. A meta-analysis that compared the nature of MASLD-related HCC to HCC due to other etiologies reported that a higher percentage of MASLD-HCC patients were non-cirrhotic (38.5% vs. 14.6%).[98] This finding led to a change in recommendation of HCC surveillance, where MASLD patients with advanced fibrosis in EASL guidelines[99] or ≥ F3 fibrosis with LSM-VCTE ≥ 16.1 kPa in American Gastroenterological Association guidelines[100] may be considered for HCC surveillance. Other than in advanced fibrosis, certain factors in MASLD patients (such as older age, male, obesity, diabetes mellitus, and patatin-like phospholipase domain-containing 3 gene) have been reported to increase the risk of HCC among non-cirrhotic MASLD patients.[99-101] Hence, an individualized risk assessment should determine the need for HCC surveillance to improve detection of HCC among non-cirrhotic MASLD patients, but further validation is required.

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SARCOPENIA AND MASLD

Sarcopenia is characterized by the loss of muscle mass and muscle strength. In the past few decades, sarcopenia has been described as common among the geriatric population and patients with severe medical illness, including cancer and even liver cirrhosis.[102] Of late, there is a growing interest in studies on the association between sarcopenia and MASLD. Notably, MASLD and sarcopenia share similar pathophysiology, especially insulin resistance, physical inactivity, and obesity.[103] Sarcopenic obesity is an independent risk factor for MASLD. The risk for MASLD was higher than the presence of obesity only. Similarly, sarcopenia in addition to visceral fat obesity and myosteatosis were significantly associated with MASLD among individuals without obesity.[104] In contrast, patients with MASLD were demonstrated to be at increased risk of sarcopenia in a longitudinal study. They had a higher rate of muscle mass loss compared to those without MASLD over 5 years.[105] Sarcopenia was also more prevalent among patients with MASH compared to patients with MASLD without MASH and controls (35.0% vs. 17.9% vs. 8.7%, $P < 0.001$).[106] In addition, patients with MASLD and sarcopenia were more likely to have significant and advanced liver fibrosis.[106,107] Sarcopenia is a strong predictor of mortality and morbidity for MASLD, MASH, and cirrhosis.[108,109] Several tools are available to evaluate muscle mass and muscle strength for sarcopenia. The SARC-F questionnaire is a brief self-reported test to detect persons at risk for adverse outcomes from sarcopenia. The screening test encompasses five components: strength, walking with assistance, rising from a chair, climbing stairs, and falling.[110] Muscle strength of upper limbs and lower body strength can be assessed using the grip strength measurements and chair stand test, respectively. Skeletal muscle mass can be evaluated by dual-energy X-ray absorptiometry and bioelectrical impedance analysis methods, while computed tomography or magnetic resonance imaging can examine both muscle quantity and quality. The severity of sarcopenia can be measured by evaluating the physical performance of patients, e.g., short physical performance battery, timed-up and go, and 400-m walk tests.[102]

The main aim of treatment for MASLD is lifestyle modification to achieve weight reduction of 7% to 10%, in particular in those with overweight/obesity. Such a degree of weight loss can lead to MASH resolution and histological improvement (see section on 'Lifestyle intervention is the cornerstone in the management of MASLD').[5] In contrast, skeletal muscle loss is one of the cardinal features of sarcopenia. Weight loss may lead to further muscle loss if energy restriction is carried out without exercise. The recommended treatment for sarcopenia is resistance exercise and optimizing nutrition intake.[111] Increased physical activity and healthy diet have been associated with lower risk of sarcopenia and MASLD and could even reduce the risk of significant liver fibrosis.[107,112] Adequate protein intake is advised for patients with sarcopenia, but protein supplementation alone without resistance exercise is ineffective in improving muscle mass and strength.[113] Conversely, oral branch-chain amino acid supplementation is particularly beneficial for patients with hepatic encephalopathy and advanced cirrhosis.[114] The European Society for Clinical Nutrition and Metabolism recommends the Mediterranean diet for MASH to improve insulin resistance and steatosis.[114] Meanwhile, the Mediterranean diet has been shown to have a positive effect on muscle mass and function in sarcopenia.[115] Vitamin D supplementation has been reported to improve insulin resistance in MASLD.[116] Likewise, vitamin D combined with protein has been shown to improve muscle strength in patients compared to a control with sarcopenia in meta-analysis.[117,118]

CONCLUSION

The increased understanding of MASLD has brought about a name change to the disease, creating greater awareness. MASLD is the most common cause of chronic liver disease and is the leading cause of liver-related morbidity and mortality. There is no doubt that all stakeholders must be involved in tackling the public health threat of obesity and obesity-related diseases, including MASLD. A simple and clear assessment and referral pathway is essential to ensure that patients with more severe MASLD are identified and referred to specialist care, while patients with less severe disease remain in primary care, where they are best managed. This can serve as a foundation as we refine the shared role between primary and specialist care providers in management of this multi-faceted condition, considering available resources and local practice. Further studies are needed to optimize the management of patients with different disease severity to prevent progression and improve outcomes.

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CONFLICTS OF INTEREST

Wah-Kheong Chan has served as a consultant or advisory board member for Roche, Abbvie, Boehringer Ingelheim, and Novo Nordisk and as a speaker for Viatris and Hisky Medical. Lee-Ling Lim reports receiving grants and/or honoraria for consultancy or lectures from Abbott, AstraZeneca, Boehringer Ingelheim, Novartis, Novo Nordisk, Roche, Sanofi, Servier, and Zuellig Pharma. Jeyakantha Ratnasingam has served as a consultant or advisory board member for Novo Nordisk and a speaker for Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Zuellig Pharma, Servier, Roche, Merck, and Abbott. The other authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Study concept and design: WKC; acquisition of data: WKC, KHC, RBR, LLL, JR, and SRV; analysis and interpretation of data: WKC, KHC, RBR, LLL, JR, and SRV; drafting of the manuscript: WKC, KHC, RBR, LLL, JR, and SRV; and critical revision of the manuscript: WKC, KHC, RBR, LLL, JR, and SRV.

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