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REVIEWS

Antidiabetic Agents in the Management of Hepatic Fibrosis in Type 2 Diabetes Mellitus and MASLD/MASH: A Narrative Review

Muhammad Ifham HANIF[1*], Triyanta Yuli PRAMANA[2], Didik PRASETYO[2], Aritantri DARMAYANI[2], Ari Prasetyo NUGROHO[2], Ega Caesaria Pratama PUTRA[3], Mentari Maratus SHOLIHAH[1], Nasywa Zahida ROCHMAH[4]

Abstract

Hepatic fibrosis is a pathological process resulting from chronic liver injury that represents the primary determinant of disease progression toward cirrhosis and cardiovascular complications. In patients with type 2 diabetes mellitus (T2DM), the risk of hepatic fibrosis is significantly elevated, particularly in the context of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). This article aims to review antidiabetic agents with evidence supporting hepatic fibrosis reduction, as well as those lacking such evidence. Different classes of antidiabetic drugs demonstrate divergent effects on hepatic steatosis, steatohepatitis, and fibrosis. Pioglitazone exhibits the most consistent evidence for improving the histological features of MASH and reducing fibrosis stage with long-term therapy. GLP-1 receptor agonists and dual GIP/GLP-1 agonists demonstrate significant effects on body weight reduction and steatohepatitis improvement, with growing evidence of fibrosis benefit. SGLT2 inhibitors confer benefits through improvement of steatosis and non-invasive fibrosis markers, alongside robust cardiovascular and renoprotective effects. In contrast, metformin, DPP-4 inhibitors, insulin, and sulfonylureas do not demonstrate meaningful evidence of hepatic fibrosis reduction. Weight loss of 7–10% remains the most consistently identified factor correlated with fibrosis regression. Therapeutic selection must therefore be individualized, comprehensive, and guided by the patient's comorbidity profile.

Keywords: type 2 diabetes mellitus; MASLD; MASH; hepatic fibrosis; pharmacological therapy

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Central Java, Indonesia
[2]Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Sebelas Maret and Moewardi General Hospital, Surakarta, Indonesia
[3]Division of Endocrinology, Diabetes, & Metabolism, Department of Internal Medicine, Faculty of Medicine, Universitas Sebelas Maret and Moewardi General Hospital, Surakarta, Indonesia
[4]Medical Doctor Professional Program, Faculty of Medicine, Universitas Padjadjaran, Bandung, West Java, Indonesia

***Corresponding author:**
Muhammad Ifham HANIF, Department of Internal Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Central Java, Indonesia
E-mail: muhammadifhamhanif@gmail.com

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), encompasses a spectrum of liver disease ranging from simple steatosis to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (Genua & Cusi, 2024). The prevalence of MASLD continues to rise in parallel with the global epidemics of obesity and type 2 diabetes mellitus (T2DM), making it the most common chronic liver disease worldwide, with an estimated prevalence of approximately 30% in the adult population (Genua & Cusi, 2024; Loomba et al., 2024).

In individuals with T2DM, the prevalence of MASLD is markedly higher, reaching 55–75%, with approximately 20–30% progressing to metabolic dysfunction-associated steatohepatitis (MASH). Patients with T2DM carry a 2–3-fold greater risk of developing advanced hepatic fibrosis compared to non-diabetic populations, even after adjusting for age and body mass index (Genua & Cusi, 2024; Loomba et al., 2024). Hepatic fibrosis is the principal predictor of liver-specific morbidity and mortality, rendering this patient population a priority target for screening strategies and therapeutic intervention (Bellanti et al., 2022; Musso et al., 2017).

The pathogenesis of fibrosis in T2DM involves complex interactions among insulin resistance, hepatic lipid accumulation, oxidative stress, and the activation of hepatic stellate cells, which trigger the deposition of extracellular matrix (Loomba et al., 2024). Interventions targeting metabolic factors—particularly weight loss and improvement of insulin resistance—have the potential to attenuate hepatic inflammation and slow or reverse fibrosis progression. However, histological improvement of fibrosis requires months to years and is highly dependent on the magnitude of weight reduction achieved (Bellanti et al., 2022; Genua & Cusi, 2024).

Several modern antidiabetic agents have demonstrated favorable effects on steatohepatitis parameters and fibrosis markers (Głuszyńska et al., 2021; Musso et al., 2017). The glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide has shown MASH resolution in clinical trials, although the magnitude of histological fibrosis regression has been variable. The dual glucose-dependent insulinotropic polypeptide/GLP-1 (GIP/GLP-1) receptor agonist tirzepatide has demonstrated promising outcomes in MASH resolution and fibrosis improvement in the SYNERGY-NASH trial (Rinella et al., 2023). Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been reported to improve hepatic steatosis and certain non-invasive fibrosis markers (Loomba et al., 2024; Takawy & Abdelmalek, 2025). Pioglitazone remains one of the most consistent agents for improving the histological features of steatohepatitis and fibrosis, albeit with usage limited by its adverse effect profile (Bandyopadhyay et al., 2023; Takawy & Abdelmalek, 2025).

A thorough understanding of the differential hepatic effects of antidiabetic drug classes is essential for the optimal management of T2DM patients with MASLD/MASH. This article aims to review antidiabetic agents with evidence supporting hepatic fibrosis reduction, as well as those without such evidence, in order to provide practical guidance for the selection of optimal therapeutic regimens.

Lifestyle-related factors, including diet and physical inactivity, play a fundamental role in the development and progression of chronic metabolic diseases by modulating systemic inflammation and insulin resistance (Ionescu et al., 2024).

METHODS

This article constitutes a narrative literature review examining the scientific evidence on the role of antidiabetic agents in the treatment of hepatic fibrosis in patients with type 2 diabetes mellitus and MASLD/MASH. A systematic literature search was conducted through electronic databases including PubMed, Scopus, and Google Scholar. Search terms were organized into three conceptual domains: (1) disease and population — diabetes mellitus type 2, MASLD, MASH, NAFLD, NASH, insulin resistance; (2) hepatic outcomes — hepatic fibrosis, liver fibrosis, hepatic steatosis, steatohepatitis, liver histology, liver biopsy, FIB-4, liver stiffness measurement, non-invasive fibrosis markers; and (3) pharmacological interventions — antidiabetic drugs, antihyperglycemic agents, pharmacotherapy, GLP-1 receptor agonist, semaglutide, liraglutide, SGLT2 inhibitor, empagliflozin, dapagliflozin, pioglitazone, thiazolidinedione, tirzepatide, dual GIP/GLP-1 receptor agonist, incretin, DPP-4 inhibitor, metformin, sulfonylurea, insulin, resmetirom. Search terms were applied both individually and in combination using Boolean operators (AND, OR).

Inclusion criteria comprised original research articles in the form of randomized controlled trials (RCTs), meta-analyses, systematic reviews, and clinical guidelines published in English or Indonesian between 2015 and 2025, sourced from peer-reviewed journals indexed in Scopus or Web of Science, with priority given to primary literature from reputable journals and international clinical guidelines from the American

Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the American Diabetes Association (ADA). Studies utilizing histological fibrosis outcomes or validated non-invasive fibrosis markers were prioritized. Exclusion criteria included animal studies, case reports, editorials, conference abstracts, and studies not reporting hepatic fibrosis-related outcomes. Landmark studies published prior to 2015 were included when deemed of high clinical relevance.

Articles were selected based on relevance to the review objectives through title, abstract, and full-text screening. Of the 30 references cited, 8 primary studies with direct hepatic fibrosis outcomes were selected for synthesis. Extracted data included drug mechanisms of action, clinical evidence from RCTs and meta-analyses, effects on hepatic steatosis, steatohepatitis, and fibrosis, as well as safety profiles and adverse effects. Evidence quality was appraised based on study design, sample size, follow-up duration, and outcomes measured, with emphasis on liver biopsy-based studies as the gold standard for fibrosis assessment.

RESULTS AND DISCUSSION

Hepatic Fibrosis in Type 2 Diabetes Mellitus and MASLD

Hepatic fibrosis is a pathological process characterized by the excessive deposition of extracellular matrix components—predominantly type I and III collagen—in response to recurrent and persistent liver injury. It represents a maladaptive wound-healing response and constitutes the pivotal transitional stage toward cirrhosis and the advanced complications of chronic liver disease (Genua & Cusi, 2024; Loomba et al., 2024). Regardless of etiology, fibrosis stage is the strongest prognostic determinant of liver-related morbidity and mortality across virtually all forms of chronic hepatic disease.

In patients with T2DM, insulin resistance plays a central role in facilitating intracellular lipid accumulation through enhanced de novo lipogenesis and impaired lipid oxidation (Mózes et al., 2022; Targher et al., 2024). In addition, adipokines and pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and leptin further exacerbate insulin resistance and metabolic dysregulation, thereby contributing to the progression of metabolic diseases and hepatic injury (Popescu et al., 2024). Hyperinsulinemia and hyperglycemia exacerbate hepatic metabolic dysfunction, amplifying lipotoxicity, oxidative stress, and the release of pro-inflammatory cytokines, which subsequently activate hepatic stellate cells into a myofibroblastic phenotype capable of collagen synthesis (Targher et al., 2024). The multiple-parallel hits model of pathogenesis is now more widely accepted than the earlier "two-hit" hypothesis; in addition to insulin resistance and obesity, genetic factors (e.g., PNPLA3, TM6SF2 variants), gut microbiome dysbiosis, and cardiometabolic comorbidities collectively determine the progression from steatosis to MASH and fibrosis (Grander et al., 2023; Ramai et al., 2021).

Patients with advanced fibrosis (≥F3) carry a substantially elevated risk of hepatic decompensation, liver-related mortality, and cardiovascular complications (Bellanti et al., 2022; Genua & Cusi, 2024). Patients with advanced fibrosis (≥F3) carry a substantially elevated risk of hepatic decompensation, liver-related mortality, and cardiovascular complications. Histological regression of fibrosis demands both time and sustained metabolic improvement; meaningful improvement is generally achieved following significant weight loss (≥7–10%) maintained over months to years of consistent intervention (Grander et al., 2023; Loomba et al., 2024; Nogueira & Cusi, 2024). The differential hepatic and metabolic effects of key antidiabetic agent classes are summarized in Figure 1, which illustrates how insulin sensitizers, incretin-based therapies, and SGLT2 inhibitors engage distinct but partially overlapping pathways to reduce steatosis, steatohepatitis, and fibrogenic drive.

Anti Diabetic Agents with Evidence of Reducing Hepatic Fibrosis

Pioglitazone (Thiazolidinedione)

Pioglitazone is a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist that enhances insulin sensitivity in peripheral tissues and the liver, redirects lipid storage from the liver toward subcutaneous adipose tissue, and thereby reduces hepatic lipotoxicity. As depicted in Figure 2, these mechanisms collectively attenuate the metabolic stress and hepatocellular inflammation that drive hepatic stellate cell activation and subsequent fibrosis. In addition to canonical PPAR-γ-mediated effects, emerging molecular data suggest the existence of non-genomic mechanisms that may further contribute to pioglitazone's hepatoprotective action (Harrison et al., 2023).

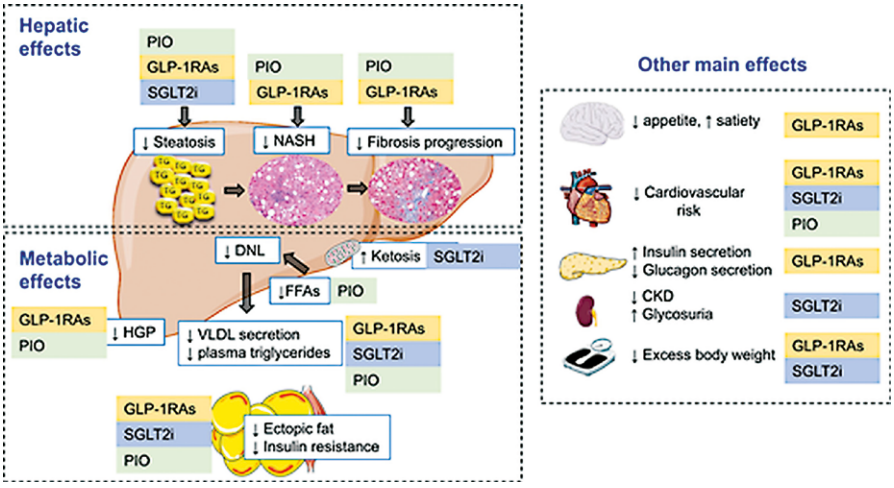

Figure 1. Hepatic and metabolic effects of antidiabetic therapy in NAFLD/MASLD

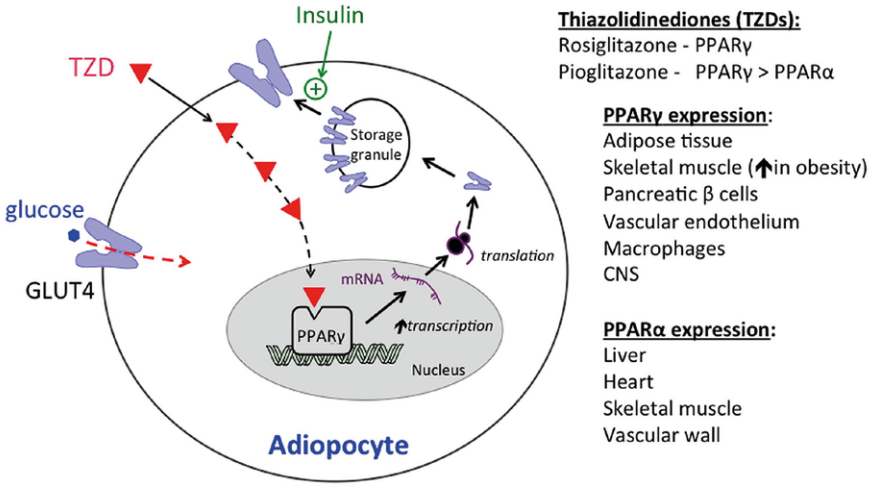

Figure 2. Mechanism of action of thiazolidinediones (pioglitazone) in the context of NAFLD/MASH

Multiple randomized controlled trials and meta-analyses have consistently demonstrated that pioglitazone improves the histological features of steatohepatitis and achieves fibrosis improvement of ≥1 stage in a meaningful proportion of patients after treatment durations of ≥12 months (Głuszyńska et al., 2021; Harrison et al., 2023; Wang et al., 2023). Major hepatology guidelines (EASL/AASLD) recommend considering pioglitazone in patients with confirmed MASH, particularly those with concurrent diabetes or glucose intolerance. The most pronounced antifibrotic effects are observed at fibrosis stages F1–F2, with partial improvement documented at F3 following prolonged therapy (≥12–18 months); however, no evidence supports reversal of F4 fibrosis (cirrhosis). Its clinical utility is limited by adverse effects including weight gain, fluid retention/oedema, and an increased risk of exacerbating congestive heart failure, necessitating careful patient selection and an individualized benefit-risk assessment prior to initiation (Głuszyńska et al., 2021; Harrison et al., 2023; Musso et al., 2017; Wang et al., 2023).

GLP-1 Receptor Agonists

GLP-1 receptor agonists act by stimulating glucose-dependent insulin secretion, suppressing appetite through central and peripheral mechanisms, delaying gastric emptying, and inducing clinically meaningful weight loss. Weight reduction represents the primary mechanism through which GLP-1 RAs reduce hepatic steatosis, attenuate hepatocellular inflammation, and diminish the fibrogenic drive from hepatic stellate cell activation. The dual hepatic pathways involved—encompassing both weight-mediated and potentially direct anti-inflammatory effects at the hepatic level—are illustrated in Figure 3 (Kanwal et al., 2024; Tamilwanan et al., 2025).

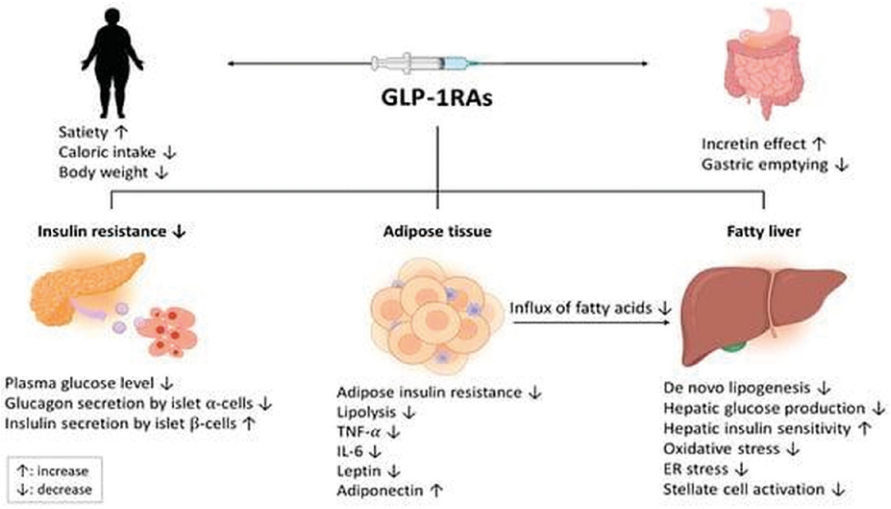

Figure 3. Therapeutic mechanisms of GLP-1 receptor agonists in NAFLD/MASLD

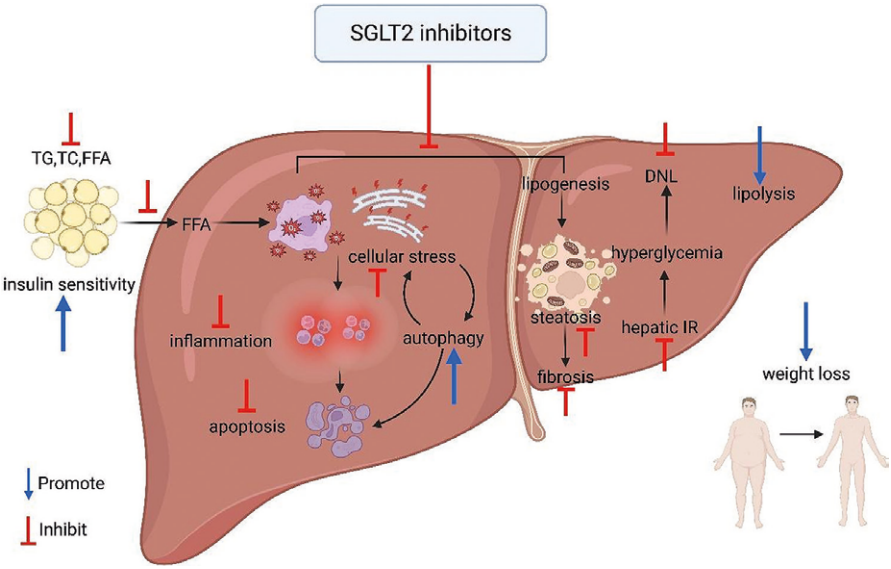

Figure 4. SGLT2 inhibitors in the context of NAFLD/MASLD pathogenesis and treatment

A phase II clinical trial of semaglutide (72 weeks) demonstrated significant improvement in MASH resolution compared to placebo; however, the primary endpoint of fibrosis improvement by ≥1 stage did not achieve statistical significance in the primary analysis, despite improvement signals in several pre-specified subgroups (Chrysavgis et al., 2024; Kanwal et al., 2024). Recent meta-analyses indicate that GLP-1 RAs improve hepatic fat content, reduce liver transaminases, and increase the likelihood of MASH resolution. Effects on non-invasive fibrosis markers trend toward improvement but remain heterogeneous across studies, with fibrosis benefit most apparent in patients achieving weight loss of ≥7–10% (Tamilwanan et al., 2025; Zhu et al., 2021). Fibrosis improvement is most consistently documented at stages F1–F2; data at F3 show an inconsistent improvement signal, and there is no evidence that GLP-1 RAs can reverse cirrhosis at F4 (Newsome et al., 2021; Zhu et al., 2021).

SGLT2 Inhibitors

SGLT2 inhibitors lower blood glucose by promoting urinary glucose excretion, thereby creating a mild sustained caloric deficit, facilitating modest weight loss, and improving insulin sensitivity. These metabolic improvements may reduce the hepatic flux of free fatty acids, attenuate lipotoxicity, and suppress the metabolic inflammation that constitutes a principal driver of fibrogenesis. The mechanistic framework linking SGLT2 inhibition to potential improvement in NAFLD progression is depicted in Figure 4 (Erfanifar et al., 2025; Li et al., 2025).

The most consistent clinical evidence for SGLT2 inhibitors pertains to reduction in hepatic fat content (steatosis) and improvement of hepatic inflammation and injury, accompanied by improvement in non-invasive fibrosis markers in a subset of studies (Erfanifar et al., 2025; Li et al., 2025). Studies with dapagliflozin

have demonstrated significant reductions in liver fat content, accompanied by improvements in alanine aminotransferase (ALT) and reductions in inflammatory cytokines (Shi et al., 2023). Studies with empagliflozin have shown significant reductions in FIB-4 scores, although the NAFLD Fibrosis Score did not change significantly in parallel (Hasan et al., 2024). A 2024 meta-analysis concluded that SGLT2 inhibitors provide improvements in steatosis and/or non-invasive fibrosis indices including FIB-4, controlled attenuation parameter (CAP), and liver stiffness measurement, particularly in patients with mild-to-moderate fibrosis (F1–F2) (Ong Lopez & Pajimna, 2024). Direct histological evidence of fibrosis reduction remains limited, and no evidence exists for regression at F4. SGLT2 inhibitors are therefore most appropriately positioned as agents that improve the metabolic milieu and potentially slow fibrosis progression, with the additional advantage of robust cardiovascular and renoprotective effects (Erfanifar et al., 2025; Li et al., 2025; Ong Lopez & Pajimna, 2024).

Tirzepatide (Dual GIP/GLP-1 Receptor Agonist)

Tirzepatide is a once-weekly dual GIP and GLP-1 receptor agonist that combines the complementary actions of both incretin hormones to enhance glycemic control while simultaneously inducing substantial weight loss through reduced energy intake and redistribution of adipose tissue. Reduction in visceral adiposity decreases hepatic free fatty acid flux, attenuating lipotoxicity, metabolic inflammation, and the fibrogenic drive. The integrated mechanism of action and downstream clinical effects of tirzepatide on the steatotic liver are illustrated in Figure 5 (Meng et al., 2023; Ong Lopez & Pajimna, 2024).

The strongest histological evidence for tirzepatide derives from the SYNERGY-NASH trial, published in the New England Journal of Medicine in 2024. In this phase III study, tirzepatide was evaluated in patients with biopsy-confirmed MASH and fibrosis stages F2–F3 over 52 weeks. All tirzepatide doses were superior to placebo for the primary endpoint of MASH resolution without fibrosis worsening, with response rates of 44% (5 mg), 56% (10 mg), and 62% (15 mg) compared to 10% in the placebo group. Fibrosis improvement of ≥1 stage without MASH worsening was achieved in approximately 51–55% of tirzepatide-treated patients compared to 30% in the placebo group. Mean body weight reduction reached 10.7–15.6% across the tirzepatide dose groups (Rinella et al., 2023).

Patients with F4 fibrosis were not enrolled in the trial; consequently, no evidence currently supports the reversal of cirrhosis with tirzepatide (Loomba et al., 2024; Ong Lopez & Pajimna, 2024; Rinella et al., 2023). The safety profile was consistent with that observed in phase III trials for diabetes and obesity, with gastrointestinal adverse effects (nausea, diarrhoea, constipation) representing the most common treatment-emergent events, generally mild to moderate in severity (Rinella et al., 2023; Takawy & Abdelmalek, 2025). The characteristics, key supporting studies, and clinical evidence of all antidiabetic agents with hepatic fibrosis-reducing effects are summarized in Table 1.

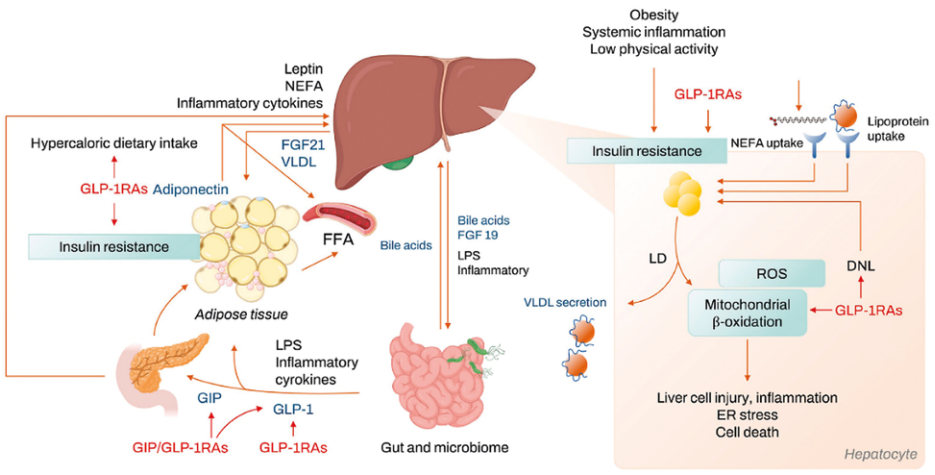

Figure 5. Mechanism of action and hepatic clinical effects of tirzepatide (dual GIP/GLP-1 receptor agonist)

Table 1
Comparison of Antidiabetic Agents with Evidence of Reducing Hepatic Fibrosis in MASLD/MASH

Drug Class / Agent	Key Studies (≥2)	Population & Fibrosis Stage	Duration	Fibrosis Outcome	Most Responsive Fibrosis Stage	Clinical Notes
TZD (Pioglitazone)	1) Wang et al., meta-analysis RCT 2023 2) Corey et al., review RCT 2021	NASH ± DM2 F1–F3	≥12–18 months	↑ Fibrosis improvement ≥1 stage in a proportion of patients	F1–F2 (strong) F3 (partial, long-term therapy)	Strongest histological evidence; weight gain, oedema, HF risk; contraindicated in decompensated cirrhosis
GLP-1 Receptor Agonist (Semaglutide / Liraglutide)	1) Newsome et al., NEJM 2021 2) Zhu et al., meta-analysis 2021	Biopsy-confirmed NASH Predominantly F1–F2	48–72 weeks	Fibrosis improvement signal; not always statistically significant	F1–F2 (conditional on ≥7–10% weight loss)	Indirect antifibrotic effect; NASH resolution more robust than fibrosis benefit
SGLT2 Inhibitor (Empagliflozin / Dapagliflozin)	1) Macaire et al., meta-analysis 2024 2) Li et al., meta-analysis 2025[26]	NAFLD/MASLD + DM2 F1–F2	24–52 weeks	Improvement in non-invasive fibrosis markers (FIB-4, LSM)	F1–F2 (marker-based)	Limited histological evidence; strong CV/ renal benefits
Tirzepatide (Dual GIP/GLP-1 RA)	1) SYNERGY-NASH, NEJM 2024 2) Gastaldelli et al., SURPASS-3 MRI 2022	Biopsy-confirmed MASH F2–F3	52 weeks	↑ Significant fibrosis improvement ≥1 stage	F2–F3 (strongest evidence)	10–15% weight loss; F4 data not yet available

Abbreviations: T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GIP, glucose-dependent insulinotropic polypeptide; SGLT2, sodium-glucose cotransporter-2; MASH, metabolic dysfunction-associated steatohepatitis; LSM, liver stiffness measurement; HF, heart failure; CV, cardiovascular.

Antidiabetic Agents Without Evidence of Reducing Hepatic Fibrosis

Metformin

Metformin is the first-line antidiabetic therapy for T2DM, with established efficacy in improving hepatic insulin sensitivity and suppressing gluconeogenesis. Although these properties are theoretically advantageous given that insulin resistance is a central driver of hepatic steatosis and inflammation, clinical evidence indicates that the metabolic benefits of metformin do not translate into histological liver improvement. Randomized controlled trials and meta-analyses consistently demonstrate that, despite modest improvements in biochemical parameters such as ALT, there is no meaningful histological improvement in steatohepatitis or fibrosis (Bandyopadhyay et al., 2023). The AASLD Practice Guidance 2023 explicitly states that metformin has not been shown to improve MASH histology and is not recommended as a specific therapy for MASH or hepatic fibrosis (Targher et al., 2024).

Inhibitor DPP-4

DPP-4 inhibitors act by elevating endogenous GLP-1 levels through inhibition of its enzymatic degradation. However, the metabolic effects of DPP-4 inhibitors are substantially more modest than those of direct GLP-1 receptor agonists, particularly with respect to body weight reduction and visceral fat redistribution—two critical determinants of improvement in metabolic liver disease (Takawy & Abdelmalek, 2025; Targher et al., 2024). Multiple clinical studies have yielded inconsistent results: some small trials have reported minor improvements in steatosis or reductions in ALT, but no consistent evidence exists for fibrosis improvement or histological MASH resolution. AASLD guidelines (2023) affirm that DPP-4 inhibitors do not confer improvement in MASH histology (Targher et al., 2024).

Insulin and Sulfonylureas

Insulin and sulfonylureas are established antidiabetic therapies that effectively lower blood glucose through promotion of insulin secretion or provision of exogenous insulin. However, no evidence supports a direct beneficial effect of either agent on the improvement of steatohepatitis or hepatic fibrosis. Both drug classes are frequently associated with weight gain—a major risk factor for the progression of steatosis and fibrosis. The ADA Standards of Care 2025 affirms that insulin and sulfonylureas carry an inherent propensity for body weight increase, necessitating careful consideration of their use in patients with obesity and metabolic comorbidities (American Diabetes Association Professional Practice Committee, ElSayed, McCoy, Aleppo, Bajaj, et al., 2025; Sahin et al., 2024).

Novel Therapy: Resmetirom

Resmetirom is a selective thyroid hormone receptor-β (THR-β) agonist that acts directly on hepatocytes to enhance fatty acid oxidation, reduce de novo lipogenesis, and attenuate intrahepatic lipid accumulation. In contrast to antidiabetic agents that exert hepatic benefits primarily through improvement of insulin resistance and weight reduction, resmetirom specifically targets hepatocyte metabolism at the organ level, thereby offering a mechanism of action orthogonal to that of the antidiabetic drug classes discussed above (American Diabetes Association Professional Practice Committee, ElSayed, McCoy, Aleppo, Bannuru, et al., 2025; Tacke et al., 2024).

In the phase III MAESTRO-NASH clinical trial, resmetirom demonstrated statistically significant improvement in MASH resolution without fibrosis worsening, as well as fibrosis improvement of ≥1 stage compared to placebo, particularly in patients with F2–F3 fibrosis. These benefits were also observed in non-diabetic patients, reinforcing resmetirom's role as a targeted hepatic therapy that is independent of glycemic control mechanisms. Resmetirom therefore represents a promising pharmacological option for attenuating hepatic fibrosis progression in MASLD/MASH, particularly in non-diabetic individuals or patients with moderate-to-advanced fibrosis (American Diabetes Association Professional Practice Committee, ElSayed, McCoy, Aleppo, Bannuru, et al., 2025; Tacke et al., 2024).

Practical Therapeutic Recommendations

Routine screening for hepatic fibrosis is recommended in all T2DM patients, particularly those with obesity or metabolic syndrome, as early identification of advanced fibrosis permits timely and more intensive therapeutic intervention. In clinical practice, this is most efficiently accomplished through a sequential strategy: initial risk stratification using non-invasive scoring tools such as the FIB-4 index and NAFLD Fibrosis Score (NFS), followed by elastography (FibroScan/liver stiffness measurement) in patients with intermediate-to-high risk scores. This stepwise approach reduces the requirement for liver biopsy while maintaining adequate sensitivity for detecting advanced fibrosis, and is particularly critical in T2DM patients given their disproportionately elevated risk of progressive fibrosis (Loomba et al., 2024; Nogueira & Cusi, 2024).

Weight loss constitutes the most important modifiable determinant of steatohepatitis improvement and hepatic fibrosis regression in patients with MASLD/MASH. Weight reduction of ≥7–10% is consistently associated with steatohepatitis resolution and fibrosis improvement of ≥1 stage (Rinella et al., 2023; Targher et al., 2024). AASLD and EASL guidelines position weight loss as the cornerstone of MASLD/MASH management, with pharmacotherapy serving as a tool to assist in achieving and sustaining that target (Targher et al., 2024).

In patients with T2DM, obesity, and MASLD/MASH, GLP-1 receptor agonists and, in particular, the dual GIP/GLP-1 agonist tirzepatide represent preferred treatment options when therapeutic goals encompass significant weight loss and steatohepatitis improvement (Rinella et al., 2023). SGLT2 inhibitors constitute a rational choice for patients with T2DM and concurrent chronic kidney disease or heart failure, given their strong cardiovascular and renoprotective evidence base (Hasan et al., 2024). Pioglitazone may be considered in patients with T2DM and confirmed MASH who do not have contraindications such as heart failure or substantial oedema risk (Harrison et al., 2023; Musso et al., 2017).

Adequate glycemic control remains an indispensable pillar of care; however, the selection of antidiabetic agents should prioritize effects on body weight and hepatic outcomes, rather than focusing exclusively on HbA1c reduction. The contemporary therapeutic paradigm is evolving from monotherapy toward combination regimens targeting multiple mechanisms simultaneously, with the potential for synergistic effects on fibrosis improvement—particularly relevant in patients with moderate-to-advanced fibrosis (Takawy & Abdelmalek, 2025; Targher et al., 2024). These findings support the importance of a patient-centered and holistic management approach in chronic metabolic diseases, integrating metabolic control, lifestyle modification, and long-term outcome monitoring (Dumitrescu et al., 2024).

CONCLUSIONS

Not all antidiabetic agents demonstrate efficacy in reducing hepatic fibrosis. Pioglitazone, GLP-1 receptor agonists, SGLT2 inhibitors, and tirzepatide represent the drug classes with the most promising evidence for improving parameters of steatohepatitis and hepatic fibrosis, with tirzepatide exhibiting the strongest histological evidence to date. Resmetirom, as an emerging targeted hepatic therapy, shows considerable promise as a specific antifibrotic agent in MASH. Nonetheless, weight loss remains the most critical determinant of fibrosis improvement, and the efficacy

of pharmacotherapy is substantially dependent on the capacity of the therapeutic agent to assist patients in achieving and sustaining weight loss targets. Conversely, metformin, DPP-4 inhibitors, insulin, and sulfonylureas do not demonstrate meaningful evidence of histological hepatic fibrosis reduction. The therapeutic approach for patients with T2DM and MASLD/MASH must be individualized, comprehensive, and comorbidity-guided, integrating lifestyle intervention, evidence-based pharmacotherapy, and long-term clinical monitoring.

SUGGESTION

Based on the current clinical evidence, several practical recommendations are proposed for the management of patients with T2DM and MASLD/MASH. First, hepatic fibrosis screening using non-invasive tools (FIB-4, NFS) and elastography (FibroScan) should be routinely implemented in T2DM patients with obesity or metabolic syndrome to enable early identification of advanced fibrosis warranting intensive intervention. Second, antidiabetic therapy selection in patients with MASLD/MASH should prioritize agents with demonstrated evidence of hepatic benefit—such as tirzepatide, GLP-1 receptor agonists, or SGLT2 inhibitors—taking into account each patient's comorbidity profile. Pioglitazone may be considered in specific cases following individualized benefit-risk assessment. Third, a minimum weight loss target of 7–10% should serve as the primary therapeutic goal, supported by structured lifestyle intervention and appropriate pharmacotherapy. Fourth, a multidisciplinary approach—encompassing endocrinology, hepatology, nutrition, and cardiology—is essential for the comprehensive management of patients with complex comorbidities. Fifth, further research is warranted to evaluate the efficacy of combination therapies, define optimal treatment durations for long-term fibrosis regression, and identify predictive biomarkers of treatment response to facilitate personalized therapeutic approaches.

Ethics Statement and Conflict of Interest Disclosures

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Availability of data and materials: The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.
Competing interests: The authors declared that they have no competing interests.
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