Advances in Co-management of Metabolic Dysfunction-Associated Fatty Liver Disease and Type 2 Diabetes Mellitus: Postprint

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes mellitus (T2DM) represent two prevalent metabolic diseases globally. Their comorbidity currently exhibits a high prevalence and can accelerate disease progression, imposing a substantial disease burden on patients and constituting a major public health challenge. MASLD and T2DM mutually influence each other and share common pathogenic mechanisms. The development of effective co-management strategies for MASLD and T2DM constitutes a critical clinical issue requiring urgent resolution. This article provides a detailed exposition of recent advances in epidemiology, pathogenesis, screening and monitoring, and treatment of T2DM complicated by MASLD. This review demonstrates that T2DM complicated by MASLD has become a common clinical phenomenon, wherein the two conditions mutually influence each other and promote disease occurrence and progression. Screening for MASLD should be implemented in patients with T2DM. Non-invasive diagnostic models, including the Fibrosis-4 index, Fatty Liver Fibrosis Score, and various other models, can be employed for routine screening, although their accuracy requires further validation. Furthermore, novel agents such as sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists have demonstrated efficacy in treating T2DM complicated by MASLD, while concurrently improving disease prognosis and preventing cardiovascular events. This article provides a reference basis for optimizing clinical diagnostic and therapeutic strategies for T2DM complicated by MASLD and for formulating clinical "co-management of diabetes and liver disease" strategies.

Full Text

Advances in the Co-Management of Metabolism Dysfunction-Associated Steatotic Liver Disease and Type 2 Diabetes Mellitus

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Abstract
Metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes mellitus (T2DM) are the two most common metabolic diseases worldwide. The coexistence of MASLD and T2DM has a high prevalence rate and accelerates disease progression, imposing a significant disease burden on patients and posing a major public health challenge. MASLD and T2DM mutually influence each other, sharing common pathogenic mechanisms. Developing effective co-management strategies for MASLD and T2DM is a critical clinical priority. This review elaborates on recent advances in the epidemiology, pathogenesis, screening, monitoring, and treatment of T2DM combined with MASLD. It highlights that the co-existence of T2DM and MASLD has become a common clinical phenomenon with each condition exacerbating the development and progression of the other. Screening for MASLD should be implemented in T2DM patients. Non-invasive diagnostic tools such as the Fibrosis 4 Index and NAFLD fibrosis score can be used for routine screening, though their accuracy requires further validation. Additionally, medications like sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists have been shown to improve outcomes in patients with T2DM and MASLD, effectively preventing cardiovascular events. This review provides reference for the optimization of clinical diagnosis and treatment strategy of T2DM combined with MASLD and the formulation of clinical "glycohepatic co-management" strategy.

Keywords
Metabolic dysfunction-associated steatotic liver disease; Type 2 diabetes mellitus; Co-management of MASLD and T2DM; Metabolic diseases; Chronic liver disease

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MASLD, also known as non-alcoholic fatty liver disease (NAFLD), encompasses a disease spectrum ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma. MASLD has become one of the most common chronic liver diseases

globally, with an increasing trend [1-2], affecting approximately one-third of the population in China [3]. Type 2 diabetes mellitus (T2DM), as a common metabolic disease, has a close comorbidity relationship with MASLD [2]. The global prevalence of MASLD in T2DM patients reaches 65.04% [4], with rates of 58.84% in East Asian countries and 7.65% in European countries. Domestic studies show that the prevalence of MASLD in T2DM patients reaches 51.8% and continues to rise [5]. The comorbidity of T2DM and MASLD significantly accelerates disease progression [6]. Globally, 42%-65% of MASLD patients with T2DM develop MASH [4,7], and over 30% have significant fibrosis [8-9]. The duration and different subtypes of T2DM are also important factors for MASLD fibrosis progression and hepatocarcinogenesis [10-13]. Conversely, MASLD exacerbates insulin resistance and glucose-lipid metabolism disorders, increasing diabetes risk [14]. Furthermore, the comorbid population shows significantly increased risks of cardiovascular disease, liver-related mortality, cirrhosis, and chronic kidney disease [6,8].

Currently, the comorbidity faces numerous challenges, such as the lack of accurate evaluation tools for screening and diagnosing T2DM combined with MASLD, particularly regarding non-invasive diagnostics. In terms of treatment, although some hypoglycemic drugs can improve metabolism, evidence for long-term benefits and personalized protocols in comorbid patients is lacking.

1. Pathogenesis of T2DM and MASLD

MASLD represents hepatic manifestation of metabolic disorders with complex pathogenesis closely related to T2DM development. Both conditions share common pathogenic mechanisms centered on a vicious cycle of insulin resistance, lipid metabolism disorders, and chronic inflammation. Insulin resistance increases peripheral adipose tissue lipolysis, releasing excess free fatty acids to the liver and promoting de novo lipogenesis, leading to abnormal triglyceride accumulation in hepatocytes and steatosis. During this process, adipose tissue secretes pro-inflammatory cytokines (such as interleukin-6, tumor necrosis factor-α) and adipokines (such as leptin resistance, reduced adiponectin) into the circulation, activating Kupffer cells and hepatic stellate cells, triggering oxidative stress and inflammatory responses that further exacerbate insulin resistance and hepatocyte injury [15]. Additionally, intestinal microecological dysbiosis promotes endotoxin translocation, activating hepatic inflammation through related signaling pathways and interfering with bile acid metabolism to promote hepatic lipid accumulation. T2DM patients have impaired pancreatic β-cell function, while hepatic fat deposition further aggravates insulin resistance through release of hepatokines (such as fibroblast growth factor 21), forming a bidirectional deterioration of the "liver-pancreas" axis [16-17]. Mitochondrial dysfunction and endoplasmic reticulum stress jointly cause lipotoxic injury to hepatocytes, driving progression from steatosis to MASH and hepatic fibrosis while promoting systemic glucose-lipid metabolism imbalance. This multi-organ, multi-pathway interaction ultimately forms a synergistic pathological network

between MASLD and T2DM, simultaneously increasing cardiovascular events and hepatic/extrahepatic complication risks [8].

2.1 Screening and Disease Progression Monitoring in T2DM with MASLD

The overlap between T2DM and MASLD has attracted widespread attention. Strengthening liver health assessment and monitoring in T2DM patients, establishing clear referral pathways, and early identification of disease progression and high-risk patients are urgent clinical needs. Routine screening for MASLD in T2DM is recommended by domestic and international guidelines such as the *Chinese Guidelines for the Management of Diabetes in the Elderly* [18] and the *Evidence-Based European Recommendations for the Dietary Management of Diabetes* [19]. Although liver biopsy remains the gold standard for MASLD diagnosis, its clinical limitations make it difficult to popularize in T2DM patients. Additionally, liver enzymes do not completely correlate with hepatic steatosis degree, thus not recommended as sole screening indicators in T2DM populations.

Multiple non-invasive diagnostic tools for MASLD have been preliminarily studied in T2DM patients, including Fibrosis-4 Index (FIB-4), NAFLD Fibrosis Score (NFS), and AST-to-Platelet Ratio Index (APRI) [20-22]. A cross-sectional study showed that FIB-4, APRI, and NFS had modest performance for screening advanced fibrosis in T2DM, with area under the curve (AUC) values of 0.85, 0.86, and 0.64, respectively [20]. Another study in T2DM patients evaluated the Fibrosis NASH Index (AUC=0.89) for MASLD assessment, which significantly outperformed FIB-4 (AUC=0.67) while maintaining stable predictive performance across different T2DM subgroups [21]. A meta-analysis examined liver stiffness measurement (LSM) predictive value in MASLD with T2DM, demonstrating good performance in identifying MASH and advanced fibrosis [22], with AUC values of 0.79 and 0.82, respectively. Furthermore, the combination of FIB-4 and LSM for screening steatohepatitis and fibrosis in T2DM is recommended by the European Association for the Study of the Liver [23] and the *American Diabetes Association Standards of Care (2025 Edition)* [24]. Although some newly developed diagnostic tools (such as Enhanced Liver Fibrosis model, FibroSpect model, Fibrosis-C3) are gradually being applied in MASLD, their accuracy in T2DM populations requires further validation [8].

T2DM monitoring is based on fasting plasma glucose, 2-hour glucose $ $200 mg/dL (11.1 mmol/L) during oral glucose tolerance test, or glycated hemoglobin (HbA1c) measurement. Related studies show that the presence of MASLD and fibrosis increases the risk of elevated HbA1c by approximately 6-fold [25], and each 1% increase in mean HbA1c increases the likelihood of worsening hepatic fibrosis by 15%, with average HbA1c levels rising as steatosis severity increases. These findings underscore the importance of glucose monitoring in MASLD patients.

2.2 Treatment Strategies for T2DM with MASLD

2.2.1 Lifestyle Intervention Lifestyle intervention is the main approach for managing MASLD, applicable to all MASLD patients including those with T2DM comorbidity [8], primarily through exercise and dietary modification. A randomized controlled study examined the effects of aerobic exercise combined with alternate-day fasting, finding that after 3 months, the intervention group showed decreased intrahepatic triglycerides and body weight, reduced fasting glucose and HbA1c levels, and improved insulin sensitivity compared with controls [26]. Other studies indicate that exercising >150 min/week and >300 min/week can reduce MASLD risk by 44% and 49%, respectively [27]. A Danish randomized controlled study in T2DM patients showed that modified dietary intervention for 6 months reduced HbA1c and insulin resistance index in T2DM patients with MASLD [28].

Bariatric surgery can effectively improve metabolic diseases but is primarily suitable for morbidly obese patients with other metabolic diseases due to its substantial weight loss effects [29]. However, sufficient evidence remains lacking in the T2DM with MASLD population. A multicenter randomized study including some T2DM patients showed that approximately 55% of MASLD patients who underwent bariatric surgery had improved symptoms after 1-year follow-up [30].

2.2.2 Pharmacological Treatment Multiple medications have been studied and recommended for T2DM and MASLD comorbidity. Traditional hypoglycemic agent metformin has unclear effects on MASH, though some studies show it can improve transplant-free survival in T2DM patients with MASLD-related advanced fibrosis and cirrhosis, and is independently associated with reduced all-cause mortality and hepatic decompensation [31-32]. Another hypoglycemic agent, peroxisome proliferator-activated receptor (PPAR) agonist pioglitazone, has been proven in multiple RCTs to significantly improve histological features of steatohepatitis, benefiting insulin sensitivity, glycemic control, lipid profiles, and cardiovascular event prevention in T2DM patients [33-34]. The American Association for the Study of Liver Diseases (AASLD) recommends pioglitazone for T2DM patients with MASH [35]. A phase II clinical study of pioglitazone in T2DM patients with MASLD showed dose-dependent reduction in liver fat content (21%-25% decrease) after 36 weeks of treatment, with significant reductions in type III collagen, Enhanced Liver Fibrosis score, and other serum fibrosis markers [36].

Novel hypoglycemic drug sodium-glucose cotransporter 2 inhibitors (SGLT2i) including empagliflozin, dapagliflozin, and licogliflozin can moderately reduce liver fat content in some T2DM patients with MASLD [37-38], with empagliflozin and licogliflozin effectively lowering liver enzyme levels. Glucagon-like peptide-1 receptor agonists (GLP-1RA) demonstrate excellent effects on glycemic control, insulin sensitivity, weight reduction, and cardiovascular disease treatment. In a 72-week phase II clinical trial in MASH patients (62% with T2DM), different

doses of semaglutide were compared, showing that 59% of patients receiving 0.4 mg semaglutide achieved MASH resolution, with dose-dependent HbA1c reduction [39]. Preliminary analysis from another semaglutide phase III trial showed that at week 72, the treatment group (0.4 mg/week) had 37.0% fibrosis improvement and 63.0% steatohepatitis resolution versus 0.5% and 34.1% in the placebo group, respectively. Other GLP-1RA drugs such as exenatide and liraglutide are also recommended for T2DM patients with MASLD, reducing liver fat content and improving glycemic control [35]. Novel dual agonists of glucose-dependent insulinotropic polypeptide and GLP-1 receptors are in clinical trials for MASH treatment, with studies showing that GLP-1 and glucagon dual agonist tirzepatide demonstrates advantages in reducing liver fat content and improving lipid profiles, though more validation is needed for glycemic control and cardiovascular prevention [40].

According to the American Diabetes Association (ADA) recommendations, MASLD novel drug thyroid hormone receptor β agonist resmetirom can also be used for T2DM patients with MASLD and F2-F3 fibrosis [24]. Therefore, for MASLD patients with T2DM, treatment should prioritize drugs with potential hepatic benefits such as GLP-1RA, GLP-1 dual agonists, and SGLT2i.

Additionally, vitamin E can reduce de novo lipogenesis and help decrease hepatic lipid content [2]. However, evidence for vitamin E application in diabetes patients with MASLD is insufficient, with recommendations for use in non-diabetic patients. An analysis in the general population showed that increased dietary vitamin E intake prevents MASLD development, particularly in T2DM patients [41].

2.2.3 Management of Cirrhosis with T2DM As MASLD becomes the leading cause of chronic liver disease, global MASLD-related cirrhosis is projected to increase by 64%-156% by 2030 [42], with further elevation in cirrhosis with T2DM ratio. Cirrhosis with T2DM differs from ordinary diabetes in clinical features, diagnosis, and monitoring. As hepatic function impairment progresses, cirrhosis affects the sensitivity of fasting glucose, 2-hour postprandial glucose (2h-PG), and HbA1c for diabetes diagnosis. IMANO et al. [43] detected 60 patients with compensated hepatitis C cirrhosis and found that 21% of diabetes cases diagnosed by 2h-PG were missed when using fasting glucose alone. ADDEPALLY et al. [44] used continuous glucose monitoring (CGM) for diabetes diagnosis and found a 14% missed diagnosis rate in cirrhosis patients using fasting glucose and HbA1c. Therefore, fasting glucose and HbA1c alone are not recommended for diabetes diagnosis in cirrhosis patients; oral glucose tolerance test (OGTT) with 2h-PG measurement is recommended for routine diabetes diagnosis in cirrhosis patients, particularly those with hepatic function impairment [45]. Similarly, HbA1c is unsuitable for glycemic monitoring in cirrhosis patients with diabetes, especially those with anemia or hepatic dysfunction.

When selecting hypoglycemic drugs for cirrhosis patients with T2DM, the impact of cirrhosis on drugs must be considered. Metformin can reduce the risk of

hepatocellular carcinoma (HCC) and prolong survival in liver disease patients, but its use in cirrhosis patients may increase risks of lactic acidosis, hypotension, and renal insufficiency [31]. Therefore, metformin should be avoided in decompensated cirrhosis or patients with renal insufficiency. GLP-1RA has low hypoglycemia risk when used alone, and the liver is not its primary metabolic organ, making it more suitable for cirrhosis patients. However, these drugs also act on the central nervous system to increase satiety and reduce food intake, causing weight loss that requires cautious use in cirrhosis patients with malnutrition or gastrointestinal dysfunction. Compared with insulin and dipeptidyl peptidase-4 inhibitors (DPP-4i), GLP-1RA can reduce cirrhosis and HCC risk in chronic liver disease patients [46-47]. Insulin is one of the safest and most effective hypoglycemic drugs for cirrhosis patients with T2DM, usable in patients with any degree of hepatic impairment and as first-line therapy for moderate-to-severe hepatic impairment. A meta-analysis showed insulin increased HCC risk by 160% in liver disease patients, though with substantial heterogeneity; after adjusting for confounders, insulin therapy still increased HCC risk [48]. Sulfonylureas and meglitinides are not recommended for cirrhosis, particularly decompensated cirrhosis, due to severe hypoglycemia risk [49]. DPP-4i may increase risks of cirrhosis decompensation, esophagogastric variceal bleeding, and hepatic failure [50], thus also not recommended for decompensated cirrhosis patients.

3. Summary and Outlook

Although multiple studies have explored the common pathogenesis, population screening, and treatment of T2DM with MASLD, many urgent issues remain unresolved. First, the medical burden of T2DM and MASLD comorbidity is heavy, with insufficient patient awareness about the importance of health examinations, posing challenges for improving glycohepatic co-management strategies and requiring strengthened patient education. Second, current screening and diagnostic assessments for glycohepatic comorbidity mostly borrow tools from MASLD, which may not accurately reflect actual conditions. Further clarification is needed regarding demographic, serological, and imaging features of the interaction between T2DM and MASLD to establish more accurate and practical non-invasive diagnostic and prognostic models for early intervention and timely treatment. Additionally, the multidirectional links between glycohepatic comorbidity and other metabolic diseases require enhanced multidisciplinary collaboration to develop individualized treatment protocols. Future multicenter, large-sample studies are needed to provide more evidence-based medicine support for "glycohepatic co-management."

Author Contributions
WANG Peng was responsible for conceptualization, design, data collection, and manuscript writing. QIU Lixia was responsible for literature organization and participated in manuscript writing. XU Shanshan and ZHANG Yang were responsible for literature review and organization. ZHANG Jing participated

in manuscript revision and quality control. DU Xiaofei was responsible for manuscript revision, quality control, final review, and supervision.

Conflict of Interest
The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.