eGastroenterology

Key takeaways from the updated multidisciplinary European MASLD guidelines

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To cite: Horn P, Tacke F. Key takeaways from the updated multidisciplinary European MASLD guidelines. *eGastroenterology* 2025;**3**:e100196. doi:10.1136/egastro-2025-100196

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/egastro-2025-100196).

Received 10 February 2025
Accepted 19 May 2025

Linked

► https://doi.org/10.1136/egastro-2024-100115
► https://doi.org/10.1136/egastro-2023-100019
► https://doi.org/10.1136/egastro-2024-100114
► https://doi.org/10.1136/egastro-2023-100005

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ABSTRACT

The new European clinical practice guidelines from three scientific societies (European Association for the Study of the Liver, European Association for the Study of Diabetes and European Association for the Study of Obesity) on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) provide detailed recommendations on diagnosis, risk stratification, monitoring strategies, treatment and prevention. Lifestyle interventions (eg, weight reduction, Mediterranean diet, exercise, alcohol abstinence) and the treatment of cardiometabolic risk factors continue to be the mainstay of treatment and prevention of the disease. Incretin mimetics that are approved to treat obesity and/or type 2 diabetes such as semaglutide and tirzepatide have benefits for ameliorating metabolic dysfunction-associated steatohepatitis (MASH). Novel developments include adapted strategies for screening (case finding) using non-invasive tests (NITs) with a focus on detecting fibrosis or cirrhosis, risk-adjusted monitoring of MASLD by NITs as well as the recommendation to use, if locally approved, the thyroid hormone receptor β-agonist resmetirom in patients with non-cirrhotic MASH fibrosis (≥F2 stage).

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as 'non-alcoholic fatty liver disease' (NAFLD) or 'metabolic dysfunction-associated fatty liver disease' (MAFLD), is now the leading cause of chronic liver disease across the globe and is associated with high cardiometabolic and hepatic morbidity and mortality. The updated European guidelines on the management of MASLD, jointly published by the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO), synthetise the developments of recent years and provide comprehensive recommendations on the diagnosis, treatment and monitoring of MASLD.[1]

NEW DISEASE DEFINITION AND RISK FACTORS

A new disease definition was introduced in 2023, with the terms MASLD and MASH (metabolic dysfunction-associated steatohepatitis) replacing the terms NAFLD and NASH (non-alcoholic fatty liver disease and steatohepatitis, respectively).[2] MASLD and MASH are now included under the umbrella term 'steatotic liver disease' (SLD) alongside alcohol-associated liver diseases (ALD), other causes of fatty liver and cryptogenic SLD (figure 1). MASLD is now positively defined by evidence of liver steatosis, for example, by imaging, and the presence of at least one cardiometabolic risk factor (see table 1), while MASH is referring to the progressive form of the disease that is characterised by the presence of ballooning and inflammation in histology. Importantly, retrospective analyses of existing cohort studies suggest a high degree of overlap between the NAFLD and MASLD populations.[3] Therefore, the guidelines continue to build on evidence generated under the NAFLD definition.

The pathophysiology of MASLD is tightly linked to overnutrition, obesity and insulin resistance, which result in increased fat deposition in hepatocytes and subsequent inflammation caused by oxidative stress and lipotoxicity.[4] Consequently, the presence of cardiometabolic risk factors (table 1), foremost the presence of type 2 diabetes (T2D) and obesity, poses the greatest risk increase for the development and progression of MASLD.[5] Additional risk factors for a progressive disease include genetic risk loci (eg, *PNPLA3* p.I148M, *TM6SF2* p.E167K), age>50 years, male sex, postmenopausal status or presence of polycystic ovary syndrome in women, obstructive sleep apnoea or the presence of multiple cardiometabolic risk factors.[5 6]

MASLD WITH MODERATE ALCOHOL CONSUMPTION (METALD)

Alcohol consumption has been identified as an important modifier of disease progression in MASLD. While potential beneficial liver effects of low alcohol consumption had been discussed in the past, current evidence strongly suggests a synergistic hepatotoxic effect of alcohol in the

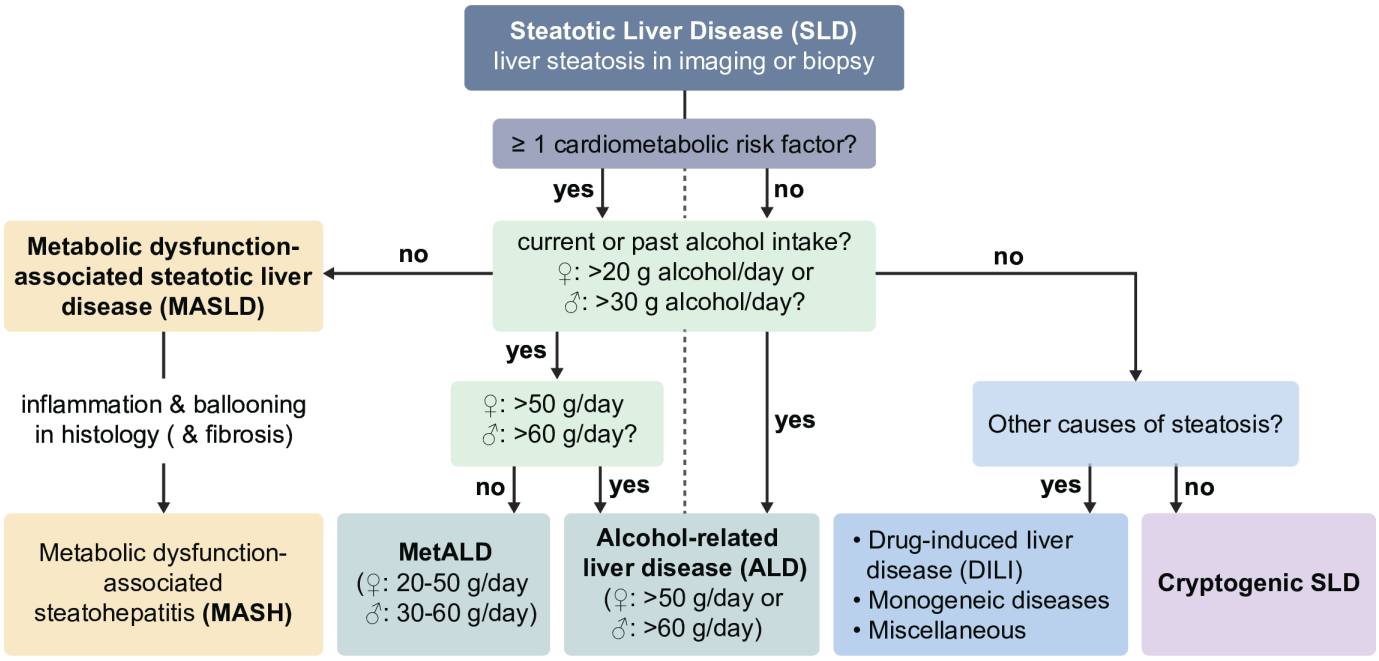

Figure 1 Classification of SLDs (reproduced with modifications from Tacke *et al*[1] under the CC BY-NC license (https://creativecommons.org/licenses/by-nc/4.0/)). MetALD, MASLD with moderate (increased) alcohol consumption.

presence of cardiometabolic risk factors and that any amount of alcohol intake is harmful in the presence of MASLD.[7]

In order to account for the impact of alcohol consumption in the context of SLD and the commonly observed mixed aetiologies in clinical practice, the term MASLD with moderate alcohol consumption (MetALD) (ie, ♀: 20–50 g/day, ♂: 30–60 g/day) has been incorporated into the new classification of SLD.[2 8] Importantly, MetALD represents a distinct entity of SLD, and existing evidence and recommendations for MASLD cannot be simply extended to the MetALD population. Individuals with MetALD tend to be younger, are predominantly male and have higher prevalence of arterial hypertension and hypertriglyceridemia but lower prevalence of T2D.[9 10] Meta-analysis of existing cohort studies suggests that MetALD is associated with higher risk of cardiovascular disease and incidence of cardiovascular

Table 1 Cardiometabolic risk factors defining MASLD (reproduced and modified from Tacke *et al*[1] under the CC BY-NC license (https://creativecommons.org/licenses/by-nc/4.0/))

Metabolic risk factor	Adult criteria	Paediatric criteria
Overweight or obesity	BMI ≥25 kg/m^2 (≥23 kg/m^2 in people of Asian ethnicity)	BMI ≥85th percentile for age/sex (BMI z score ≥+1) (or ethnicity adjusted equivalent)
	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)	Waist circumference ≥95th percentile (or ethnicity adjusted equivalent)
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 hour 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 hour plasma glucose during OGTT ≥11.1 mmol/L (≥200 mg/dL) OR Treatment for type 2 diabetes	Same as adult criteria
Plasma triglycerides	≥1.7 mmol/L or lipid-lowering treatment	Plasma triglycerides age <10 years, ≥1.15 mmol/L or age ≥10 years, ≥1.70 mmol/L OR lipid-lowering treatment
HDL cholesterol	≤1.0 mmol/L in men and ≤1.3 mmol/L in women or lipid-lowering treatment	Plasma HDL cholesterol ≤1.0 mmol/L or lipid-lowering treatment
BP	≥130/85 mmHg or treatment for hypertension	BP age <13 years, BP ≥95th percentile or ≥130/80 mmHg (whichever is lower) OR age ≥13 years or 130/85 mmHg OR specific antihypertensive drug treatment

BMI, body mass index; BP, blood pressure; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease; OGTT, oral glucose tolerance test.

and cancer-related mortality.[11] Notably, alcohol use might be a significant contributor to the mortality observed in individuals with SLD. In a population-based cohort study, the presence of MetALD but not MASLD without alcohol consumption was associated with excess mortality in individuals with cardiometabolic risk factors,[12] and people with MetALD have a higher risk of developing liver-related events and mortality compared with MASLD.[8 12] Furthermore, the validity of non-invasive tests (NITs) (discussed in more detail below) for the detection of liver fibrosis in people with MetALD is currently under investigation. Recent cross-sectional data from Korea indicate that the fibrosis-4 (FIB-4) index is performing well as an initial screening tool with similar performance metrics for MASLD and MetALD,[13] but more research is needed to evaluate the validity of existing clinical care pathways, including the application of transient elastography, for risk stratification in MetALD.

Importantly, there is a grey area in the diagnosis of MASLD, MetALD and ALD, which can largely be attributed to the difficulties in reliably assessing alcohol use. Alcohol use is generally under-reported in clinical practice and clinical trial settings.[14] Consequently, there is a great risk of misclassifying SLD. A recent registry-based cohort study found that up to 17% of individuals diagnosed with MASLD (ie, without significant alcohol use) were diagnosed with ALD or alcohol use disorder before or after their MASLD diagnosis.[15] Therefore, the EASL–EASD–EASO MASLD guidelines recommend documenting past and present alcohol intake in all individuals with SLD, using validated instruments of specific biomarkers when available, and discouraging alcohol use in individuals with SLD.[1]

SCREENING AND MONITORING

Mostly owing to the high prevalence of low-risk MASLD and cost-effectiveness concerns, screening for SLD in the general population is not recommended. However, screening for the presence of MASLD with significant fibrosis should be performed in the following constellations of high-risk MASLD: presence of (1) T2D, (2) abdominal obesity and ≥1 additional cardiometabolic risk factor or (3) repeatedly abnormal liver enzymes. The guideline recommends a multistage procedure using NITs to assess the risk of MASLD with advanced fibrosis (figure 2). In the case of an intermediate risk (ie, FIB-4: 1.3–2.67), the guidelines propose two alternative strategies. The first strategy (option A), which is in line with other international guidelines on MASLD, is to proceed to further risk stratification with a second-line test such as transient elastography. The second strategy (option B) is intended for situations where second-line testing is not

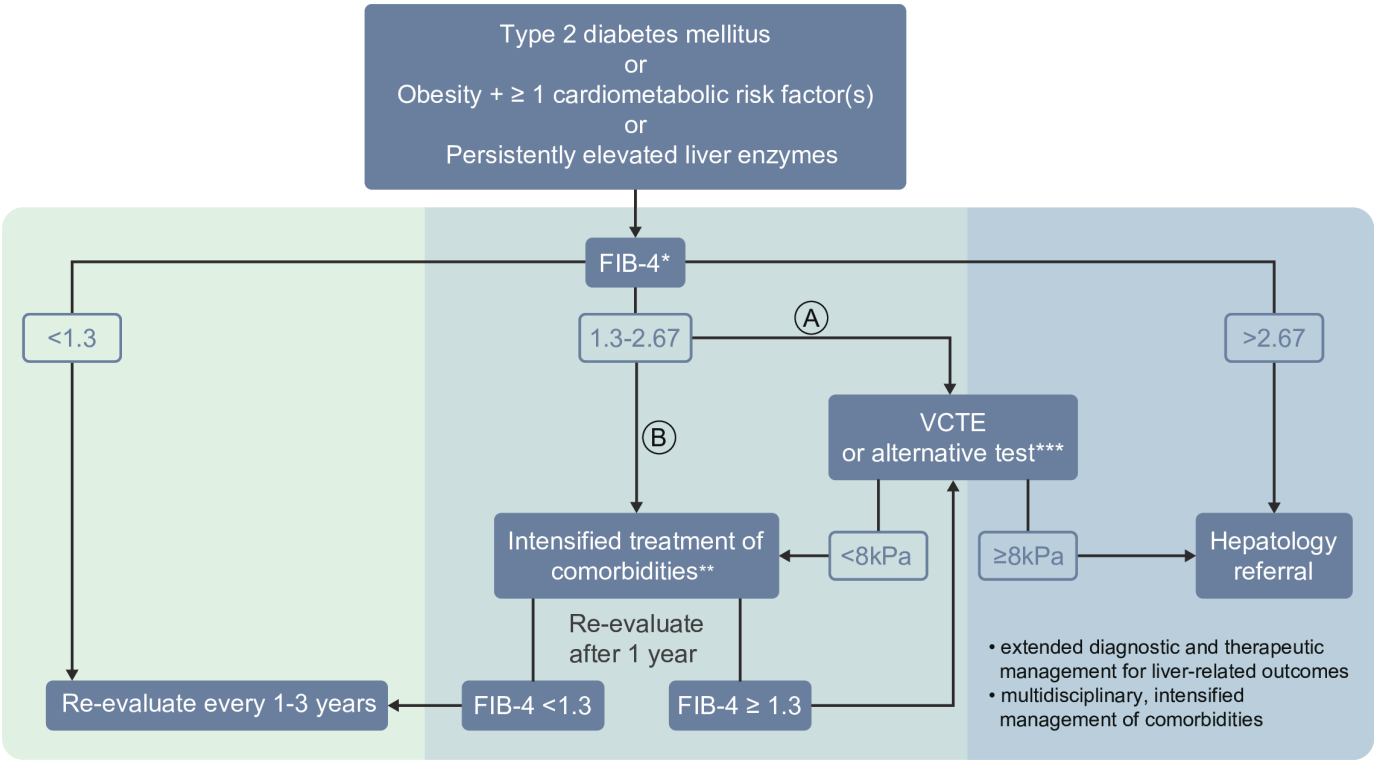

Figure 2 Algorithm for non-invasive risk stratification of individuals with suspected MASLD (reproduced with modifications from Tacke *et al*[1] under the CC BY-NC license (https://creativecommons.org/licenses/by-nc/4.0/)). *FIB-4 cut-offs are valid for age≤65 years (for >65 years, the lower FIB-4 cut-off is 2.0). **For example, lifestyle interventions, treatment of comorbidities (eg, glucagon-like protein-1 receptor antagonist) and bariatric surgery. ***Alternative test, for example, magnetic resonance elastography (MRE), shear wave elastography (SWE) or enhanced liver fibrosis (ELF) test, with their respective cut-offs. Ⓐ and Ⓑ are options, depending on the disease course, clinical context and local resources. FIB-4, fibrosis-4 index; MASLD, metabolic dysfunction-associated steatotic liver disease; VCTE, vibration-controlled transient elastography.

easily available and where people with suspected MASLD did not yet receive adequate treatment of their cardiometabolic comorbidities. In such circumstances, people with suspected MASLD may undergo an intensified treatment of cardiometabolic comorbidities and be re-tested with FIB-4 after 1 year to evaluate potential improvements in liver disease. If FIB-4 does not improve below the low-risk cut-off, risk stratification should proceed according to the first strategy.

Non-invasive methods for the assessment of liver fibrosis are increasingly moving into the focus of risk stratification and monitoring of MASLD.[16] A variety of tools are available, which can be divided into serum-based biomarkers and scores (suitable for ruling out advanced liver fibrosis) and imaging-based measurements of liver stiffness (more suitable for predicting advanced liver fibrosis).[16] In addition, these tests are becoming increasingly important for assessing fibrosis progression, as well as the prognostic assessment of overall survival and the risk of liver-related events.[17 18] NITs may also be useful in monitoring the response to treatment, but more data are needed before a firm recommendation can be made. While liver biopsy may still be required in select cases to rule out concomitant liver disease, non-invasive methods can often replace liver biopsy for staging of fibrosis.

The development of hepatocellular carcinoma (HCC) is an important and frequent complication of MASH. In accordance with current HCC guidelines, screening by means of biannual ultrasound examinations, possibly in combination with assessment of the tumour marker alpha-fetoprotein, is recommended for individuals with MASLD-associated liver cirrhosis.[19] MASLD with advanced fibrosis (stage F3) may warrant inclusion in an HCC screening programme if there is an increased risk of HCC, for example, in the presence of T2D and obesity, advanced age, alcohol or smoking.

Due to the increased risk for the occurrence of cardiometabolic risk factors and corresponding comorbidities,[20–22] people with MASLD should be examined for the presence of T2D, dyslipidaemia, hypertension and chronic kidney disease at the time of diagnosis and at regular intervals thereafter and treated accordingly. Patients with MASLD are also encouraged to participate in respective cancer screening and early detection programmes due to the increased risk of extrahepatic cancers.[23]

PREVENTION

A Mediterranean diet, avoidance of highly processed and sugar-sweetened foods and drinks and an active lifestyle are associated with a lower incidence of MASLD and HCC.[24 25] Policy measures such as restricting advertising of unhealthy foods, subsidising healthy foods, promoting food reformulation by industry and improving food and health literacy in the population through labelling of nutritional content could be a way to reduce the prevalence of obesity, T2D and MASLD in the population.[26]

NON-PHARMACOLOGICAL MANAGEMENT

Obesity and insulin resistance are the most prominent risk factors for the development and progression of MASLD. Consequently, weight reduction through dietary interventions and increased physical activity remains the mainstay of treatment for MASLD. Weight reduction can lead to improvement in transaminases, as well as reductions in liver fat, inflammatory activity and fibrosis.[27–29] The European guidelines recommend aiming for a weight reduction of at least 5% of the initial weight to reduce liver fat, 5–10% to reduce inflammatory activity and more than 10% to reduce liver fibrosis in individuals with overweight.[30] The non-pharmacological measures for weight reduction are listed in detail in figure 3. Normal-weight individuals with MASLD also present with metabolic alterations, including insulin resistance and visceral obesity. A weight reduction of 3–5% in individuals with normal weight can lead to remission of MASLD and therefore is recommended.[31] In these cases, the same principles of lifestyle interventions as for individuals with obesity apply.

The basis of lifestyle interventions is calorie restriction with a high-quality diet, which can be modelled on the Mediterranean diet. The Mediterranean diet has a high proportion of olive oil, vegetables, fruit, nuts and seeds, wholemeal products, fish and seafood. Highly processed foods (ie, no/little highly processed foods), (sugar-)sweetened drinks, alcohol and nicotine should be avoided. Physical activity can support weight reduction and has potential positive effects on liver disease regardless of body weight loss.[32] More than 150 min/week of moderate activity or 75 min/week of intensive activity appear to be optimal,[1] although the benefits of specific forms of exercise have not been studied in detail. Participation in structured weight loss and lifestyle intervention programmes appears to be particularly useful for patients with advanced liver disease. Ideally, lifestyle interventions should be managed by a multidisciplinary team, evaluated regularly and be cost-effective and affordable.

PHARMACOLOGICAL THERAPY

The high frequency of comorbid conditions in the spectrum of cardiometabolic risk factors often necessitates pharmacological interventions, for example, to treat diabetes and dyslipidaemia. Accumulating evidence suggests that adjustments of such pharmacological therapy can have positive effects on the progression of MASLD and consequently are an essential component in disease management. Depending on the stage of the disease and the presence of coexisting cardiometabolic disease conditions, glucagon-like peptide-1 (GLP1) receptor agonists and co-agonists, sodium glucose transporter 2 inhibitors (SGLT2i), metformin and statins should be prioritised for their respective indications. These drug classes are associated with reduced cardiovascular morbidity and mortality and can positively influence the disease activity of MASH and potentially reduce the risk of developing HCC.

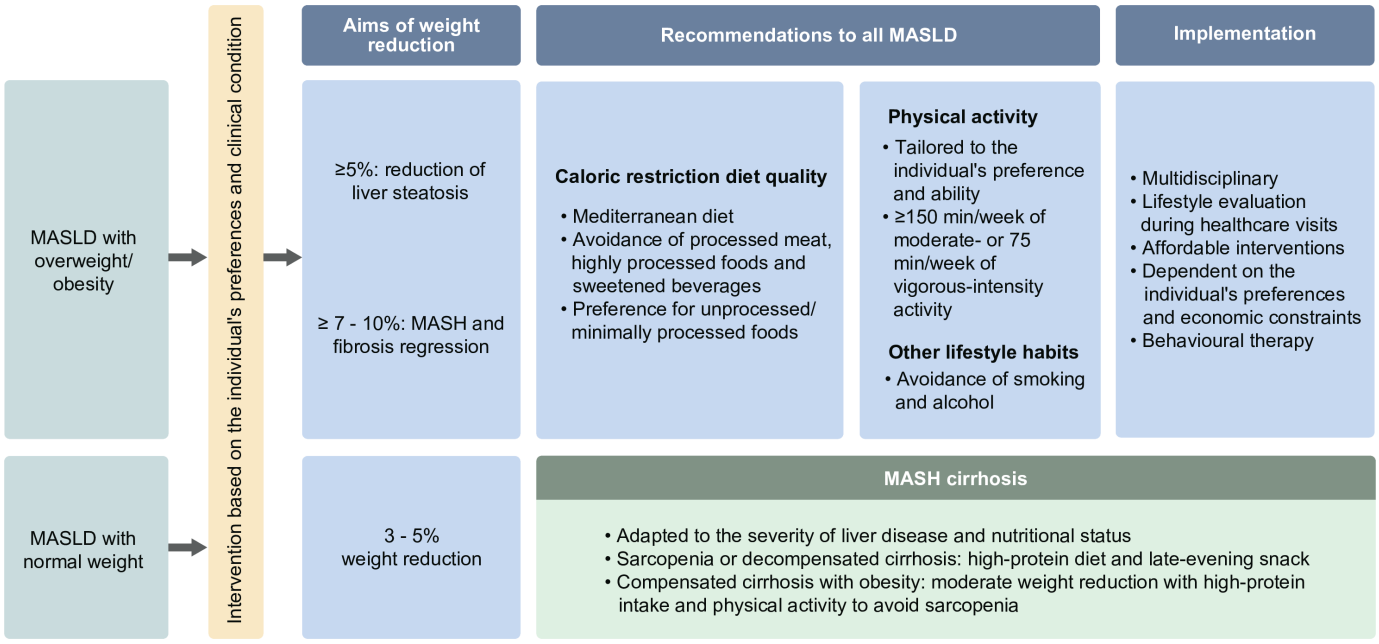

Figure 3 Recommendations for lifestyle interventions in individuals with MASLD (reproduced with modifications from Tacke *et al*[1] under the CC BY-NC license (https://creativecommons.org/licenses/by-nc/4.0/)). MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease.

Incretin mimetics are used for pharmacological weight reduction and for the treatment of T2D. Depending on the specific compound, they lead to a weight reduction of approximately 10–20% (over 1 year), are typically injected subcutaneously once a week and mainly have gastrointestinal side effects (nausea, vomiting, diarrhoea, constipation). They are the only drug class already approved (for obesity and T2D) outside of the USA with existing positive histological endpoint data on MASH. The two GLP1 receptor agonists liraglutide and semaglutide showed positive effects on the resolution of MASH in phase II studies,[33 34] and phase III data on MASH resolution and improvement in the degree of fibrosis compared with placebo after 72 weeks of treatment are available for semaglutide.[35] Positive data on MASH resolution and fibrosis reduction from phase II studies are also available for the GLP1 receptor co-agonists tirzepatide and survodutide.[36 37]

No histological outcome data are currently available for the use of SGLT2i, metformin or statins in people with MASLD. Still, positive effects on transaminases, liver fat and risk of hepatic decompensation or HCC argue for their use for their respective indications in MASLD: SGLT2i are used to treat T2D, heart failure and chronic kidney disease and some SGLT2i are effective in reducing liver fat and serum transaminases (eg, empagliflozin[38]); the use of metformin for the treatment of T2D is associated with higher transplant-free survival, fewer hepatic decompensations and a lower risk of HCC in patients with advanced, compensated MASH[39 40]; the use of statins for lipid lowering in compensated liver cirrhosis is associated with a lower rate of HCC[41]; and statin use is also associated with a lower risk of developing MASLD, MASH and liver fibrosis in population-based studies.[42]

Based on the positive results of the phase III MAESTRO-NASH study,[43] the Food and Drug Administration (FDA) has granted accelerated approval for the thyroid hormone receptor β-agonist resmetirom for the treatment of non-cirrhotic MASH with significant fibrosis (≥F2) in the USA. Subject to local approval and the specific label, resmetirom should therefore be considered for the treatment of individuals with non-cirrhotic MASH and significant fibrosis. Both liver biopsy and NITs can be considered for the selection of suitable patients.[1] Taken together with the promising data on other drug classes, such as incretin mimetics and co-agonists, we can expect an increasingly dynamic therapeutic landscape in the near future.

SURGICAL AND ENDOSCOPIC THERAPY

Bariatric/metabolic surgery is an additional treatment option for severe obesity and is currently the most effective treatment to achieve permanent (>2 years) weight reduction. In a randomised, controlled trial, gastric sleeve surgery or Roux-Y bypass led to a resolution of steatohepatitis without worsening fibrosis in 70% of participants after 1 year and to an improvement in fibrosis in a smaller proportion.[44] Furthermore, bariatric surgery can reduce the incidence of cardiovascular events in non-cirrhotic, fibrotic MASH.[45] Consequently, the current guidelines recommend considering bariatric surgery in adults with non-cirrhotic MASLD and an approved indication for bariatric surgery. In compensated cirrhosis, bariatric surgery should only be performed in experienced centres after a thorough risk-benefit assessment and by an experienced multidisciplinary team. Evidence is still lacking

to recommend endoscopic-bariatric procedures for the treatment of MASH.

MANAGEMENT OF END-STAGE MASLD AND MASH

Patients with MASH cirrhosis are at high risk of developing liver-related events. If decompensated liver cirrhosis or HCC is present, the indication for liver transplantation should always be considered.

The management of liver cirrhosis due to MASH does not fundamentally differ from other aetiologies. Still, the significantly increased cardiometabolic risk should always be integrated into disease management and risk assessment. Particularly in the context of liver transplantation, cardiometabolic risk factors should be carefully assessed and treated accordingly to improve outcomes after liver transplantation.

Individuals with cirrhosis and obesity may benefit from moderate weight reduction as this has been shown to reduce portal pressure and may prevent hepatic decompensation.[46 47] However, since liver cirrhosis is associated with an increased risk of malnutrition and sarcopenia, weight reduction should be carried out with caution and be adapted to the severity of liver disease, nutritional status and the presence of sarcopenia. Continuous moderate weight reduction with a moderately hypocaloric diet with adequate protein intake (>1.5 g/kg ideal body weight per day) and sufficient physical activity can help to maintain muscle mass.[48]

The presence of clinically significant portal hypertension (CSPH) is an important risk factor for hepatic decompensation including variceal bleeding. The BAVENO VII guidelines recommend the use of NITs where the combination of a liver stiffness measurement (LSM) <15 kPa and a platelet count≥150×10^9 may exclude CSPH and an LSM>25 kPa can be used to rule in CSPH.[49] However, readings of liver stiffness are confounded in obesity with a body mass index >30 kg/m² and can lead to false positive diagnoses of CSPH.[50] The ANTICIPATE-NASH model has been specifically developed for this situation and can provide guidance for estimating the risk of CSPH in individuals with obesity.[51]

CONCLUSION AND OUTLOOK

The extensive scientific efforts of recent decades to gain a better understanding of MASLD have led to a more solid evidence base and more detailed clinical recommendations that give us more certainty in managing MASLD. This applies both to the early detection and risk assessment of the disease (often without the need for liver biopsy), as well as treatment and monitoring. The optimal treatment of this complex disease requires interdisciplinary and interprofessional co-operation. In particular, the first specific drug authorisation gives us hope that we will have a broad spectrum of specific therapeutic measures at our disposal in the coming years. Nevertheless, further efforts should be made to establish effective prevention programmes and achieve a structural improvement in the care of this complex and diverse group of affected individuals.

Contributors PH and FT have written and revised the manuscript. FT is the guarantor of this work and accepts full responsibility for its integrity.

Funding PH's work was supported by a Digital Clinician Scientist fellowship from the Berlin Institute of Health. Work in the lab of FT has been funded by the German Research Foundation (DFG Ta434/8-1 and CRC1382, Project-ID 403224013).

Competing interests PH has received research funding from Novo Nordisk and MSD (funding to the institution). He has received speaking fees from Orphalan and travel support from Ipsen and Falk. FT's lab has received research funding from Gilead, Agomab, AstraZeneca and MSD (funding to the institution). He has received honoraria for consulting or lectures from AstraZeneca, Gilead, AbbVie, BMS, Boehringer, Ipsen, Madrigal, Falk, Inventiva, MSD, GSK, Orphalan, Pfizer, Novo Nordisk, Sanofi and Novartis. FT is an Associate Editor of *eGastroenterology*.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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