

PREVENTING THE PROGRESSION OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: EARLY RISK IDENTIFICATION AND STAGE- ADAPTED INTERVENTION

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide and represents an important target for preventive medicine. Although progression is heterogeneous, metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis identify patients at increasing risk of cirrhosis and liver-related complications. Fibrosis stage is the strongest predictor of liver-related outcomes, making early identification of individuals at risk of progression a major clinical objective. Type 2 diabetes, obesity and visceral adiposity, and multiple cardiometabolic risk factors define populations in whom systematic liver risk assessment is particularly relevant. Sequential non-invasive testing, beginning with the fibrosis-4 index (FIB-4) and followed, when indicated, by elastography or additional biomarkers, enables clinically relevant fibrosis to be detected before advanced liver disease becomes apparent. Prevention requires sustained weight reduction, physical activity, optimal cardiometabolic risk management and, in selected patients with non-cirrhotic MASH and significant fibrosis, targeted pharmacological therapy. Effective prevention therefore requires a shift from late-stage hepatology towards multidisciplinary, risk-based and stage-adapted disease modification.

Keywords: MASLD, MASH, fibrosis, prevention, early diagnosis.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), the term introduced to replace non-alcoholic fatty liver disease within the new steatotic liver disease nomenclature, emphasizes the close relationship between hepatic steatosis and cardiometabolic dysfunction [1]. MASLD has become the most prevalent chronic liver disease worldwide, paralleling the increasing prevalence of obesity, type 2 diabetes (T2D) and metabolic syndrome [2,3].

The clinical spectrum ranges from steatosis without significant inflammation or fibrosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive fibrosis, cirrhosis and hepatocellular carcinoma. Progression is neither uniform nor inevitable. Paired-biopsy studies estimate progression by one fibrosis stage over approximately 14 years in simple steatosis compared with approximately 7 years in steatohepatitis [4].

This heterogeneity is central to prevention. Given the high prevalence of MASLD, the goal is

not to refer every individual with steatosis to specialist hepatology care, but to identify early those with a meaningful risk of progression.

Fibrosis stage is particularly important because long-term observational studies consistently associate increasing fibrosis severity with liver-related morbidity and mortality [5,6]. Preventing advanced fibrosis therefore provides a direct link between early diagnosis and long-term outcome.

This review discusses prevention across the MASLD continuum, focusing on early recognition of high-risk individuals, non-invasive fibrosis assessment, modification of cardiometabolic drivers and stage-adapted therapeutic intervention.

MASLD PROGRESSION: WHY TIME MATTERS

MASLD develops along a continuum, but the opportunity for disease modification is greatest before advanced fibrosis develops. Steatosis and early inflammatory disease may remain reversible for years,

whereas established advanced fibrosis or cirrhosis shifts therapeutic objectives towards preventing decompensation and other liver-related complications. In routine practice, however, early MASLD is usually asymptomatic and often remains within primary care, diabetes or obesity services, while hepatology referral may occur only after elevated liver stiffness, thrombocytopenia, imaging signs of chronic liver disease or overt complications. Waiting for conventional manifestations of advanced disease therefore reduces the opportunity for prevention. Detection should shift towards earlier stages without resorting to indiscriminate population screening.

Current guidelines favour targeted case finding in groups with an increased probability of clinically relevant fibrosis. Individuals with T2D, obesity associated with additional metabolic risk factors, persistently abnormal liver enzymes or radiological evidence of steatosis are particularly relevant populations [7,8].

The central preventive question is therefore not simply whether steatosis is present, but whether clinically relevant fibrosis is present or likely to develop.

WHO IS AT RISK OF PROGRESSION?

Progression reflects interaction between non-modifiable susceptibility and modifiable disease drivers. Age, sex, ethnicity and genetic variants such as PNPLA3 and TM6SF2 contribute to interindividual variability but currently offer limited direct opportunities for intervention.

Major modifiable drivers include obesity, particularly visceral adiposity, insulin resistance, T2D, dyslipidaemia, poor diet and physical inactivity, which promote hepatic lipid accumulation, lipotoxicity, oxidative stress and inflammation. Alcohol exposure may further amplify injury even when metabolic dysfunction predominates.

Among these factors, T2D is particularly important. The relationship between MASLD and T2D is bidirectional: insulin resistance promotes steatosis and hepatic injury, whereas MASLD contributes to worsening metabolic dysfunction. Patients with T2D have substantially increased prevalence of MASH and advanced fibrosis. In addition, individual participant-level data show that diabetes is associated with increased risks of hepatic decompensation and hepatocellular carcinoma in patients with steatotic liver disease [9].

Obesity also requires assessment beyond body mass index alone. Visceral and ectopic fat may be more closely related to hepatic and systemic

metabolic dysfunction, while clinically relevant MASLD can also occur in non-obese individuals with genetic susceptibility or adverse fat distribution.

Metabolic risk factors should therefore be viewed not merely as accompanying comorbidities, but as biologically linked drivers of disease progression and therapeutic targets.

EARLY DIAGNOSIS SHOULD MEAN EARLY FIBROSIS RISK ASSESSMENT

Because MASLD is so prevalent, early diagnosis requires risk stratification. Liver enzymes alone are inadequate because significant fibrosis may occur despite normal aminotransferases, while imaging-confirmed steatosis provides limited prognostic information.

Non-invasive tests (NITs) allow fibrosis risk to be assessed before advanced disease becomes clinically apparent. European and American recommendations support a sequential approach, beginning with a simple blood-based test and reserving specialised investigations for indeterminate or elevated risk [7,8].

The fibrosis-4 index (FIB-4), based on age, AST, ALT and platelet count, is well suited to first-line assessment because it uses routine variables and can be implemented outside hepatology.

A FIB-4 value below 1.3 generally identifies patients with a low probability of advanced fibrosis. In individuals older than 65 years, a threshold of 2.0 is more appropriate because age reduces specificity [10]. FIB-4 also performs less reliably in younger adults and should be interpreted in clinical context. Intermediate or high values require further stratification rather than being considered diagnostic. Vibration-controlled transient elastography (VCTE) is the most widely applicable second-line imaging test; the enhanced liver fibrosis (ELF) test is an alternative where available, while magnetic resonance elastography offers high accuracy but more limited accessibility.

Recent international consensus recommendations continue to endorse FIB-4 followed by VCTE or ELF according to availability [11]. This approach is particularly useful for prevention because the first step can be performed in primary care, diabetology, endocrinology or other metabolic clinics rather than requiring specialist referral.

Sequential NIT pathways thus reduce unnecessary referrals among low-risk patients while allowing unsuspected significant or advanced

fibrosis to be identified before clinical decompensation.

MODIFYING THE METABOLIC DRIVERS OF DISEASE

Risk identification must be followed by intervention, and lifestyle modification remains the foundation of MASLD management across disease stages.

Weight reduction has the strongest evidence for improving hepatic disease activity, with a dose-response relationship between weight loss and improvement in steatosis, steatohepatitis and fibrosis. In biopsy-proven NASH, weight loss of at least 10% was associated with particularly high rates of steatohepatitis resolution and fibrosis regression [12].

More modest, sustained weight reduction is also clinically valuable; the practical goal should therefore be durable rather than uniformly prescribed weight loss.

Physical activity improves insulin sensitivity, cardiovascular fitness and hepatic fat even beyond its effect on body weight. Dietary advice should emphasise sustainable energy reduction and diet quality rather than short-term restriction.

Long-term implementation remains difficult, and lifestyle measures alone are often insufficient in severe obesity or persistent metabolic dysfunction. Modern obesity pharmacotherapy and, in selected patients, bariatric procedures have therefore expanded options for targeting the metabolic driver of MASLD.

MASLD AS A SYSTEMIC DISEASE: ONE INTERVENTION, MULTIPLE OUTCOMES

MASLD is part of a broader cardiovascular-renal-metabolic network in which insulin resistance, visceral adiposity, chronic inflammation, atherogenic dyslipidemia and endothelial dysfunction contribute simultaneously to liver, cardiovascular and renal disease [13].

Accordingly, cardiovascular risk management remains essential regardless of liver disease severity. Hypertension and dyslipidemia should be treated according to standard indications, and statins should not be withheld because MASLD is present.

Glycemic control should also be optimized. GLP-1 receptor agonists and dual incretin-based therapies can reduce weight and improve glycemic and cardiovascular outcomes, while sodium-glucose cotransporter-2 inhibitors provide established cardiovascular and renal benefits in T2D and may reduce hepatic fat, although they are not specific antifibrotic therapies.

Thus, weight reduction and metabolic control should be understood as systemic disease modification rather than simply treatment of fatty liver.

WHEN PREVENTION REQUIRES LIVER-TARGETED PHARMACOTHERAPY

Once significant fibrosis is present, preventing progression to cirrhosis becomes an important form of secondary prevention.

Resmetirom, an oral selective thyroid hormone receptor- β agonist, demonstrated both MASH resolution without fibrosis worsening and fibrosis improvement without MASH worsening in the phase 3 MAESTRO-NASH trial [14].

In the phase 3 ESSENCE trial, once-weekly semaglutide 2.4 mg likewise increased both MASH resolution without fibrosis worsening and fibrosis improvement without MASH worsening in patients with F2–F3 fibrosis [15].

Targeted pharmacological treatment is therefore now available for selected patients with non-cirrhotic MASH and significant fibrosis. Updated international and AASLD recommendations integrate NIT-based risk stratification with consideration of resmetirom or semaglutide in F2–F3 disease and emphasize individualization according to metabolic and hepatic phenotype [16,17].

Other agents remain investigational. Tirzepatide achieved high rates of MASH resolution and signals of fibrosis improvement in the phase 2 SYNERGY-NASH trial [18], while additional metabolic and antifibrotic agents remain under evaluation.

For prevention, the key implication is that increasingly effective therapy raises the clinical value of identifying significant fibrosis before cirrhosis develops.

Table 1

Opportunities for prevention across the MASLD continuum (MASLD = metabolic dysfunction-associated steatotic liver disease; FIB-4 = fibrosis-4 index; T2D = type 2 diabetes; MASH = metabolic dysfunction-associated steatohepatitis)

Clinical stage	Main risk	Preventive objective	Main clinical strategy
Metabolically at-risk individual without recognised liver disease	Unrecognised MASLD and fibrosis development	Identify individuals requiring liver risk assessment	Recognition of T2D, obesity/visceral adiposity and multiple metabolic risk factors; first-line FIB-4 when indicated
Steatosis / F0–F1	Progression to MASH and fibrosis	Reduce metabolic injury and prevent fibrosis development	Sustained weight reduction, physical activity, dietary intervention and optimal glycaemic, lipid and blood-pressure control
MASH with F2–F3 fibrosis	Progression to cirrhosis and liver-related events	Resolve disease activity and promote/maintain fibrosis regression	Intensive lifestyle and cardiometabolic management plus indication- and phenotype-adapted pharmacotherapy
Cirrhosis / F4	Decompensation, hepatocellular carcinoma and liver-related mortality	Prevent complications and preserve hepatic reserve	Cirrhosis-specific surveillance and care combined with continued metabolic and cardiovascular risk management

FROM STAGE-BASED TO PATIENT-TAILORED PREVENTION

Disease stage alone does not capture MASLD heterogeneity. Similar fibrosis stages may arise from different combinations of insulin resistance, adiposity, genetic susceptibility and inflammatory mechanisms, contributing to variable progression and treatment response [19].

Prevention is therefore likely to combine stage with phenotype.

In early disease, intervention may primarily target obesity and metabolic dysfunction. In F2–F3 disease with severe obesity or T2D, incretin-based therapy may address several drivers simultaneously, whereas a more liver-directed strategy may be appropriate when major metabolic treatment needs are absent.

Current recommendations do not support indiscriminate combination therapy, although sequential or combination strategies may become relevant as evidence develops. Recent practice guidance emphasises structured patient selection and treatment monitoring rather than a uniform algorithm [20].

Genetic profiling, advanced biomarkers, multi-omics and the gut-liver axis may ultimately refine risk stratification but currently remain supplementary to established clinical tools. Personalized prevention does not require sophisticated molecular testing before action can be taken; it begins with recognizing dominant

metabolic drivers, establishing fibrosis risk and matching intervention intensity to both.

HEPATOLOGY AT THE CORE OF MULTIDISCIPLINARY PREVENTION

The epidemiology of MASLD requires a multidisciplinary model of care with hepatology at its core. Most individuals at risk of progression are already interacting with the healthcare system, often in primary care, diabetes, obesity, cardiovascular or renal services.

Primary care can identify metabolic risk and initiate first-line fibrosis assessment; diabetology, endocrinology and obesity services manage populations with a high prevalence of significant fibrosis; cardiology and nephrology frequently encounter related manifestations of the same systemic disease.

Hepatologists remain central to second-line assessment, confirmation of disease severity, exclusion of alternative liver disease, treatment of significant fibrosis and management of cirrhosis. However, waiting for specialist referral before initiating risk assessment misses the main opportunity for early detection.

Multidisciplinary care should therefore be organized around a coordinated pathway in which hepatology provides specialist risk assessment and disease-specific management, while other disciplines contribute to early identification and

modification of the metabolic drivers of progression. This “shift-left” approach offers a realistic model for prevention: moving recognition and intervention earlier in the natural history of MASLD, while maintaining hepatology at the core of specialist risk assessment and disease-specific management.

CONCLUSIONS

MASLD is highly prevalent, but advanced liver disease is not inevitable. The preventive challenge is to identify, early in the disease course, those patients most likely to progress.

Fibrosis is the principal determinant of liver-related prognosis. Sequential non-invasive assessment beginning with FIB-4 and followed, when necessary, by VCTE, ELF or other validated tests enables clinically relevant fibrosis to be detected beyond specialist hepatology settings.

Prevention combines sustained lifestyle and metabolic intervention with targeted disease modification in selected patients with non-cirrhotic MASH and significant fibrosis, aiming to prevent progression to cirrhosis while improving extrahepatic outcomes.

Because MASLD is both heterogeneous and systemic, management should be increasingly stage- and phenotype-adapted and multidisciplinary.

Ultimately, success in modern hepatology should be measured not only by how advanced liver disease is treated, but also by how many high-risk patients are identified early enough to prevent it.

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