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REVIEW

OPEN

Epidemiology, screening, and co-management of type 2 diabetes mellitus and metabolic dysfunction–associated steatotic liver disease

Xiaolong Qi[1,2] | **Jie Li**[3] | **Cyrielle Caussy**[4,5] | **Gao-Jun Teng**[2,6] | **Rohit Loomba**[5,7]

[1]Department of Radiology, Center of Portal Hypertension, Zhongda Hospital, Medical School, Southeast University, Nurturing Center of Jiangsu Province for State Laboratory of AI Imaging and Interventional Radiology (Southeast University), Nanjing, China

[2]Basic Medicine Research and Innovation Center of Ministry of Education, Zhongda Hospital, Southeast University, Nanjing, China; State Key Laboratory of Digital Medical Engineering, Nanjing, China

[3]Department of Infectious Diseases, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China

[4]Faculté de Médecine Lyon Sud, Université Lyon 1, Hospices Civils de Lyon, Lyon, France

[5]MASLD Research Center, Division of Gastroenterology and Hepatology, University of California, San Diego, La Jolla, California, USA

[6]Department of Radiology, Center of Interventional Radiology and Vascular Surgery, Zhongda Hospital, Medical School, Southeast University, Nanjing, China

[7]School of Public Health, University of California, San Diego, La Jolla, California, USA

Correspondence
Xiaolong Qi, Department of Radiology, Liver Health Consortium in China (CHESS), Center of Portal Hypertension, Zhongda Hospital, Medical School, Southeast University, Nurturing Center of Jiangsu Province for State Laboratory of AI Imaging & Interventional Radiology (Southeast University) Nanjing, China.
Email: qixiaolong@vip.163.com

Abstract

Metabolic dysfunction–associated steatotic liver disease (MASLD), previously known as NAFLD, is increasingly recognized as a prevalent global burden. Type 2 diabetes mellitus (T2DM), another important metabolic disease, is considered a major contributor to the development of MASLD. MASLD and T2DM have a strong association with each other due to shared pathogenic mechanisms. The co-existence of the 2 diseases increases the risk of liver-related adverse outcomes and imposes a heavier burden on extrahepatic outcomes, representing a substantial public health issue. Effective assessment and management of T2DM combined with MASLD necessitate a multidisciplinary approach. The emergence of numerous RCTs has shed light on the treatment of T2DM combined with MASLD. This review uncovers the epidemiology of the intertwined T2DM and MASLD, offers insights into the evaluation of hepatic fibrosis in patients with T2DM, glucose monitoring in the MASLD population, and provides comprehensive co-management strategies for addressing both diseases.

Abbreviations: APRI, aspartate transaminase to platelet ratio index; BUDCA, berberine ursodeoxycholate; FIB-4, Fibrosis-4 index; FLI, fatty liver index; GLP-1RAs, glucagon-like peptide-1 receptor agonists; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance; IR, insulin resistance; LSM, liver stiffness measurement; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; NFS, NAFLD fibrosis score; NITs, noninvasive tests; PA, physical activity; PPAR, peroxisome proliferator-activated receptor; SGLT2i, sodium-glucose transporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

Xiaolong Qi and Jie Li contributed to this work equally.

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD), formerly named as NAFLD (Table 1), represents a range of pathological conditions, including simple steatosis, metabolic dysfunction–associated steatohepatitis (MASH), and progression to fibrosis, cirrhosis and even HCC. The global prevalence of NAFLD stands at about 25%,[4] with Asia reaching rates as high as 29.62%.[5] In 2020, NAFLD underwent a name change to metabolic dysfunction–associated fatty liver disease.[2] More recently, a new nomenclature for steatotic liver disease was introduced, with MASLD identified as a subtype.[6] Studies report a 99% overlap between cases of NAFLD and MASLD, and therefore, the term MASLD will be used in the manuscript.[7] The change in these nomenclatures over the past 4 years underscored the importance of metabolic risk factors, especially type 2 diabetes mellitus (T2DM). With ~529 million people affected by diabetes, T2DM represents the majority of cases.[8] The presence of T2DM adversely affects glucose and lipid metabolism, leading to multiple systemic disturbances and organ dysfunction. Extensive evidence has noticed the overlapping of MASLD and T2DM.[9] T2DM drives the progression of MASLD, developing hepatic and extrahepatic adverse outcomes at an accelerated pace.[10] Reciprocally, MASLD escalates the likelihood of T2DM onset[11] and has a detrimental effect on glucose metabolism among the T2DM population. In clinical realms, the co-existence of the 2 diseases necessitates timely assessment of liver disease progression in patients with T2DM, and screening for diabetes in patients with MASLD.[12] Weight loss is the backbone of the treatment of T2DM and MASLD. While sustained weight loss through lifestyle interventions may not always be sufficient, hypoglycemic medications, emerging therapeutic agents, and bariatric surgery hold promise for the treatment of these comorbid conditions.

SEARCH STRATEGY AND SELECTION CRITERIA

A comprehensive literature review was performed on PUBMED to identify pertinent full-text articles related to MASLD and T2DM over the past 2 decades. The search involved a meticulous exploration of articles utilizing keywords, including “non-alcoholic fatty liver disease”, “non-alcoholic steatohepatitis”, “NAFLD”, “NASH”, “metabolic dysfunction-associated fatty liver disease,” “metabolic-associated fatty liver disease,” “MAFLD”, “metabolic dysfunction-associated steatotic liver disease,” “metabolic dysfunction-associated steatohepatitis,” “MASLD,” “MASH,” “diabetes,” “type 2 diabetes mellitus” and “T2DM” in different combinations and with various synonyms. Each section of the search was tailored with specific keywords like “epidemiology,” “prevalence,” “incidence”, “adverse outcomes,” “decompensation,” “cardiovascular disease,” “non-invasive tests,” “FIB-4,” “APRI,” “NFS,” “life style intervention,” “diet,” and “exercise” to refine the results. A RCT published on PUBMED from inception to January 2024 and those registered on ClinicalTrials.gov without time limitations were included, provided they involved biopsy-proven patients with MASH with T2DM and reported intervention outcomes. Only publications in the English language were taken into consideration.

EPIDEMIOLOGY OF COMORBID T2DM AND MASLD

There is an increasing body of evidence that signals a rising intersection between T2DM and MASLD.[13] In 2019, Younossi ZM et al[14] reported that the estimated global prevalence of MASLD in individuals with T2DM was 55.48%. More recently, a meta-analysis involving 1,832,125 patients with T2DM suggested that this number has risen to 65.04%.[9] In the eastern and western countries, the proportion of MASLD in the T2DM population was 58.84% and 72.65%, respectively. Among countries, Turkey had the highest prevalence of

TABLE 1 The change of nomenclatures from NAFLD, MAFLD to MASLD

Nomenclatures	Definitions
NAFLD[1]	The presence of hepatic steatosis is detected by imaging or histology, with no other causes of hepatic fat accumulation.
NASH[1]	The presence of ≥ 5% hepatic steatosis and inflammation with hepatocyte injury, with or without any fibrosis.
Metabolic dysfunction–associated fatty liver disease (MAFLD)[2]	Hepatic steatosis is evaluated by imaging, blood biomarkers/scores, or liver histology combined with T2DM or overweight/obesity; if patients are diagnosed with hepatic steatosis with lean/normal weight, the diagnosis of MAFLD requires at least 2 metabolic risk abnormalities.
Metabolic dysfunction–associated steatotic liver disease (MASLD)[3]	The presence of hepatic steatosis is confirmed by imaging or liver biopsy concurrent with at least 1 cardiometabolic risk factor and no other discernible cause.

Abbreviation: T2DM, type 2 diabetes mellitus.

MASLD in patients with T2DM, reaching alarmingly 94.35%. In Croatia, Italy, Jordan, and Sweden, MASLD affected over 80% of patients with T2DM. Additionally, the prevalence of MASH in patients with T2DM with MASLD was 46.88%.[9] Data from the 2017–2018 National Health and Nutrition Examination Surveys determined that the prevalence of high-risk MASH ranged between 8.7% and 22.5% in the T2DM population, suggesting at least 2 million adults in the United States are affected.[15] Undoubtedly, T2DM is an important factor driving the progression of MASLD. Among patients with T2DM aged ≥ 50 years in the United States, 14% had developed advanced fibrosis and 5.9% had cirrhosis.[16] Globally, 35.54% of individuals with T2DM with MASLD demonstrated clinically significant fibrosis (F2-F4), while the percentage of advanced fibrosis (F3-F4) was 14.95%.[9]

As MASLD is considered a hepatic manifestation of a dysmetabolic state, it is closely associated with the development of T2DM. A multicenter, longitudinal study enrolled 178 biopsy-proven patients with MASLD. During a follow-up period of 5.6 ± 4.4 y, 17.1% of patients with significant fibrosis experienced new-onset diabetes, which was significantly higher compared to the proportion of 7% in patients with mild fibrosis. The presence of significant fibrosis was associated with a 2.95 times higher risk for the development of T2DM and was conferred as an independent predictor for T2DM.[17]

SHARED PATHOGENETIC MECHANISMS LINKING T2DM AND MASLD

The pathogenetic mechanisms of MASLD and T2DM are complicated and intricate. Insulin resistance (IR) has long been recognized as a pivotal factor for the development of the 2 diseases. Excessive deposition of hepatic diacylglycerol triggers the activation of protein kinase Cε, causing its translocation to the cell membrane, thereby hindering hepatic insulin signaling.[18] This impaired insulin signaling leads to decreased glycogen synthesis and increased gluconeogenesis, resulting in fluctuations in insulin and glucose levels. On the other hand, ectopic lipid accumulation in skeletal muscle contributes to muscle IR. Instead of glycogen synthesis, muscle exhibits a preference for de novo lipogenesis.[18] Besides, dysfunction of adipose tissue, characterized by decreased adiponectin levels, increased flux of long-chain fatty acids, and pro-inflammatory cytokines, further exacerbates systemic IR. Other factors, such as bile acids, dysbiosis,[19] and hepatokines,[20] have emerged as significant contributors to the progression of MASLD and T2DM. The 2 diseases intertwined closely, calling for heightened awareness and research into their interplay (Figure 1).

ADVERSE CLINICAL OUTCOMES OF T2DM COMBINED WITH MASLD

T2DM is an established risk factor for the faster progression of liver-related adverse events. An individual participant-level meta-analysis showed that patients with T2DM faced a 5-year risk of developing hepatic decompensation and HCC at 13.85% and 3.68%, respectively, which was substantially higher than patients without T2DM (3.95% and 0.44%, respectively).[10] Both baseline T2DM and glycated hemoglobin (HbA1c) were identified as independent predictors for the onset of hepatic decompensation and HCC.[10] Jarvis H et al[21] conducted an analysis of 12 observational studies involving ~22.8 million individuals who were either at

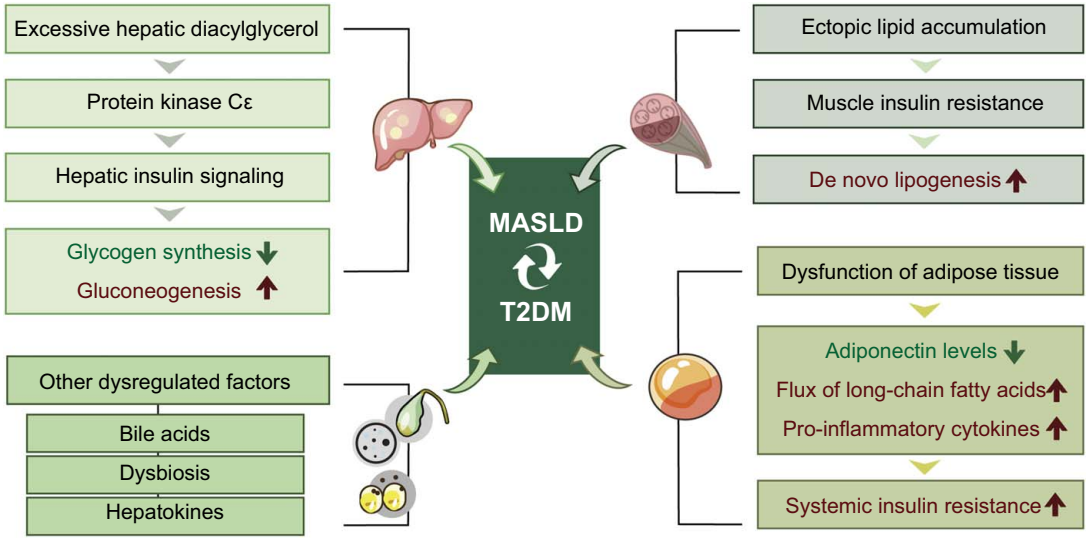

FIGURE 1 Shared pathological mechanism of T2DM and MASLD. Abbreviations: MASLD, metabolic dysfunction–associated steatotic liver disease; T2DM, type 2 diabetes mellitus.

risk of MASLD or already diagnosed with it. Following a median 10-year period, T2DM was proven to significantly increase the 2.25-fold risk of incident severe liver disease events, including cirrhosis, complications of cirrhosis, and liver-related death.[21]

It is critical to note that the overlap of MASLD and T2DM not only increases the likelihood of liver-related adverse outcomes but also amplifies the risk of extrahepatic adverse outcomes. CVD is the leading cause of mortality in the MASLD and T2DM population.[22] A nationwide, longitudinal cohort study conducted in Korea, incorporating over 500 thousand individuals with T2DM, showed that patients with T2DM and a fatty liver index (FLI) of $\geq$ 60 faced significantly higher 5-year absolute risks of myocardial infarction and ischemic stroke, with figures of 1.73 and 3.16, respectively.[23] In comparison, those without MASLD presented with lower corresponding risks of 1.29 for myocardial infarction and 0.65 for ischemic stroke. Notably, these risks increased with the severity of MASLD.[23] An analysis conducted by Park J et al[24] revealed that individuals newly diagnosed with T2DM who exhibited hepatic steatosis and/or advanced fibrosis were at a higher risk for myocardial infarction, stroke, heart failure, and all-cause mortality. Another longitudinal study found that after 6–8 years of follow-up, the progression of atherosclerosis was detected in 37.9% of patients with T2DM with steatosis and 48.6% of patients with both steatosis and fibrosis.[25] This percentage was considerably higher than the 34.3% observed in patients without steatosis.[25] A cohort study illustrated that every 1 kPa increase in liver stiffness measurement (LSM) corresponded to a 1.02-fold increase in the risk of cardiovascular mortality and a 1.04-fold risk of all-cause mortality in MASLD individuals with T2DM.[26] An LSM $>$ 9.6 kPa constituted a significant risk factor for both cardiovascular and all-cause mortality.[26] MASLD was also found to be associated with subclinical myocardial remodeling and dysfunction and cardiac arrhythmias in the T2DM population.[22] Moreover, patients co-existed with the 2 conditions harbored a higher risk of chronic microvascular diseases, especially CKD. In comparison to nondiabetic patients with MASLD and those without diabetes and MASLD, the diabetic MASLD population experienced a notable 1.14-fold and 1.82-fold increased risk of CKD, respectively.[27] MASLD-related advanced fibrosis had a higher risk of developing CKD, even after adjusting for confounding factors.[28] A wealth of evidence has firmly established that the combination of T2DM and MASLD escalated the risk of CVD, cerebrovascular disease, CKD, and all-cause mortality rate (Figure 2).

ASSESSMENT OF HEPATIC FIBROSIS AND GLYCEMIC CONTROL

Screening the progression of hepatic fibrosis in T2DM

Hepatic fibrosis is strongly associated with liver-related adverse outcomes and all-cause mortality,[29] leading to numerous studies focusing on assessing hepatic fibrosis in populations with T2DM. In clinical practice, noninvasive screening tools primarily include serum biomarkers or algorithms and imaging modalities. The most commonly employed noninvasive tests (NITs) are Fibrosis-4 index (FIB-4), the NAFLD fibrosis score (NFS), and aspartate transaminase to platelet ratio index (APRI). However, these NITs showed modest performance in the context of T2DM. A cross-sectional study involving 213 patients found that the AUC of FIB-4, APRI, and NFS for screening advanced fibrosis among the T2DM population was 0.85, 0.86, and 0.64, respectively, which were all inferior to the competency of N-terminal propeptide of type 3 collagen, a direct serum biomarker of fibrosis.[30] Another cohort study showed that the AUC of FIB-4 for screening advanced fibrosis in patients with T2DM was only 0.653, significantly lower than the AUC of 0.826 in patients without T2DM.[31] Pina A et al[32] validated the

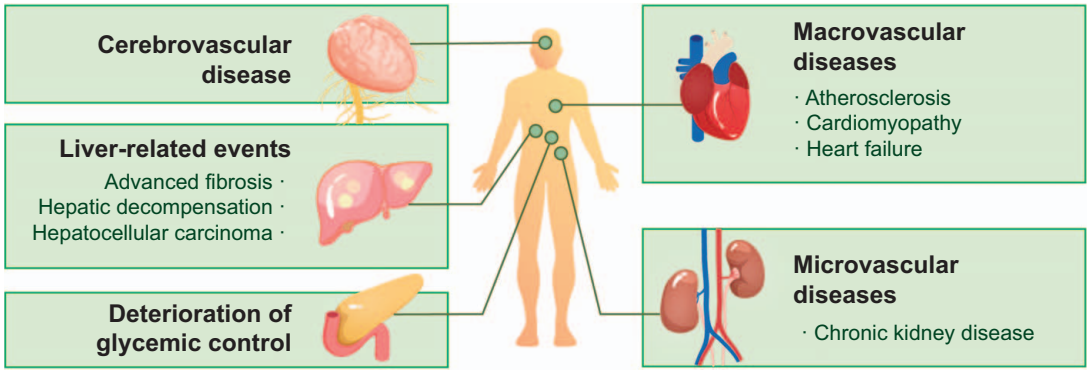

FIGURE 2 Increased risk of adverse outcomes of T2DM combined with MASLD. Abbreviations: MASLD, metabolic dysfunction–associated steatotic liver disease; T2DM, type 2 diabetes mellitus.

performance of a novel index named Fibrotic NASH Index in the T2DM population and demonstrated that the AUC of Fibrotic NASH Index reached 0.89, which was superior to the AUC of 0.67 for FIB-4. Furthermore, the diagnostic accuracy of Fibrotic NASH Index remained stable in patients with T2DM, with varying disease duration and different HbA1c levels. Other newly developed tools, such as the Enhanced Liver Fibrosis panel, FibroSpect, and FIB-C3 model, encompass serum biomarkers that directly reflect hepatic fibrosis.[33] Although these tools are gradually being employed in patients with MASLD, their diagnostic accuracy has not yet been validated in the T2DM population.

Among the various imaging methods, LSM using vibration-controlled transient elastography is the most commonly used surrogate to assess hepatic fibrosis. A meta-analysis enrolled 1780 patients with biopsy-confirmed MASLD combined with T2DM, showing that LSM had an AUC of 0.82 for identifying advanced fibrosis and 0.79 for fibrotic MASH, making it the most accurate compared to other NITs (FIB-4, NFS, APRI, and AGILE 3+). Utilizing a sequential approach starting with FIB-4 and then employing LSM for those with FIB-4 values above 2.67 allowed for identifying the highest proportion of patients at low risk of advanced fibrosis.[34] Several guidelines,[35–40] or guidance[3] have endorsed the screening of steatohepatitis and liver fibrosis among the T2DM population (Table 2).

Currently, there is no consensus on how to screen hepatic fibrosis in the T2DM population. Researchers have validated the poor performance of FIB-4 and other NITs when they are used alone but have yet to develop novel diagnostic methods for stratifying the risk of hepatic fibrosis in patients with T2DM. The sequential combination of screening methods, as advocated by some international guidelines within the context of chronic liver diseases,[3,35] appears to be a feasible approach in the T2DM population. However, the selection of NITs, combined sequence, and specific cutoff values are still uncertain. In addition, these sequential combinations would need to be assessed in clinical care pathways implemented in primary care or in diabetology clinics corresponding to their clinical context of use. Besides,

TABLE 2 International guidelines or guidance on recommendations for screening MASLD and liver fibrosis in the T2DM population

Year	Guidelines/guidance	Recommendations for screening
2023	AASLD Practice Guidance[3]	Patients with NAFLD should be screened for the presence of T2DM. All patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4. High-risk individuals, such as those with T2DM, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis. In patients with pre-DM, T2DM, or 2 or more metabolic risk factors (or imaging evidence of hepatic steatosis), primary risk assessment with FIB-4 should be repeated every 1–2 years.
2024	ADA[41]	Adults with T2DM or prediabetes, especially those with obesity or cardiometabolic risk factors or established cardiovascular disease, should be screened/risk stratified for clinically significant liver fibrosis through FIB-4, even if they have normal liver enzymes.
2022	AACE co-sponsored by the AASLD[37]	Clinicians should consider persons with obesity and/or features of metabolic syndrome, those with prediabetes or T2DM, and those with hepatic steatosis on any imaging study and/or persistently elevated plasma aminotransferase levels (over 6 mo) to be “high risk” and screen for NAFLD and advanced fibrosis. In persons with T2DM, clinicians should consider screening for clinically significant fibrosis (stages F2-F4) using the FIB-4, even if they have normal liver enzyme levels. Clinicians should further risk stratify persons with T2DM with cardiometabolic risk factors and/or elevated plasma aminotransferase levels ($>$ 30 U/L) using the FIB-4, elastography, and/or ELF test.
2021	AGA[38]	Recommend clinicians screen all patients with T2DM for fibrosis. Patients with T2DM should have their medical history recorded and receive laboratory tests (liver function tests) and FIB-4 tests. Patients with FIB-4 scores between 1.3 and 2.67 need to receive liver stiffness measurement for further risk stratification.
2020	APASL[39]	Screening for MAFLD by ultrasonography should be considered in at-risk populations such as patients with overweight/obesity, T2DM, and metabolic syndrome.
2016	EASL-EASD-EASO[40]	In patients with T2DM, the presence of NAFLD should be looked for, irrespective of liver enzyme levels, since patients with T2DM are at high risk of disease progression.

Note: The term NAFLD/NASH/MAFLD were retained under the relevant international guidelines or guidance.
Abbreviations: AACE, American Association of Clinical Endocrinology; AASLD, American Association for the Study of Liver Diseases; ADA, American Diabetes Association; AGA, American Gastroenterological Association; APASL, Asian Pacific Association for the Study of the Liver; DM, diabetes mellitus; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4 index; MAFLD, metabolic dysfunction–associated fatty liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease; T2DM, type 2 diabetes mellitus.

most clinical studies have not differentiated MASLD/MASH-related hepatic fibrosis from other etiologies-induced fibrosis, potentially introducing bias in the assessment and follow-up management of these conditions.

GLUCOSE MONITORING IN MASLD WITH T2DM

A significant concern among T2DM with MASLD population lies in the association between glycemic control and the severity of MASLD. A longitudinal pilot study from Italy reported that patients with T2DM with MASLD and clinically significant fibrosis had pronounced higher HbA1c compared to patients with T2DM with simple steatosis during a 5-year follow-up period.[42] The presence of MASLD and significant fibrosis heightened the risk of elevated HbA1c by a staggering 5.96–6.15 times after adjusting for age, body mass index, and some antidiabetic medications at baseline.[42] This study underscored that MASLD and MASH-related fibrosis negatively impact long-term glycemic profiles. On the other hand, poor glycemic control potentially drives the progression of MASLD. In a separate study involving 713 patients with biopsy-proven MASLD/MASH, 49% had diabetes.[43] The researchers found that a mere 1% increase in mean HbA1c correlated with a 15% rise in the likelihood of heightened liver fibrosis, and the average HbA1c levels in the year leading up to biopsy escalated with more severe grades of steatosis and ballooned hepatocytes.[43] These findings suggest a bidirectional relationship between advanced MASLD and poor glycemic control, with each exacerbating the progression of the other. This emphasizes the crucial need for vigilant glucose monitoring throughout the disease course.

Of note, a higher risk of hypoglycemia has been observed in patients with T2DM with cirrhosis.[44] This phenomenon also manifested in patients with co-existence of T2DM and MASLD. A retrospective study including 1,946,581 patients with T2DM found that those with FLI $\geq$ 60 had an increased 26% risk of severe hypoglycemia compared to those with FLI $<$ 30. The study further used aspartate aminotransferase/alanine aminotransferase $\geq$ 0.8 as a surrogate marker for liver fibrosis and showed that patients with T2DM with MASLD-related fibrosis had a 1.38-fold risk of hypoglycemia compared to patients with T2DM alone.[45] Therefore, it is important to monitor glycemic levels using proper markers in patients with T2DM with MASLD. Routinely, the diagnosis and glucose monitoring of T2DM is based on fasting plasma glucose, a 2-hour plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test or measurement of HbA1c.[36] However, patients with impaired liver function experience increased IR and decreased insulin clearance, leading to hyperinsulinemia. This is indicated by higher postprandial glucose levels but normal fasting plasma glucose and HbA1c in the early stage of diabetes.[46] Although HbA1c is considered a valuable tool for glucose monitoring, it is an indirect marker reflecting mean levels of blood glucose. With the deterioration of liver function, the sensitivity of HbA1c is diminished because of anemia, hypersplenism, gastrointestinal bleeding, and other decompensated cirrhosis complications. Therefore, a joint statement published by the French Association for the Study of the Liver and the Francophone Diabetes Society recommended self-monitoring of capillary blood glucose and/or continuous glucose monitoring as alternatives in patients with cirrhosis and moderately or severely impaired liver function.[47]

Previous studies have mainly focused on identifying appropriate measurements for glycemic control among individuals with chronic liver diseases, but there are still gaps in research. Firstly, there is limited data assessing glucose homeostasis, estimating liver-related events, or all-cause mortality in patients with T2DM with concurrent MASLD-related cirrhosis. Additionally, there is inconsistency in the classification between T2DM and hepatogenous diabetes. Most cross-sectional studies did not strictly identify the sequence of disease occurrence due to the covert clinical course of diabetes and cirrhosis. The American Diabetes Association guideline did not specifically separate hepatogenous diabetes from T2DM, while experts from French Association for the Study of the Liver and Francophone Diabetes Society have noticed different clinical characteristics and prognoses between hepatogenous diabetes and T2DM. It is important to establish a sound system for diabetes diagnosis and glucose monitoring among patients with MASLD.

CO-MANAGEMENT OF T2DM AND MASLD

Lifestyle intervention

Lifestyle intervention is the mainstay of managing T2DM and MASLD.[3,36,37,48] A study found that engaging in $\geq$ 150 minutes/week of physical activity (PA) was associated with a 44% reduced risk of MASLD, and $\geq$ 300 minutes/week had 49%, 59%, and 63% lower odds for MASLD, significant fibrosis, and cirrhosis, respectively.[49] A longitudinal study involving 5207 individuals with a mean follow-up of 10.6 years showed that increasing total PA was associated with a decreased risk of all-cause mortality in patients with MASLD.[50] In addition to PA, clinical trials have attempted to analyze the potential benefits of modified dietary. A Denmark RCT enrolled 165 patients with T2DM, of whom 141 (88%) had MASLD. These patients were randomly assigned to a low-carbohydrate, high-fat diet and a high-carbohydrate, low-fat diet in a 2:1 ratio.[51] Both diet groups showed

significant reductions in HbA1c levels and homeostatic model assessment for IR (HOMA-IR) after the 6-month intervention, with the low-carbohydrate, high-fat group achieving more pronounced improvement. However, there was no statistically significant difference in achieving a ≥ 2-point improvement in NAFLD Activity Score between the 2 groups.[51] A new intervention combining alternate-day fasting with aerobic exercise for 3 months was evaluated in an RCT.[52] Compared with the control group, the combination group showed significant decreases in intrahepatic triglyceride content and body weight, as well as an increase in insulin sensitivity. Fasting glucose and HbA1c showed a reduction of 5.28 mg/dL and 0.08%, respectively, but without statistical significance among different groups. It seems challenging to achieve comprehensive improvement in both T2DM and MASLD. Therefore, it is essential for nutritionists and physical therapists to formulate a detailed protocol for patients, considering factors such as total calorie intake, the percentage of carbohydrates, proteins, and fat, timing for eating and fasting, as well as the type, amount, and the intensity of PA. Although this weight reduction is relatively well tolerated even in cases of severe MASH, this weight reduction must be supervised by a trained health care team to avoid excessive restrictive diet that could lead to vitamin deficiencies or deficits and increase the risk of weight rebound and weight cycling.[53] Maintaining a healthy balance between calorie intake and energy expenditure is crucial.

PHARMACOLOGICAL TREATMENT

Antidiabetic medications

Currently, several trials are underway exploring the efficacy and safety of treatments for MASLD/MASH, and some of them specifically targeted patients with MASLD/MASH combined with T2DM (Table 3). Given that T2DM is a recognized risk factor for MASLD progression,[10,12] most RCTs have included patients with established T2DM and considered it as a variable for randomized stratification. Among numerous hypoglycemic medications, peroxisome proliferator-activated receptor (PPAR) agonists and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown promising results in liver histological improvement and glycemic benefits.

PPAR agonists

Pioglitazone, a representative thiazolidinediones, activates PPAR-γ. Several studies have shown that pioglitazone significantly reduced liver fat content and improved glycemic profiles, showing superiority over other hypoglycemic drugs.[54,60,61,62] The AASLD[3,36,37] has recommended pioglitazone for treating patients with MASH who have co-existing T2DM. However, concerns about weight gain as an adverse effect of pioglitazone have been raised. Interestingly, a post hoc analysis of an RCT investigated the influence of pioglitazone on the changes in visceral fat and subcutaneous fat in patients with MASH with T2DM or glucose intolerance.[63] Despite patients receiving 6-month pioglitazone experiencing an average weight gain of 4.8 ± 0.7 kg, the ratio of visceral-to-subcutaneous fat distribution significantly decreased from 0.54 to 0.36, which was closely associated with decreases in liver fat, improvements in liver histology, and markers of insulin resistance. It is postulated that PPAR-γ agonist may ameliorate the severity of MASH and T2DM by re-distributing adipose tissue and improving its function.[63] Furthermore, a phase 2 study introduced PLX065,[64] a deuterium-stabilized (R)-enantiomer of pioglitazone.[65] A total of 117 patients with MASH, 41% of whom had T2DM, randomly received PXL065 (7.5, 15, 22.5 mg) or placebo for 36 weeks. The PXL065 group demonstrated a dose-dependent reduction in liver fat content (21%–25%) and significant reductions in propeptide of type 3 collagen, enhanced liver fibrosis, and other serum fibrosis biomarkers.[64] Several glycemic parameters, including HbA1c, serum insulin, c-peptide, HOMA-IR, adipose tissue insulin resistance, and adiponectin, showed a significant improvement in the PXL065 (22.5 mg) group compared to the placebo group in the whole population. The weight change in the PXL065 group was relatively minimal.[64] These encouraging results have prompted further trials involving PXL065. Furthermore, In the NATIVE, a phase 2b randomized-controlled trial, lanifibranor, a pan-PPAR agonist, demonstrated higher efficacy than placebo over 6 months of treatment in patients with biopsy-proven MASH in improving both MASH resolution as well as ≥ 1 stage fibrosis without worsening of MASH.[66] Among 103 patients with co-existing T2DM, lanifibranor showed a significant reduction in HbA1c, fasting glucose, insulin, and HOMA-IR levels both in 800 mg and 1200 mg lanifibranor groups relative to placebo.[66]

GLP-1RAS AND DUAL GLP-1 AND GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE AGONIST

A systematic review comparing the efficacy of PPAR agonist, GLP-1RAs, and sodium-glucose cotransporter-2 inhibitors (SGLT2i) indicated that pioglitazone, lanifibranor, and GLP-1RAs all showed significant improvements in the histological features of MASH.[67] GLP-1RAs are favored due to their beneficial effects on glycemic control, insulin sensitivity, body weight reduction, and cardiovascular outcomes improvement.[68] Considering the impressive metabolic effects of GLP-1RAs, researchers have explored their potential in managing MASH and T2DM. A

TABLE 3 RCTs of hypoglycemic treatments for patients with MASLD and T2DM

NCT number (or published year)	Total patients number (T2DM%)	Arms	Intervention duration	Primary outcomes		Glucose metabolism profiles					Body weight	BMI
				Settings	Results	Fasting glucose	HbA1c	C-peptide	HOMA-IR	Adiponectin		
PPAR agonist												
NCT00994682 (2016[a,][54])	101 (100)	Pioglitazone vs. placebo	18 mo	Number of patients with a reduction of at least 2 points in the NAS without worsening of fibrosis	58% patients in the pioglitazone group achieved the primary outcome, significantly higher than the 17% in the placebo group (treatment difference: 41%, 95% CI: 23, 59; $p < 0.001$)	↓↓↓	↓↓↓	NA	↓↓↓	↑↑↑	NA	↑
NCT03008070	247 (NA)	IVA337 (lanifibranor)	24 wks	SAF activity score decrease of at least 2 points with no worsening of the CRN fibrosis score (IVA337 1200 mg > placebo)	The responders' rates were 41.0%, 49.4%, and 27.2% in the IVA337 800 mg, 1200 mg, and the placebo groups, respectively. There was a significant difference between the IVA337 1200 mg group and the placebo group ($p = 0.004$; RR: 1.82, 95% CI: 1.24, 2.4), but no differences between IVA337 800 mg and the placebo group ($p = 0.061$; RR: 1.52, 95% CI: 0.98, 2.12).	↓	↓	NA	↓	↑	NA	NA
NCT01694849	275 (40)	GFT505	52 wks	Percentage of responders with disappearance of steatohepatitis without worsening of fibrosis	The responders rates were 22.6%, 21.3%, and 17.4% in the GFT505 80 mg, 120 mg, and the placebo groups, respectively, (full analysis set). Neither significant difference was observed between the GFT505 80 mg and placebo group ($p = 0.854$; OR: 1.092, 95% CI: 0.427, 2.795), nor between the GFT505 80 mg and placebo group ($p = 0.816$; OR: 0.897, 95% CI: 0.361, 2.232).	No change	No change	↓	↓	No change	NA	NA

NCT01002547	105 (100)	Pioglitazone + vitamin E vs. vitamin E + placebo of pioglitazone vs. placebo of both	3 y	Number of patients with reduction of at least 2 points in the NAS without worsening of fibrosis	The number of patients who had a reduction of at least 2 points in the NAS without worsening of fibrosis was 24 (64.9%), 13 (36.1%), and 7 (21.9%) in pioglitazone + vitamin E, vitamin E, and the placebo group.	Pioglitazone + vitamin E↓	NA	NA	NA	NA	Pioglitazone + vitamin E↑	Pioglitazone + vitamin E↑
GLP-1 receptors agonist												
NCT03987451 (2023[55])	71 (75)	Semaglutide vs. placebo	48 wks	Proportion of patients with an improvement in liver fibrosis of one stage or more without worsening of MASH after 48 wks	No significant difference between the groups (11% patients in the semaglutide group vs. 29% patients in the placebo group; odds ratio 0.28 [95% CI: 0.06, 1.24]; $p = 0.087$)	↓↓↓	↓↓↓	No change	NA	NA	NA	↓↓↓
NCT02970942 (2021[56])	320 (62)	Semaglutide vs. placebo	72 wks	Resolution of MASH with no worsening of fibrosis after 72 wks	The percentage of patients was 40% in the 0.1 mg semaglutide group, 36% in the 0.2 mg semaglutide group, 59% in the 0.4 mg semaglutide group, and 17% in the placebo group ($p <$ 0.001 for 0.4 mg semaglutide vs. placebo)	NA	↓	NA	NA	NA	NA	NA
NCT01237119 (2016[57])	52 (52)	Liraglutide vs. placebo	48 wks	Resolution of steatohepatitis (disappearance of hepatocyte ballooning) without worsening of fibrosis from baseline to end of treatment	Significantly higher proportion of patients in the liraglutide group had resolution of definite MASH compared with the placebo group (liraglutide 39% vs. placebo 9%, relative risk 4.3 [95% CI: 1.0, 17.7]; $p = 0.019$)	↓↓↓	↓↓↓	NA	↓	NA	↓↓↓	↓↓↓
SGLT-2 inhibitors												
NCT02649465 (2022[58])	40 (100)	Tofogliflozin vs. glimepiride	48 wks	Improvement in each histological score of steatosis, hepatocellular ballooning, lobular	The tofogliflozin group had significant histological improvements in all variables (steatosis, hepatocellular ballooning, and lobular inflammation, fibrosis) when comparing	Tofogliflozin↓↓ Glimepiride↓↓	Tofogliflozin ↓↓ Glimepiride ↓↓	Tofogliflozin no change Glimepiride: ↑	NA	NA	Tofogliflozin↓↓ Glimepiride↑	Tofogliflozin↓↓-glimepiride ↑

TABLE 3. (*continued*)

NCT number (or published year)	Total patients number (T2DM%)	Arms	Intervention duration	Primary outcomes		Glucose metabolism profiles					Body weight	BMI
				Settings	Results	Fasting glucose	HbA1c	C-peptide	HOMA-IR	Adiponectin		
				inflammation, and fibrosis at baseline and after 48 wks of treatment	before and after treatment (all $p < 0.01$), while the glimepiride group only showed a significant reduction in hepatocellular ballooning ($p = 0.025$). However, there was no significant difference between the groups in fibrosis scores (60% vs. 35%, $p = 0.172$).							
DPP4 inhibitors												
NCT01260246 (2016[59])	12 (100)	Sitagliptin vs. placebo	24 wks	Improvement in liver fibrosis on histology from baseline to end of treatment	Sitagliptin was not significantly better than placebo at reducing liver fibrosis score (mean difference between sitagliptin and placebo: 0.4, 95% CI: −0.98, 1.78; $p = 0.82$)	NA	↓↓	NA	No change	↑↑	No change	No change

Note: RCTs that set liver histology as primary end points and with available NCT numbers were listed.

[a]This study included patients with MASH with prediabetes or T2DM.

Abbreviations: CRN, Clinical Research Network; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment method for insulin resistance; NA, not available; NAS, NAFLD activity score; SAF, steatosis-activity-fibrosis; T2DM, type 2 diabetes mellitus.

↓/↑means indicators decreased/increased but without significant difference or *p* value did not provide;↓↓/↑↑means indicators significantly decreased/increased compared with baseline; ↓↓↓/↑↑↑means indicators significantly decreased/increased compared with other groups; ＞means significantly better than; ≈means no significant change.

72-week, phase 2 trial enrolled 320 patients with noncirrhotic MASH confirmed by biopsy, 62% of whom had T2DM.[56] They randomly received subcutaneous semaglutide once daily at different doses or placebo. This trial successfully achieved its primary end point, with 59% of patients in the 0.4 mg semaglutide group experiencing MASH resolution with no worsening of fibrosis, significantly higher than the 17% in the placebo group. The semaglutide group also demonstrated superior reductions in HbA1c in a dose-dependent manner compared to the placebo group.[56] Further, a trial tested once-weekly subcutaneous 2.4 mg semaglutide in patients with MASH-related compensated cirrhosis.[55] Although this trial did not improve fibrosis without worsening MASH, semaglutide did reduce liver fat content and liver stiffness measurement and improved glycemic and lipid profiles. Overall, semaglutide shows promise as a medication for treating MASLD/MASH with T2DM. The 2023 AASLD guidance recommended considering semaglutide for treatment in patients with MASH with T2DM or obesity.[3] Additionally, other GLP-1RAs, such as exenatide, liraglutide[57] and dulaglutide, were also administrated in patients with MASLD with T2DM, showing positive effects on reducing liver fat content and improving glycemic profiles (Table 3).

More recently, novel agents such as dual agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptors are being investigated for the treatment of MASH-related fibrosis in clinical trials. Efinopegdutide, a dual GLP-1 and glucagon agonist, for instance, has shown superiority in decreasing liver fat content and improving lipid profiles, while the efficacy in glycemic control and cardiovascular prevention requires more validation.[69] Tirzepatide, a dual agonist of glucose-dependent insulinotropic polypeptide and GLP-1 receptors, has been approved for the treatment of T2DM in the United States.[70] A substudy of the SURPASS-3 trial inclusive of patients with T2DM with FLI $\geq$ 60 showed that 10 mg and 15 mg tirzepatide markedly reduced pooled 8.09% of the absolute reduction in liver fat content assessed by MRI-proton density fat fraction, significantly higher than the insulin degludec group.[71] Around 60%~78% of patients in the tirzepatide group reduced up to 10% liver fat content, better than the 35% in the insulin degludec group.[71] A phase 2b trial is underway to examine the efficacy of tirzepatide versus placebo in patients with biopsy-proven MASH with fibrosis with or without T2DM in improving either MASH resolution or fibrosis improvement.

METFORMIN

Metformin is the first-line oral agent for treating T2DM. Despite its wide-ranging metabolic functions and protective effects against various diseases, metformin showed no improvement in hepatic fibrosis and modest benefits on hepatic steatosis in clinical trials.[72] However, a paradoxical finding emerged from a multicenter, international cohort study that included 299 patients with T2DM with MASH-related Child-Pugh A cirrhosis.[73] After a median follow-up of 5.1 years, patients who used metformin at baseline had a significantly higher cumulative likelihood of liver transplant-free survival and a lower cumulative incidence of hepatic decompensation compared to metformin non-users. Adjusting for confounding factors, metformin was independently associated with a decreased risk of all-cause mortality, hepatic decompensation, and HCC.[73] A retrospective study confirmed similar results in patients with T2DM with MASH-related bridging fibrosis or compensated cirrhosis.[74] Given the complex pharmaceutical mechanism of metformin, further research is warranted to explore its potential hepatoprotective effects.

OTHER HYPOGLYCEMIC AGENTS

SGLT2i exerts a significant role in the treatment of T2DM, CVD, and CKD. However, their therapeutic advantage in the MASH population, with or without T2DM, is not as robust as GLP1-RAs.[58,60,75] A meta-analysis encompassing 12 trials of SGLT2i included 850 patients with MASLD who were overweight or obese, of whom 90% had diabetes.[76] This meta showed that SGLT2i markedly improved liver function (serum alanine aminotransferase and gamma-glutamyltransferase levels) and reduced liver fat content and LSMs compared with placebo.[76] A retrospective study from Korea inclusive of over 80 thousand patients with T2DM combined with FLI $\geq$ 60 showed that patients using SGLT2i achieved the highest incidence of MASLD resolution assessed by FLI scores in comparison to those using thiazolidinediones, dipeptidyl peptidase-4 inhibitors, or sulfonylureas.[77] Furthermore, SGLT2i constituted the lowest number of liver-related adverse events per 100,000 person-years among the 4 classes of oral antidiabetic medications.[77] Although SGLT2i has demonstrated effectiveness in reducing liver fat content in clinical trials, investigating its efficacy in MASLD/MASH has limitations, such as relatively small sample size, short intervention durations, and primary outcome assessments mainly based on imaging methods rather than comprehensive evaluation of liver histology. These limitations restrict the validation of SGLT2i efficacy in the MASH with T2DM population. Similarly, dipeptidyl peptidase-4 inhibitors did not show great benefits in the treatment of MASH and T2DM.[59,61,78,79]

PHARMACOLOGIC THERAPIES BEING DEVELOPED FOR MASH OR OTHER INDICATIONS

Resmetirom has emerged as a groundbreaking development, becoming the first medication approved by the US Food and Drug Administration in treating patients with noncirrhotic MASH with moderate to advanced liver fibrosis. In a precedent-setting phase 2 trial, resmetirom demonstrated its efficacy in reducing hepatic fat fraction after 12-week and 36-week interventions.[80] In the recent Phase 3 MAESTRO-NASH trial, resmetirom successfully met both the primary end points at week 52.[81] In the 80 mg and 100 mg resmetirom groups, 24.2% and 25.9% patients, respectively, witnessed an improvement of ≥ 1 stage in fibrosis without NAFLD Activity Score worsening, respectively.[81] Additionally, 25.9% and 29.9% experienced MASH resolution with no worsening of fibrosis in these respective groups.[81] Of 67% of participants with co-exsiting T2DM in this trial, the levels of glucose, insulin, and HOMA-IR were also improved in resmetirom groups compared with the placebo group, albeit to a lesser extent than other parameters.[81] As a thyroid hormone receptor-β selective agonist, resmetirom exerts its effects by targeting the liver and modulating energy by multiple mechanisms. Although the notable advancements in liver histological improvements attributed to resmetirom are commendable, certain issues would require continued follow-up. These include potential management of patients with co-existing hypothyroidism, and long-term safety of the pituitary-thyroid hormone axis and bone mineral metabolism. Further studies are needed to determine the cost-effectiveness of resmetirom among patients with MASLD and T2DM.[82] Other newly developed medications also emerged as potential alternatives for the treatment of MASH in combination with T2DM. In a phase 2 proof-of-concept trial, 100 patients with MASLD with T2DM were recruited and received either 500 mg, 1000 mg berberine ursodeoxycholate (BUDCA), or placebo in a 1:1:1 ratio for 18 weeks.[83] The study found that patients receiving the higher dose of BUDCA had a significant 4.8% reduction in absolute liver fat content compared to the 2% in the placebo group. The mean HbA1c levels decreased by 0.3% and 0.6% in the 500 mg and 1000 mg BUDCA groups, respectively, while HbA1c increased by 0.1% in the placebo group. BUDCA was well tolerated, with mild diarrhea being the most frequent adverse event.[83] The recent HARMONY trial evaluated the efficacy and safety of once-weekly efruxifermin (28 mg or 50 mg), a bivalent Fc–FGF 21 analog, in the treatment of patients with MASH-related moderate or severe fibrosis (70% of whom had concomitant T2DM).[84] The study proved that a 24-week intervention with efruxifermin resulted in improvements in hepatic fibrosis by ≥ 1 stage without worsening of MASH. In the 28 mg and 50 mg efruxifermin groups, 39% and 41% of patients achieved the primary outcome, respectively. Efruxifermin also generated pronounced glycemic control and improvement in insulin sensitivity.[84] Pegozafermin (BIO89-100), a long-acting glycopegylated FGF21 analog, has demonstrated both safety and efficacy in the treatment of MASH. Initially evaluated in a phase 1b/2a RCT, pegozafermin exhibited favorable safety profiles across various doses, ranging from 3, 9, 18, or 27 mg administered once weekly to 18 or 36 mg administered twice weekly.[85] The most frequently reported adverse event was increased appetite, while it was not linked with weight gain.[85] A subsequent proof-of-concept, open-label trial spanning 20 weeks involved a subcutaneous injection of pegozafermin 27 mg/week.[86] Within the pegozafermin cohort, 63% of patients substantially improved the NAFLD Activity Score components with no worsening of fibrosis.[86] All the patients achieved a reduction of at least 30% in liver fat content. Additionally, liver function, lipid profiles, and HbA1c showed marked enhancements.[86] Building on these findings, a phase 2b study involving 222 patients with fibrotic NASH indicated substantial benefits with pegozafermin treatment.[87] Specifically, 23%–26% of patients in the 30 mg/week group and 26%–27% of those in the 44 mg/twice weekly group demonstrated improvements in liver fibrosis over the 24-week treatment period, surpassing the placebo group.[87] These positive results underscored the therapeutic potential of pegozafermin in treating MASH. Another agent, PXL770, which directly activates adenylate-activated protein kinase, was investigated in the STAMP-NAFLD trial.[88] A total of 121 patients with MASLD (44% combined with T2DM) were randomly assigned to PXL770 and placebo for 12 weeks. Although the reduction in liver fat content did not reach statistical significance, there was a noticeable improvement in glycemic parameters (fasting plasma glucose and HbA1c) in the PXL770 group.[88] With ongoing advancements in pharmacology, it is conceivable that more effective medications will become available to improve the treatment of MASH and T2DM.

STATINS USAGE

Patients with MASLD with T2DM commonly exhibit dyslipidemia, another important risk factor for CVD. It is crucial to address lipid abnormalities as part of the holistic management approach for MASLD with the T2DM population. Statins, a well-known class of lipid-lowering drug, bring about lipid metabolism improvement and cardiovascular benefits. However, the utilization of statins has been limited in patients with chronic liver diseases due to concerns about the safety profile. An expert panel statement reviewed 10 key clinical studies on statin treatment and

demonstrated the normalization of liver functions in the MASLD/MASH population.[89] A post hoc analysis from pioglitazone trial[54] targeting patients with MASLD with prediabetes or T2DM revealed that the levels of serum aminotransferase did not significantly increase after 36-month follow-up in patients prescribed with statins, indicating the long-term safety of statin therapy in such population.[90] Several studies have reported positive outcomes with statin therapy. An open-label RCT compared the efficacy of a combination regimen of ezetimibe and rosuvastatin with rosuvastatin monetherapy among patients with MASLD.[91] The combination group exhibited a pronounced reduction of liver fat content assessed by MRI-proton density fat fraction, with a higher response rate noted in patients with MASLD with T2DM. Nevertheless, liver fibrosis evaluated by LSM did not significantly change between the groups.[91] A nationwide case-control cohort study enrolled over 11 million Korean individuals who underwent national physical health examination.[92] The study showed that statin therapy was significantly associated with the reduced risk of MASLD (diagnosed by FLI and hepatic steatosis index) and significant fibrosis (calculated by BARD score) development, and maintained its efficacy in the population with diabetes.[92] Another cross-sectional study inclusive of patients with T2DM with biopsy-proven MASH proved that statin usage was independently and negatively correlated with MASH and significant fibrosis in multivariate analyses.[93] Further, a moderate-to-high intensity treatment regimen, which comprised atorvastatin, rosuvastatin, or any statin combined with ezetimibe, remained a significant factor for MASH and significant fibrosis, while low-to-moderate statin therapy (simvastatin, pravastatin, fluvastatin, or lovastatin) did not demonstrate a similar association.[93] The AASLD[3] and American Diabetes Association[94] have both stated the safety of statins even among patients with compensated cirrhosis, and American Diabetes Association specifically recommended the usage of statins for CVD risk reduction in patients with T2DM with MASLD throughout the disease spectrum, exclusive of decompensated cirrhosis.[94]

BARIATRIC SURGERY

Bariatric surgery has been proven to be effective in ameliorating metabolic diseases. A meta-analysis confirmed that bariatric surgery resulting in the resolution of steatosis, inflammation, ballooning degeneration, and fibrosis was achieved in 66%, 50%, 76%, and 40% of patients with MASLD, respectively.[95] A recent multicenter, randomized, open-label study including 288 patients with obesity and MASH, with or without T2DM, had compared the efficacy of either gastric bypass or sleeve gastrectomy versus lifestyle modifications. In this study, approximately 55% of the participants in both bariatric surgery groups had an improvement in MASH versus 16% in the lifestyle group after 1 year of follow-up. Moreover, 38% of the participants in the bariatric groups improved at least 1 stage of fibrosis without worsening of MASH versus 23% in the control lifestyle intervention.[96] Due to its exceeding impact on weight loss, bariatric surgery is mainly applied in patients who are morbidly obese and comorbid with other metabolic diseases. According to the 2023 AASLD guidance, bariatric surgery can be an option in patients with MASLD who meet criteria for metabolic weight loss surgery, while decompensated cirrhosis is an absolute contraindication.[3] In patients with MASLD with T2DM who are not morbidly obese, the application of bariatric surgery requires careful consideration (Figure 3).

DILEMMA IN CURRENT RESEARCH

While numerous studies have investigated the increasing overlap between T2DM and MASLD, there are still several uncertainties that need to be addressed. Firstly, it is crucial to identify demographic and metabolic factors that contribute to the progression of MASLD in the context of T2DM and reciprocally. Among the T2DM population, researchers have found that independent predictors of MASLD include young age, higher hemoglobin levels, lower HDL cholesterol levels, and the absence of dialysis.[97] Premenopausal women faced a significantly higher risk of incident T2DM compared with postmenopausal women and age-matched men.[98] Heretofore, different cohort studies conducted in diverse populations have reported varying risk factors, making it difficult to effectively detect and assess disease progression. Secondly, in patients with both T2DM and MASLD, few studies have prospectively explored the prevalence and progression of microvascular complications of diabetes or assessed the risk of extrahepatic cancers. Thirdly, various diagnostic methods for MASLD may not accurately mirror real-world occurrences, posing a challenge for timely screening of liver disease in the T2DM population. Besides, further investigations are needed to determine whether the usage of insulin and other antidiabetic agents impacts liver disease outcomes in patients with MASLD and T2DM.

CHALLENGES OF COMPREHENSIVE MANAGEMENT IN MEDICAL SYSTEM

Despite the rising medical burden of MASLD and T2DM, there remains a significant lack of awareness of the importance of liver health checks among patients with MASLD and T2DM. Historically, MASLD has been

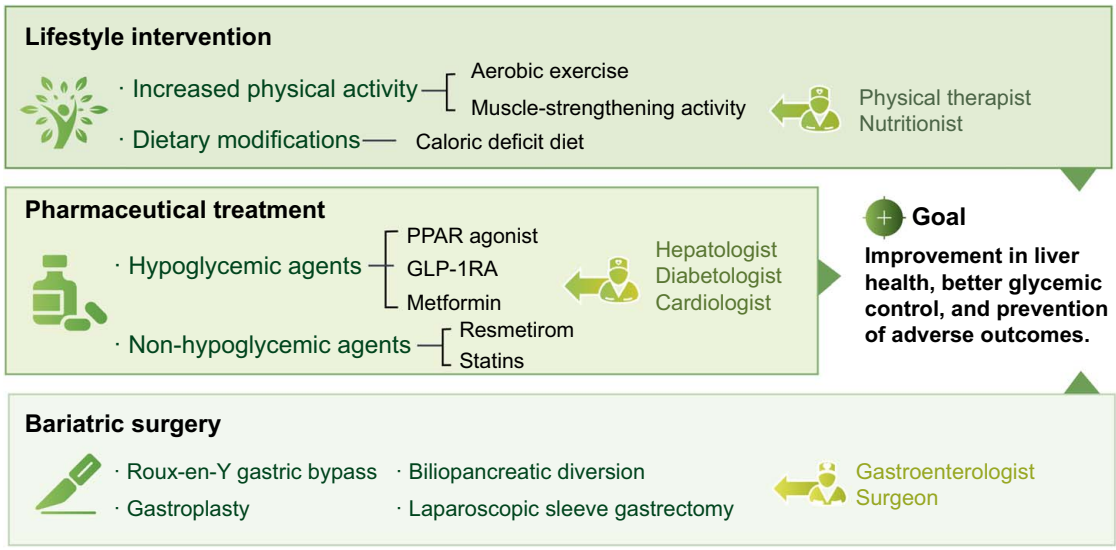

FIGURE 3 Co-management for T2DM combined with MASLD. Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; MASLD, metabolic dysfunction–associated steatotic liver disease; PPAR, peroxisome proliferator-activated receptor; T2DM, type 2 diabetes mellitus.

perceived mainly as a liver manifestation of metabolic syndrome, often overlooked without specific examination. The long asymptomatic period phase conceals the progression of MASLD from simple steatosis to advanced fibrosis, cirrhosis, and HCC. Therefore, the initial task is health education within the patients with T2DM, emphasizing the growing recognition of MASLD, and the necessity for proactive screening and surveillance of MASLD.[99] Specialists have advocated for an annual assessment of liver fibrosis in patients with T2DM to enable timely interventions.[100] At the wake of this issue, the challenge revolves around developing noninvasive tools with high diagnostic accuracy and prognostic value for MASLD-related liver fibrosis, available in primary care settings since advanced imaging techniques or patented biomarkers are often beyond the reach of community populations. Serra-Burriel M et al[101] developed the LiverRisk score for identifying liver-related outcomes in the general population; its applicability in patients with T2DM warrants further validation. Despite the emergence of various NITs, significant efforts are still required to integrate them into the current management approaches.

On a global scale, the traditional management approach of T2DM and MASLD falls within the realms of diabetology/endocrinology and hepatology departments, respectively. However, the proposal of the new nomenclature MASLD has highlighted the critical need for multidisciplinary cooperation to develop an integrated approach towards managing MASLD and T2DM. Noteworthy is the Chinese initiative known as the co-management of diabetes-liver diseases strategy supported by the Liver Health Alliance in China and the National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, launched in 2023. The primary objective of the co-management of diabetes-liver diseases strategy is to establish a multidisciplinary team to devise an efficient medical system focusing on the "prevention-screening-management" continuum for the 2 diseases. Looking ahead, a global initiative concerning MASLD and T2DM is gradually taking shape, aiming to address these health concerns on an international scale.

CONCLUSION

The bidirectional relationship between T2DM and MASLD has been widely recognized. The inconspicuous nature of MASLD and diabetes pose a challenge to disease identification. Ideally, a well-defined referral pathway should be in place to identify patients at higher risk of disease progression and potential complications, accurately direct patients to specialized clinics for further evaluation, and establish appropriate follow-up frequency and assessment methods in a cost-effective way. Navigating the intricate landscape of managing T2DM and MASLD requires a multidisciplinary team consisting of hepatologists, diabetologists, gastroenterologists, nutritionists, physical therapists, and cardiologists. Early intervention and timely treatment are essential for the 2 diseases. While classical hypoglycemic medications have shown promise, they still fall short of meeting clinical needs. Novel agents are therefore anticipated to optimize treatment response and prevent adverse outcomes. Overall, the rapid advancement of clinical techniques combined with the collaborative efforts of experts from different fields is expected to bring great improvements in the co-management of T2DM and MASLD.

AUTHORS CONTRIBUTIONS

Xiaolong Qi, Jie Li, Cyrielle Caussy, GJT, and Rohit Loomba: Guarantor of article; Xiaolong Qi, Jie Li, Cyrielle Caussy, Gao-Jun Teng, and Rohit Loomba: study concept and study supervision; Xiaolong Qi, Jie Li, Cyrielle Caussy, and Rohit Loomba: manuscript drafting; Cyrielle Caussy, Gao-Jun Teng, and Rohit Loomba: manuscript supervision. All authors read and revised the manuscript.

CONFLICTS OF INTEREST

Cyrielle Caussy consults and received grants from Echosens, E-sopics, and Novo Nordisk. She consults for AstraZeneca, Bayer, Eli Lilly, MSD, and Pfizer. She received grants from Gilead. Rohit Loomba consults and received grants from Arrowhead, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Galmed, Gilead, Intercept, Inventiva, Ionis, Janssen, Madrigal, Merck, NGM Bio, Novo Nordisk, Pfizer, and Terns. He consults for 89bio, Aardvark, Altimmune, Alnylam/Regeneron, Amgen, CohBar, Glympse, HighTide, Inipharm, Metacrine, Novartis, Sagimet, Theratechnologies, and Viking. He received research grants from Boehringer-Ingelheim, Galectin, Hanmi, and Sonic Incytes. He is the co-founder of LipoNexus. The remaining authors have no conflicts to report.

ORCID

Xiaolong Qi https://orcid.org/0000–0002–3559–5855
Jie Li https://orcid.org/0000–0003–0973–8645
Cyrielle Caussy https://orcid.org/0000–0001–8089–2907
Gao-Jun Teng https://orcid.org/0000–0002–5690–9550
Rohit Loomba https://orcid.org/0000–0002–9116–2835

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