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The Bidirectional Relationship Between Type 2 Diabetes and NAFLD/MASH: Pathophysiology, Screening Strategies, and Therapeutic Opportunities

Ni Made Dwitya Arianingtyas*, I Ketut Suryana
RSUD Wangaya Denpasar Bali, Indonesia
Email: dwityasdg@gmail.com*

KEYWORDS
Type 2 diabetes mellitus; NAFLD; MASLD; MASH; insulin resistance; screening

ABSTRACT
Type 2 diabetes mellitus (T2DM) and nonalcoholic fatty liver disease (NAFLD), including its progressive forms—metabolic dysfunction–associated steatotic liver disease (MASLD) and steatohepatitis (MASH)—are closely linked manifestations of metabolic syndrome, bidirectionally influencing each other. Insulin resistance, adipose tissue dysfunction, inflammation, oxidative stress, and genetic–epigenetic factors contribute to their simultaneous development and progression to fibrosis. This review aims to explore the pathophysiological mechanisms connecting T2DM and NAFLD/MASH, evaluate bidirectional screening strategies, and summarize pharmacological and lifestyle treatments for patients with both conditions. The review is based on a narrative analysis of clinical evidence, screening guidelines, and therapeutic approaches from relevant documents, excluding external sources. T2DM and NAFLD/MASH are interconnected through insulin resistance, lipotoxicity, adipose dysfunction, inflammatory pathways, and genetic–epigenetic factors. T2DM increases NAFLD progression to MASH and fibrosis, while NAFLD raises the risk of prediabetes and T2DM. A layered screening strategy involving biomarkers, fibrosis scores, and imaging is recommended for high-risk populations. Lifestyle interventions—including weight loss, diet, and exercise—are fundamental, supported by modern antidiabetic agents and liver-targeted therapies. T2DM and NAFLD/MASH are intertwined, requiring integrated screening and management strategies that address both metabolic and liver disease progression. Lifestyle changes remain essential, with emerging pharmacological treatments offering additional benefits. Further research is needed to refine screening methods and optimize treatment approaches for patients with these interconnected metabolic conditions.

DOI:

Corresponding Author: Ni Made Dwitya Arianingtyas*
Email: dwityasdg@gmail.com

INTRODUCTION

Type 2 diabetes mellitus (T2DM) and nonalcoholic fatty liver disease (NAFLD), including their progressive forms now classified as metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), represent two major and increasingly prevalent components of the metabolic syndrome spectrum whose global health burden continues to escalate dramatically. Current epidemiological data reveal that NAFLD affects approximately 25-30% of the general adult population worldwide, with significantly higher prevalence rates of 55-70% among individuals with T2DM and up to 90% in severely obese populations. Conversely, T2DM prevalence has reached epidemic proportions, affecting over 537 million adults globally as of 2021, with projections suggesting this number will exceed 783 million by 2045. The intersection of these two conditions creates a particularly high-risk population: individuals with both T2DM and NAFLD face substantially elevated risks of progression to advanced liver fibrosis (2-3 fold increased risk), cirrhosis, hepatocellular carcinoma, and cardiovascular mortality compared to those with either condition alone. This dual burden imposes enormous public health consequences through increased morbidity, premature mortality, reduced quality of life, and escalating healthcare costs estimated at hundreds of billions of dollars annually worldwide. The bidirectional relationship between these diseases—where each condition accelerates the development and progression of the other—creates a self-perpetuating pathogenic cycle that demands urgent attention from clinicians, researchers, and healthcare policymakers.

Not only do these two conditions frequently co-occur, but they also engage in a bidirectional relationship characterized by mutual aggravation through interconnected pathophysiological axes involving insulin resistance, metabolic dysfunction, and chronic low-grade inflammation. This relationship has been extensively documented in longitudinal cohort studies demonstrating that NAFLD independently predicts incident T2DM even after adjusting for traditional risk factors, while T2DM significantly accelerates the progression from simple steatosis to MASH and advanced fibrosis.[1–4] Insulin resistance serves as the central mechanistic driver, triggering hyperglycemia and profound disorders of lipid metabolism, while hepatic fat accumulation and inflammatory processes in the liver reciprocally disrupt systemic glucose homeostasis, thus forming a pathogenic vicious cycle that proves exceedingly difficult to interrupt through conventional single-disease management approaches (Dewidar et al., 2020; Gastaldelli & Cusi, 2019; Marušić et al., 2021; Ota, 2021).

At the pathophysiological level, the interaction of T2DM and NAFLD/MASH involves adipose tissue, liver, pancreas, and intestine as one network of organs that communicate with each other. Dysfunction of adipose tissue with increased lipolysis and release of free fatty acids (FFA) into the circulation contributes to hepatic steatosis and worsens systemic insulin resistance. Inflammation of adipose tissue through macrophage infiltration and production of proinflammatory cytokines disrupts insulin signaling and triggers systemic inflammation that impacts the liver and other organs (Kohlgruber & Lynch, 2015). On the other hand, oxidative stress and lipotoxicity in hepatocytes activate signaling pathways such as JNK and NF-κB, inducing hepatocellular injury, inflammation, and fibrosis, while deepening insulin resistance and pancreatic β cell dysfunction (Cao et al., 2023; Chen & Vitetta, 2020; W. H. Lee et al., 2025; Rada et al., 2020; Ramatchandirin et al., 2023; Vilas-Boas et al., 2021; Watt et al., 2019).

The contribution of genetic and epigenetic factors further confirms the complexity of this relationship. Gene variants such as PNPLA3 and TM6SF2 are associated with increased accumulation of hepatic fat, inflammation, and degrees of fibrosis, while also playing a role in metabolic disorders in T2DM (Jonas & Schürmann, 2021; Tan et al., 2023). Epigenetic regulation through DNA methylation, histone modification, and microRNA expression in liver, pancreas, adipose tissue, and skeletal muscle tissues affects insulin secretion, insulin resistance, lipid metabolism, and inflammatory responses (Ling & Rönn, 2019). Environmental factors such as diet, obesity, and intrauterine exposure modulate this epigenetic landscape, thereby shaping individual susceptibility to T2DM and NAFLD/MASH and explaining the heterogeneity of clinical phenotypes (Jonas & Schürmann, 2021).

The gut microbiota and gut–liver axis add a layer of mechanisms linking T2DM and NAFLD/MASH. Intestinal dysbiosis with increased mucosal permeability allows the translocation of lipopolysaccharides (LPS) and other bacterial components into the portal circulation, triggering liver inflammation and insulin resistance (Jayakumar & Loomba, 2019; Nawrot et al., 2021). Changes in the composition and function of the microbiota affect the production of metabolites such as short-chain fatty acids, bile acids, and tryptophan metabolites that can be both protective and destructive, and play a role in hepatic inflammation and fibrogenesis (Chen & Vitetta, 2020; Safari & Gérard, 2019; Teunis et al., 2022). This convergence of mechanisms makes the gut, liver, and adipose tissue strategic targets for multidimensional interventions in these interrelated metabolic diseases.

The clinical consequences of this two-way relationship are far-reaching. The presence of T2DM increases the risk of NAFLD progression to NASH/MASH, advanced fibrosis, cirrhosis, and hepatocellular carcinoma, while NAFLD itself is an independent predictor of the occurrence of prediabetes and new T2DM (Ahmadizar & Younossi, 2024; Boeriu et al., 2023; Dewidar et al., 2020; Marušić et al., 2021). This condition encourages the need for a two-way screening strategy: NAFLD screening in T2DM patients using serum biomarkers, noninvasive fibrosis scores such as FIB-4, NAFLD Fibrosis Score, and ELF scores, as well as noninvasive imaging such as ultrasonography, transient elastography, and MRI/MRE; as well as prediabetes and T2DM screening in NAFLD patients with fasting glucose assessment, HbA1c, oral glucose tolerance test, and other metabolic risk markers (A.F. et al., 2020; Boeriu et al., 2023; Ciardullo et al., 2020, 2023; Diaconu & Guja, 2022; Khandelwal et al., 2021; Malek et al., 2021; S. et al., 2020; Shieh et al., 2020; Vieira Barbosa & Lai, 2021; E. Zhang et al., 2015; S. Zhang et al., 2023).

At the management level, the focus of therapy shifts from an organ-specific approach to an integrated strategy that targets insulin resistance, inflammation, and fibrosis. Lifestyle interventions through 7–10% weight loss, improved diet, and increased physical activity have been shown to lower intrahepatic fat, improve glycemic control, reduce inflammation, and lower the risk of fibrosis (Chai et al., 2023; de Lima Ribeiro et al., 2023; Hydes et al., 2020; Parry & Hodson, 2020; Prabhakar & Bhuvaneswari, 2021; Schmid et al., 2022; Takahashi et al., 2018). Modern antidiabetic drugs such as GLP-1 receptor agonists, SGLT2 inhibitors, and pioglitazone have shown benefits on liver fat content, inflammation, and fibrosis, in addition to improving glycemic control and cardiovascular output (Dahlén et al., 2022; Drucker, 2025; Kongmalai et al., 2023; Konings et al., 2025; Pramanik et al., 2024; Zisis et al., 2025). Concurrently, liver-targeted therapies such as resmetyromes and various agents that modulate FXR, PPAR, as well as inflammatory and fibrogenic pathways are being developed for MASH and advanced fibrosis, with immediate implications for high-risk T2DM patients (Kim & Rinella, 2025; Polyzos et al., 2020).

Despite significant advances in understanding pathogenic mechanisms, screening strategies, and treatment options, there are still unmet knowledge gaps and clinical needs. Validation of the most efficient and cost-effective screening algorithms in high-risk T2DM populations, the integration of genetic, epigenetic, and microbiota factors into risk scores, and the determination of the optimal combination of lifestyle interventions, antidiabetic pharmacotherapy, and liver-targeted therapy remain major challenges (Ahmadizar & Younossi, 2024; Boeriu et al., 2023; Ferdous & Ferrell, 2024; Gastaldelli & Cusi, 2019).

At the clinical implementation level, simultaneous bidirectional screening protocols and coordinated multidisciplinary management of T2DM and NAFLD/MASH offer the most promising approach to breaking the mutually reinforcing pathological cycle that characterizes these interconnected conditions, ultimately aiming to reduce morbidity and mortality, prevent costly complications, and substantially improve patients' quality of life and functional capacity. This integrated approach represents a fundamental shift in clinical paradigm—from managing diabetes and liver disease as separate entities toward recognizing and addressing them as interconnected manifestations of systemic metabolic dysfunction requiring comprehensive, coordinated care.

The novelty and significance of this review lie in its comprehensive, contemporary synthesis of the rapidly evolving evidence base regarding the T2DM-NAFLD/MASH interface, with particular emphasis on translating mechanistic insights into actionable clinical strategies for screening, risk stratification, and treatment optimization. By systematically examining the bidirectional pathophysiological connections, evaluating the strengths and limitations of available screening modalities, and critically assessing emerging therapeutic options, this review provides clinicians and researchers with an evidence-based framework for implementing integrated care approaches. In the context of escalating global health burden from both T2DM and NAFLD/MASH, such comprehensive understanding and practical guidance are essential for improving outcomes in this high-risk, rapidly growing patient population.

METHOD

This comprehensive narrative review was compiled through systematic analysis of peer-reviewed literature addressing the pathophysiological, clinical, diagnostic, and therapeutic dimensions of the bidirectional relationship between type 2 diabetes mellitus (T2DM) and nonalcoholic fatty liver disease (NAFLD), including metabolic dysfunction-associated steatotic liver disease (MASLD) and steatohepatitis (MASH). The document selection process prioritized high-quality evidence sources published primarily between 2019 and 2025, including systematic reviews, meta-analyses, randomized controlled trials, large prospective cohort studies, and authoritative clinical practice guidelines from major international organizations such as the American Diabetes Association (ADA), European Association for the Study of the Liver (EASL), and American Association for the Study of Liver Diseases (AASLD).

Data extraction and analysis followed a structured approach focusing on five key domains: (1) shared and distinct pathophysiological mechanisms linking T2DM and NAFLD/MASH, including molecular signaling pathways, genetic-epigenetic factors, and gut-liver axis interactions; (2) epidemiological evidence demonstrating the bidirectional nature of the relationship and clinical implications; (3) screening strategies and diagnostic approaches for detecting NAFLD in diabetic patients and vice versa, including performance characteristics of biomarkers, risk scores, and imaging modalities; (4) pharmacological interventions targeting both metabolic and hepatic manifestations, with emphasis on emerging therapies; and (5) lifestyle modifications and their mechanisms of benefit.

The narrative synthesis methodology was selected as most appropriate for this review given the multifaceted nature of the topic, which spans molecular biology, clinical epidemiology, diagnostic technology, and therapeutics. This approach enables comprehensive integration of diverse evidence types and identification of consistent patterns across studies while acknowledging heterogeneity in study designs, populations, and outcomes. Information synthesis emphasized internal consistency, biological plausibility, and clinical relevance of findings.

A significant methodological limitation of this review is the restriction to documents provided within the specified corpus, precluding systematic database searches across PubMed, EMBASE, Cochrane Library, and other major repositories. This constraint may result in incomplete capture of the most recent evidence and emerging therapeutic developments. Additionally, the narrative synthesis approach, while enabling breadth of coverage, lacks the systematic risk-of-bias assessment, statistical pooling, and explicit reproducibility protocols characteristic of formal systematic reviews and meta-analyses. Future updates should incorporate comprehensive database searches with explicit inclusion/exclusion criteria, systematic quality assessment using validated tools such as GRADE (Grading of Recommendations Assessment, Development and Evaluation), and where feasible, quantitative meta-analysis of comparable outcome data to strengthen evidence synthesis rigor. Despite these limitations, the review provides valuable contemporary synthesis of key concepts and clinical approaches for managing the T2DM-NAFLD/MASH intersection.

RESULT AND DISCUSSION

Similar Pathogenic Mechanisms

Insulin resistance is a central and common pathogenic mechanism in nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM), underpinning the complex two-way relationship between these two conditions. NAFLD, which is characterized by the accumulation of fat in hepatocytes without alcohol cause, and T2DM, a chronic metabolic disorder in glucose regulation, share overlapping pathophysiological pathways and are primarily driven by impaired insulin action. Insulin resistance disrupts glucose metabolism and triggers lipid accumulation, thus contributing to the progression of both diseases and their complications, such as nonalcoholic steatohepatitis (NASH) and complications of diabetes. This interrelated pathophysiology makes management and screening strategies interdependent, while opening up therapeutic opportunities targeting insulin resistance to reduce the impact of both conditions (Dewidar et al., 2020; Marušić et al., 2021; Ota, 2021).

At the molecular level, insulin resistance interferes with the liver's ability to maintain glucose and lipid homeostasis. Under normal circumstances, insulin suppresses hepatic glucose production and increases lipid storage in adipose tissue. However, in insulin resistance conditions, the liver continues to perform gluconeogenesis despite high insulin levels, thus triggering hyperglycemia. Simultaneously, dysfunction of lipid metabolism increases the flow of free fatty acids to hepatocytes, mitochondrial dysfunction, oxidative stress, and inflammatory responses, which exacerbate steatosis and promote fibrosis. Activated cytokines and immune cells create a proinflammatory environment that links metabolic stress to liver injury and systemic insulin resistance. Genetic, epigenetic, and environmental factors also modulate this process, describing the same multifaceted pathogenic tissue in NAFLD and T2DM with insulin resistance as the center (Nogueira & Cusi, 2024; Ota, 2021).

This shared mechanism creates a self-sustaining cycle, in which NAFLD can worsen insulin resistance and increase the risk of T2DM, while hyperglycemia and metabolic disorders in diabetes aggravate the progression of liver diseases, such as NASH and fibrosis. Clinical data suggest that the presence of T2DM significantly increases the risk of advanced NAFLD and liver-related complications. Thus, the screening strategy must consider the presence of one of the conditions in order to detect and deal with the other condition early. Current recommendations emphasize assessment of liver function in patients with T2DM and metabolic syndrome, as well as monitoring of glucose metabolism in NAFLD patients as part of an integrated management approach to break this cycle (Dewidar et al., 2020; Marušić et al., 2021).

Therapeutically, addressing insulin resistance is important to manage NAFLD and T2DM. Pharmacological agents originally developed for diabetes, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2i), have shown beneficial effects on the reduction of liver fat, inflammation, and fibrosis, in addition to improving glycemic control. In addition, drugs that increase insulin sensitivity such as pioglitazon have been shown to improve liver histology in NASH patients with insulin resistance. Lifestyle interventions, such as weight loss, diet modification, and increased physical activity, remain foundational because they effectively improve insulin sensitivity and, thus, treat both diseases. This therapeutic convergence emphasizes the need for integrated management strategies that target common pathogenic roots, rather than a separate approach per organ (Dewidar et al., 2020; Kanbay et al., 2021; Nogueira & Cusi, 2024).

Inflammation within adipose tissue is an important mechanism that drives this metabolic disorder. Obesity-related expansion of adipose tissue triggers the infiltration of immune cells, especially macrophages, that produce inflammatory cytokines that interfere with insulin signaling pathways. This low-degree chronic inflammation not only worsens adipose tissue dysfunction, but also contributes to systemic insulin resistance that affects the liver and other peripheral tissues. This inflammatory environment alters adipocyte function, lowers protective adipokine, and increases lipolysis, thereby enlarging the flow of FFA to the liver and facilitating the progression of NAFLD to MASH (Gu et al., 2023; Kohlgruber & Lynch, 2015).

The bidirectional interaction between adipose tissue and the liver involves a variety of metabolic and inflammatory mediators. For example, fibrotic changes and the secretion of profibrotic factors such as endotrophins from adipose tissue have been reported to be associated with the degree of liver fibrosis in MASH. These mediators increase inflammation and hepatic fibrosis, so the degree of severity of the pathology of adipose tissue is directly related to the progression of liver disease. Therapeutic agents that target these pathways, such as PPAR agonists and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have shown efficacy in lowering insulin resistance and adipose tissue inflammation, as well as improving glycemic and histological control of the liver in affected patients (Gabbia & De Martin, 2023).

These findings confirm a two-way relationship between NAFLD/MASH and T2DM, where adipose tissue acts as well as a source as well as a booster of metabolic and inflammatory signals that contribute to disease progression. An understanding of these complex interactions forms the basis for developing integrated screening strategies and therapeutic interventions that address hepatic and systemic metabolic disorders simultaneously. The focus on reducing inflammation of adipose tissue is becoming a promising approach to improve output in patients with the double burden of this metabolic disease (Gu et al., 2023).

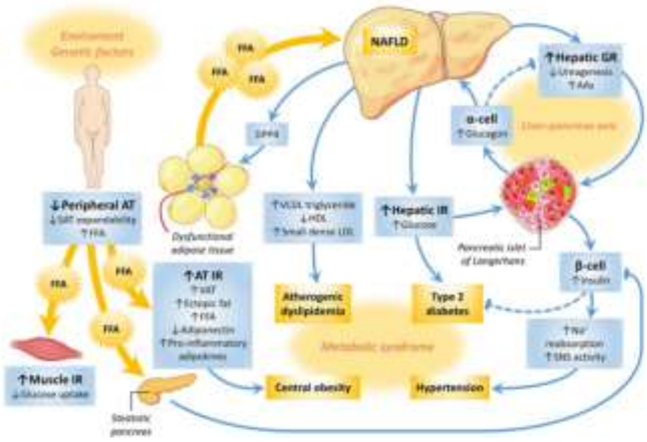

Figure 1. The pathophysiology of NAFLD as a continuum from obesity to metabolic syndrome and diabetes.

Environmental factors affect the expression of genes that trigger weight gain. When the expansion capacity of subcutaneous adipose tissue (SAT) reaches its limit, there is an increase in the mobilization of free fatty acids (FFAs), thus triggering the deposition of visceral fat and ectopic fat. One of the ectopic deposition sites is the muscles, where increased FFAs cause insulin resistance (IR) by inhibiting insulin-mediated glucose uptake. On the other hand, insulin resistance in adipose tissue causes increased lipolysis and enlarges the flow of FFAs to the liver, thereby giving rise to hepatic insulin resistance as well as increasing glucose production, de novo lipogenesis, VLDL release, and atherogenic dyslipidemia. Excess FFAs also reach the pancreas and cause β cell dysfunction through the mechanisms of lipotoxicity, hyperglycemia, and eventually diabetes (twin cycle hypothesis). Increased liver fat also triggers glucagon resistance (GR) in the metabolism of amino acids (AAs), which decreases the ureagenesis process and causes hyper-aminoasidemia. Increased levels of AAs stimulate glucagon secretion to compensate for hepatic glucagon resistance, resulting in a cycle that aggravates the condition (liver–pancreatic axis). This hyperglycagoemia also plays a role in increased hepatic glucose release. Systemic insulin resistance causes hyperinsulinemia, which can increase sodium reabsorption and activate the sympathetic nervous system, thus contributing to the occurrence of hypertension. Inflamed and dysfunctional adipose tissue becomes increasingly resistant to insulin, as well as releasing pro-inflammatory adipokin and lowering the secretion of the anti-inflammatory adiponectin. In the liver, triglycerides and toxic metabolites induce lipotoxicity, mitochondrial dysfunction, and endoplasmic reticulum stress, leading to hepatocyte damage, apoptosis, and fibrosis. These dysfunctional hepatocytes also synthesize and secrete dipeptidyl peptidase-4 (DPP-4), which triggers inflammation of adipose tissue macrophages and aggravates insulin resistance. AAs: amino acids, AT: adipose tissue, DPP4: dipeptidyl peptidase 4, FFA: free fatty acid, GR: glucagon resistance, HDL: high-density lipoprotein, IR: insulin resistance, LDL: low-density lipoprotein, NAFLD: nonalcoholic fatty liver disease, SAT: subcutaneous adipose tissue, SNS: sympathetic nervous system, VAT: visceral adipose tissue, VLDL: very low-density lipoprotein. A pointed arrow indicates stimulation or enhancement, a blunt arrow indicates inhibition or emphasis. The dotted arrow indicates a progressive decline on a path (A.F. et al., 2020).

Factors from Gené from Epigen

Genetic and epigenetic factors play an important role in the two-way relationship between type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD), particularly the severe form of metabolic dysfunction-associated steatohepatitis (MASH). These two conditions have significant overlapping genetic predispositions and affect pathophysiology, progression, and clinical outcomes. Genome-wide association studies (GWAS) have identified several common genetic variants that increase susceptibility to T2DM and NAFLD/MASH. Among them, PNPLA3—which is associated with hepatic fat accumulation and inflammation—also contributes to metabolic dysregulation in T2DM, thus confirming that genetic factors may magnify the risk when both diseases appear together (Jonas & Schürmann, 2021; Liu et al., 2025; Ni et al., 2024; Tan et al., 2023).

Epigenetic mechanisms also modulate genetic predisposition by regulating gene expression in response to environmental and lifestyle factors such as nutrition and physical activity. Changes in DNA methylation, histone modification, and microRNA expression are reported to affect the development and progression of NAFLD and T2DM, and may even have an impact on transgenerational disease risk. These epigenetic changes are dynamic and potentially reversible, thus opening up opportunities for precision medicine interventions that can modify the course of the disease based on the genetic and epigenetic profiles of the individual (Jonas & Schürmann, 2021; Liu et al., 2025; Ni et al., 2024; Tan et al., 2023).

Recent integrative analyses reinforce this complex interaction by showing that the genetic architecture simultaneously involves multiple genes that play a role in glucose metabolism, inflammation, and lipid handling pathways. A cross-trait meta-analysis study confirms that such overlapping genes are involved in pathways that contribute to insulin resistance, hepatic steatosis, and systemic metabolic disorders. This emphasizes the biological basis for why T2DM and NAFLD/MASH often appear together and affect each other in two directions. This understanding of shared genetic and epigenetic pathways provides important insights for developing screening strategies as well as new therapeutic opportunities that target both conditions simultaneously (Jonas & Schürmann, 2021; Liu et al., 2025; Ni et al., 2024; Tan et al., 2023).

Gene-environment interactions also affect the phenotypic expression of the two diseases, so genetic risk alone is not enough without considering epigenetic regulation and lifestyle factors. These interactions support the development of genotype-based risk stratification and personalized therapy approaches that include lifestyle modifications, pharmacological interventions, and the potential for epigenetic therapies to prevent or reduce disease progression in high-risk individuals (Jonas & Schürmann, 2021; Liu et al., 2025; Ni et al., 2024; Tan et al., 2023).

Epigenetic mechanisms include DNA methylation, histone modification, and regulation by non-coding RNAs such as microRNAs. In NAFLD and T2DM, altered DNA methylation patterns are found in key metabolic tissues, such as the liver, pancreatic islet, adipose tissue, and skeletal muscle. These changes affect the expression profile of genes that regulate insulin secretion, insulin resistance, lipid metabolism, and inflammatory responses. Changes in DNA methylation in the pancreatic islets can interfere with insulin secretion—a hallmark of T2DM—while similar changes in liver cells can increase lipid accumulation and inflammatory processes that promote the progression of NAFLD to MASH (Jonas & Schürmann, 2021; Ling & Rönn, 2019).

Environmental factors such as diet, obesity, age, and intrauterine exposure contribute to epigenetic modifications that affect the risk of NAFLD and T2DM, suggesting an important role for the environment in modulating genetic susceptibility. Epigenetic changes are often reversible, thus opening up the opportunity for targeted therapies that can modify epigenetic markers to improve clinical outcomes. In addition, some epigenetic changes can be inherited transgenerationally, so the risk of disease in offspring is partly influenced by the metabolic status and environmental exposure of the parents (Jonas & Schürmann, 2021).

The interaction between genetic polymorphism and epigenetic regulation also explains the phenotype variation between NAFLD and T2DM patients. Genetic variants in TM6SF2 related to lipid metabolism can affect the degree of NAFLD, but their manifestations depend on the epigenetic landscape shaped by environmental factors and metabolic status. Understanding these complex interactions is important to develop better screening strategies, risk prediction tools, and personalized therapeutic interventions to effectively manage T2DM and NAFLD/MASH (Jonas & Schürmann, 2021).

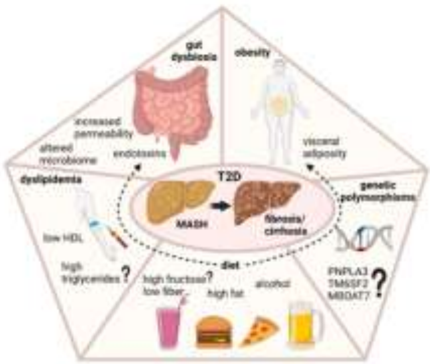

Figure 2. Factors that influence the progression of metabolic dysfunction–associated steatohepatitis (MASH) in individuals with type 2 diabetes mellitus (T2DM).

Increased waist circumference and waist-to-hip ratio are risk factors for the occurrence of MASH and advanced fibrosis in people with T2DM. Meanwhile, the role of genetic variants—which are known to accelerate the progression of MASH in non-diabetic populations—remains unclear in the context of T2DM. On the other hand, dietary factors such as increased fat and alcohol consumption and low fiber intake can trigger intestinal dysbiosis and contribute to the progression of diabetes-related MASH. Low HDL levels, but not high LDL levels, have been identified as risk factors for advanced fibrosis in T2DM patients. MASH – metabolic dysfunction-associated steatohepatitis, T2DM– type 2 diabetes, HDL – high-density lipoproteins, LDL – low-density lipoproteins (Gancheva et al., 2024).

Molecular Signaling Pathways

Molecular signaling pathways are crucial in regulating liver function and glucose metabolism, processes that are interconnected and affect systemic energy balance. In the context of type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD), particularly metabolic dysfunction-associated steatotic liver disease (MASH), disruptions in these pathways contribute to disease progression, providing opportunities for therapeutic targeting. Insulin receptors and downstream effectors, such as the PI3K/Akt pathway, play a vital role in regulating glucose uptake and inhibiting gluconeogenesis, but in NAFLD and T2DM, metabolic stressors like lipid accumulation and reactive oxygen species (ROS) activate inflammatory pathways such as JNK and NF-κB, worsening insulin resistance in hepatocytes. These pathways also promote hepatic fibrosis and MASH progression through TGF-β signaling, further impairing liver function in diabetic patients .

Additionally, various hepatokines and transcription factors are key regulators of liver metabolism. Activin E, adropin, and ANGPTL4 influence insulin sensitivity, glucose metabolism, and lipid regulation, with therapeutic potential in T2DM and NAFLD. Furthermore, nuclear receptors like PPARs and FXRs regulate genes involved in fatty acid oxidation, lipogenesis, and bile acid metabolism, affecting insulin sensitivity and glucose production. Dysregulation of FXR signaling leads to hepatic fat accumulation, contributing to NAFLD pathogenesis. In T2DM, lipotoxicity and oxidative stress disrupt pancreatic β-cell function, impairing insulin secretion. In NAFLD/MASH, lipotoxicity exacerbates oxidative stress and mitochondrial dysfunction, leading to hepatocyte injury and inflammation. Targeting oxidative stress and modulating lipotoxicity through antioxidant defenses or inhibiting NOX activity presents a promising therapeutic strategy to improve clinical outcomes in T2DM and NAFLD/MASH .

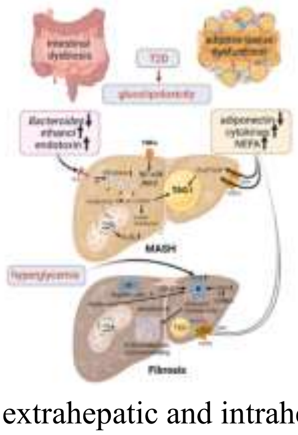

Figure 2. Interaction between extrahepatic and intrahepatic factors that promote the progression of diabetes-associated metabolic dysfunction–associated steatohepatitis (MASH).

A high-energy, high-fat diet triggers intestinal dysbiosis and promotes visceral fat expansion. Increased intestinal permeability allows for the translocation of inflammatory endotoxins (LPS) towards the liver. Excessive fat accumulation in adipose tissue leads to changes in adipokine secretion, uncontrolled lipolysis due to insulin resistance, and inflammation—all of which accelerate the buildup of hepatic lipids in MASH. However, in advanced fibrosis, lipid transport through FATP5 and lipid accumulation decreases. Under conditions of reduced mitochondrial respiration capacity in T2DM, lipotoxic mediators and oxidative stress are increased. Excess lipid load and LPS also trigger endoplasmic reticulum stress (ER stress), which further aggravates insulin resistance and inflammation through activation of the JNK and NF-κB pathways. Kupffer cells and liver sinusoid endothelial cells (LSECs) activate and release proinflammatory cytokines, which then activate hepatic stelata cells—a key component in the fibrogenesis process because they regulate the production of extracellular matrices. CTGF – connective tissue growth factor (also known as cellular communication network factor 2, CCN2) ECM – extracellular matrix MASH – metabolic dysfunction-associated steatohepatitis T2DM– type 2 diabetes FATP5 – fatty acid transporter 5 TAG – triacylglycerols NEFA – non-esterified fatty acids TCA – tricarboxylic acid cycle (Gancheva et al., 2024).

Screening Strategies for NAFLD in Diabetes

The screening strategy for non-alcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus (T2DM) is increasingly important because of the two-way relationship between the two conditions. NAFLD, which ranges from simple steatosis to more advanced forms such as non-alcoholic steatohepatitis (NASH) and fibrosis, is particularly prevalent in individuals with T2DM. Interrelated pathophysiology—including insulin resistance, chronic inflammation, and metabolic dysregulation—can accelerate the progression of both diseases. With the increased risk of bad liver outcomes and cardiovascular complications, early identification and monitoring of NAFLD in diabetic patients is crucial. Noninvasive imaging modalities are the main screening tool due to the limitations of invasive liver biopsy, which are expensive, and have sample variability (A.F. et al., 2020; S. Zhang et al., 2023).

Ultrasound (US) is widely used as a first-line modality for NAFLD screening due to its accessibility, low cost, and adequate diagnostic accuracy for detecting moderate to severe steatosis. Meta-analyses show that US has good sensitivity and specificity for detecting hepatic steatosis, making it feasible as an early screening in the diabetic population. However, US is less sensitive to detecting mild steatosis and is not optimal for assessing the degree of fibrosis. Therefore, US is often equipped with advanced imaging techniques (A.F. et al., 2020).

Transient elastography (TE), including vibration-controlled transient elastography (VCTE), is an important second step for risk stratification through the measurement of liver stiffness as a surrogate marker of fibrosis. TE is a rapid, noninvasive, and validated test to assess fibrosis in NAFLD patients, such as diabetic patients. Studies show that the combination of serum-based fibrosis scores and TE increases the identification of patients at high risk of liver-related complications, thus enabling targeted management. Thus, TE is recommended in sequential screening algorithms after US or serum biomarkers (S. Zhang et al., 2023).

Magnetic resonance imaging (MRI) and magnetic resonance elastography (MRE) provide accurate quantification of fat levels and the degree of liver fibrosis. Although more expensive and not as extensive as the US or TE, both modalities offer high diagnostic precision and are beneficial for establishing advanced diagnosis or evaluating dubious findings from other examinations. Recent cost-utility analyses suggest that MRI-based strategies are cost-effective for NAFLD screening and staging in high-risk populations such as T2DM patients, especially as a confirmatory screening after early noninvasive screening (Younossi et al., 2025; E. Zhang et al., 2015).

Biomarkers play an important role in NAFLD screening strategies in diabetic patients. Liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) can be early biochemical signals, but both are less specific and sensitive to advanced fibrosis or steatohepatitis. Therefore, a composite panel of biomarkers and risk scores were developed to improve the accuracy of the predictions. The NAFLD Fibrosis Score (NFS), which includes age variables, hyperglycemia, body mass index (BMI), platelet count, albumin, and AST/ALT ratio, shows strong performance in identifying advanced fibrosis through verified cutoff values to rule out or establish meaningful liver damage. Similarly, the Fibrosis-4 index (FIB-4) uses age, liver enzymes, and platelet count to assess the risk of fibrosis, although its accuracy may change in T2DM due to metabolic and inflammatory overlap (Ahmadizar & Younossi, 2024; Boeriu et al., 2023).

Advanced biomarker algorithms such as the Enhanced Liver Fibrosis (ELF) score, which measures matrix remodeling markers (hyaluronic acid, tissue inhibitor of metalloproteinases-1, and procollagen peptide III), add specificity to the evaluation of the degree of fibrosis. Tests such as FibroTest and NashTest combine biochemical parameters, such as lipid and glucose levels, so that they reflect the metabolic environment typical of T2DM with NAFLD complications. The test has been validated to predict liver fibrosis and steatohepatitis with adequate specificity, thereby improving screening accuracy without the need for liver biopsies in many cases (Ahmadizar & Younossi, 2024; Boeriu et al., 2023).

Easily obtainable clinical parameters-based risk scores facilitate early screening and triage in primary services or diabetes clinics. The Fatty Liver Index (FLI) uses BMI, waist circumference, triglycerides, and gamma-glutamyl transferase (GGT) to estimate the probability of hepatic steatosis. Screening strategies using FIB-4 and NFS consecutively can rule out advanced fibrosis in a large proportion of T2DM patients, thereby reducing unnecessary referrals and invasive procedures. However, the remaining at-risk groups still require further evaluation with imaging techniques such as transient elastography or magnetic resonance elastography for a more accurate assessment of fibrosis (Boeriu et al., 2023; Ciardullo et al., 2020).

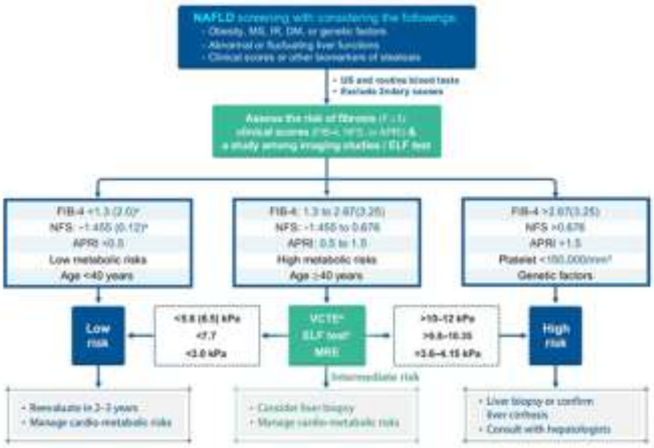

Figure 3. Evaluation algorithm for nonalcoholic fatty liver disease (NAFLD).

Score calculation: NFS (NAFLD Fibrosis Score) NFS = −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m²) + 1.13 × IFG/DM (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelets (×10⁹/L) − 0.66 × albumin (g/dL). FIB-4 (Fibrosis-4 score) FIB-4 = (× AST) / [PLT(×10⁹/L) × √ALT]. APRI (AST to Platelet Ratio Index). APRI = [AST (IU/L) / ULN / PLT (×10⁹/L)] × 100 mAbbreviated description: MS = metabolic syndrome, IR = insulin resistance, DM = diabetes mellitus, US = ultrasonography, FIB-4 = fibrosis-4, NFS = NAFLD Fibrosis Score, APRI = AST to platelet ratio index, ELF = enhanced liver fibrosis, VCTE = vibration-controlled transient elastography, MRE = magnetic resonance elastography Note: a. Higher cutoff Used for patients > 65 years of age b. Influenced by the Body's Factors, and the suggested cutoff value varies c. Requires further validation (D. H. Lee, 2020).

Diabetes Screening Screening in NAFLD Patients

Diabetes screening in nonalcoholic fatty liver disease (NAFLD) patients is crucial due to the two-way relationship between type 2 diabetes mellitus (T2DM) and NAFLD or metabolic dysfunction-associated steatotic liver disease (MASLD). NAFLD is prevalent in about 70% of individuals with T2DM, and T2DM significantly accelerates the progression of NAFLD to advanced liver fibrosis and nonalcoholic steatohepatitis (NASH). The American Diabetes Association (ADA) and European Association for the Study of the Liver (EASL) recommend systematic screening for T2DM and prediabetes in NAFLD patients using fasting glucose, hemoglobin A1c, oral glucose tolerance tests, and noninvasive imaging such as ultrasound. Screening is crucial as it helps identify early diabetes to prevent further complications. Risk assessments in NAFLD patients often consider obesity, metabolic syndrome, insulin resistance, and a family history of diabetes, with noninvasive fibrosis scores like FIB-4 and NAFLD Fibrosis Score (NFS) helping to evaluate the risk of advanced liver fibrosis.

The interaction between NAFLD and T2DM exacerbates both conditions, with NAFLD worsening insulin resistance and inflammation, while hyperglycemia in T2DM contributes to hepatic fat accumulation and fibrosis progression. Key biochemical markers such as elevated glycated hemoglobin (HbA1c) and aspartate aminotransferase (AST) are associated with liver fibrosis and impaired glucose metabolism. Anthropometric indices like triglyceride-glucose (TyG) and waist-to-height ratio (WHtR) are validated as predictors of hepatic steatosis and diabetes risk in NAFLD patients. Screening guidelines emphasize a targeted approach, with associations like EASL and ADA recommending fibrosis screening and liver enzyme monitoring in NAFLD patients with diabetes. Early detection enables comprehensive management, combining lifestyle changes, glucose-lowering drugs, and antifibrosis agents to prevent the progression of both liver disease and diabetes-related complications.

Pharmacological Therapy for the Treatment of Diabetes

Pharmacological management of non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated steatohepatitis (MASH), particularly in the context of type 2 diabetes mellitus (T2DM), has seen significant progress. Drugs initially developed for diabetes, such as thiazolidinediones (TZDs) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), show promise in treating liver disease. Pioglitazone, a TZD, improves insulin sensitivity and reduces hepatic fat, inflammation, and fibrosis, benefiting patients with both T2DM and NAFLD/MASH. GLP-1 RAs also help by promoting insulin secretion, weight loss, and liver fat reduction, improving liver enzymes and possibly preventing fibrosis progression. Additionally, sodium-glucose cotransporter-2 inhibitors (SGLT2i), which enhance glucose control and promote weight loss, have demonstrated hepatoprotective effects by lowering liver fat and inflammation. Despite the limited effect of metformin on liver histology, it remains beneficial in managing overall metabolic control in diabetic patients with liver disease when combined with other agents.

Recent research has identified several new agents, such as SGLT2i, GLP-1 RAs, and dipeptidyl peptidase-4 inhibitors (DPP-4i), which show benefits beyond glycemic control, including reducing liver fat and inflammation—key factors in NAFLD and MASH progression. Clinical trials of GLP-1 RAs like semaglutide and the emerging agent tirzepatide have shown promising effects on liver histology, weight loss, and metabolic improvement. Tirzepatide, a dual incretin receptor agonist, is especially effective in lowering glucose and improving liver function, offering hope for personalized diabetes management that integrates both metabolic and hepatic benefits. This shift in therapy reflects an evolving understanding of the pathophysiological interaction between insulin resistance, inflammation, and hepatic lipid metabolism, positioning these drugs as potential treatments for halting or reversing liver fibrosis in patients with T2DM and NAFLD/MASH.

Pharmacological Therapy Targeted at the Liver

Recent advancements in pharmacological management for non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated steatohepatitis (MASH), particularly in relation to the two-way association with type 2 diabetes mellitus (T2DM), have made significant strides. Traditionally, lifestyle interventions such as weight loss, physical activity, and dietary changes were the primary approaches, but limited long-term success, especially in high-risk T2DM patients, has led to the development of pharmacological therapies targeting liver-specific pathologies. A notable breakthrough came in 2024 with the approval of resmetyrome, a thyroid-β hormone receptor agonist, as the first FDA-approved drug for MASH, marking progress in targeted hepatic therapy. Other investigational drugs, such as farnesoid X receptor (FXR) agonists and peroxisome proliferator-activated receptor (PPAR) modulators, are in advanced clinical trials, showing promise in addressing overlapping pathologies between T2DM and NAFLD. Furthermore, therapies targeting insulin resistance, like thiazolidinediones, have demonstrated benefits in reducing hepatic inflammation, though their side effects limit widespread use. Selective PPAR modulators and drugs like glucagon-like peptide-1 receptor agonists (GLP-1 RAs) offer potential in improving liver fat content and fibrosis. Effective screening strategies, including noninvasive biomarkers and elastography, enable early identification and integrated management of both diabetes and liver disease, which could alter the disease's progression. Additionally, pharmacological agents like sodium-glucose co-transporter inhibitors (SGLT2), anti-inflammatory, and antifibrotic drugs are emerging as critical tools in treating NAFLD and T2DM. These therapies, particularly in combination, aim to reduce liver fat, inflammation, and fibrosis, offering synergistic benefits that address both liver and metabolic dysfunctions. More research and clinical trials are necessary to optimize these treatments and enhance their efficacy in patients with T2DM and MASH.

Lifestyle Interventions

Lifestyle interventions, particularly those focused on diet and weight management, are crucial in addressing the interconnected relationship between type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD), including its progressive form, metabolic dysfunction-associated steatohepatitis (MASH). These diseases share common pathophysiological mechanisms, such as insulin resistance and metabolic dysregulation, and weight loss has been shown to improve both conditions simultaneously. A weight loss of 7-10% through a hypocaloric diet significantly reduces intrahepatic fat, improves glycemic control, and reduces liver inflammation, which benefits patients with both T2DM and NAFLD. Multidisciplinary approaches combining dietary modifications with increased physical activity are more effective than single-modality interventions. Diets like low-carb and Mediterranean styles improve glycemic control, reduce liver fat, and promote insulin sensitivity. Lifestyle changes also reduce systemic inflammation and oxidative stress, which are key factors in the progression of NAFLD to MASH. Gradual weight loss, rather than extreme methods, improves liver histology and insulin resistance. Bariatric surgery and endoscopic weight loss methods have shown efficacy in obese patients, leading to sustained weight loss and metabolic benefits. Clinical studies support the benefits of weight loss in improving metabolic outcomes, such as lower HbA1c levels and reduced liver fibrosis risk. However, more research is needed to optimize interventions based on individual patient characteristics. Exercise also plays a key role by improving insulin sensitivity, reducing liver lipogenesis, and decreasing liver fat, which helps in glycemic control and liver health. Regular physical activity reduces pro-inflammatory cytokines, lowering liver inflammation and preventing steatohepatitis. Exercise combined with dietary modifications improves clinical outcomes, cardiovascular health, and quality of life. It is a low-cost, accessible intervention with pleiotropic benefits, supporting sustained metabolic improvement and serving as a cornerstone in the management of T2DM and NAFLD.

Gut Microbes and Metabolic Interactions

Gut microbiota, particularly through the gut-liver axis, plays a central role in the development and progression of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM). The two-way relationship between these diseases is largely mediated by changes in the gut microbiome, which impacts systemic metabolism and inflammation. Intestinal dysbiosis, or an imbalance in the gut microbiota, increases intestinal permeability, allowing bacterial components and metabolites like lipopolysaccharides (LPS) to reach the liver, triggering inflammation and insulin resistance, worsening both NAFLD and T2DM. The composition of the microbiota in these patients shows an increase in the Firmicutes/Bacteroidetes ratio, which correlates with impaired energy uptake and lipid metabolism. Experimental studies confirm that transplanting microbiota from mice with metabolic disorders to germ-free mice can induce NAFLD symptoms, proving the causative role of the microbiota. Modulating the gut microbiota through prebiotics, probiotics, synbiotics, or drugs targeting the intestinal barrier is being explored as a therapeutic approach to improve liver function and insulin sensitivity. Dietary interventions and bariatric surgery have shown promising effects on these diseases. Metabolites like short-chain fatty acids (SCFAs) and secondary bile acids produced by the microbiota regulate energy metabolism, insulin sensitivity, and inflammation. New strategies targeting these metabolites or their receptors are being developed, showing potential for treating NAFLD and T2DM. Additionally, combining microbiota-focused therapies with conventional antidiabetic treatments, such as using probiotics to enhance the effects of glucose-lowering drugs, offers a personalized therapeutic approach that could optimize treatment outcomes for patients.

Future Research Directions

The relationship between type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD), including its progressive form, metabolic dysfunction-associated steatotic liver disease (MASH), has become a key focus in recent research. Both diseases are intertwined by mechanisms such as insulin resistance, adipose tissue dysfunction, and chronic inflammation, though the exact molecular and genetic basis remains unclear. Factors like genetic mutations (e.g., PNPLA3 and TM6SF2) add complexity, yet their integration into predictive and therapeutic models is still in progress. Clinical challenges persist in screening and diagnosing patients, as current non-invasive methods are insufficient for identifying risks of progression from simple steatosis to steatohepatitis and fibrosis. Moreover, effective treatments for both T2DM and NAFLD/MASH are lacking, with therapies mainly targeting T2DM. Ongoing research must refine screening methods and develop comprehensive therapies targeting both conditions. Emerging areas, such as the gut-liver axis and microbiome alterations, also show promise for therapeutic advancements. The integration of genomic and multi-omics techniques, along with pharmacogenomics, could lead to personalized medicine that tailors interventions to genetic profiles, enhancing efficacy and minimizing side effects. Finally, personalized therapies, like tirzepatide, show potential in managing both T2DM and NAFLD without worsening MASH, pointing to a future of more tailored and effective treatments.

CONCLUSION

Type 2 diabetes mellitus (T2DM) and nonalcoholic fatty liver disease (NAFLD)/metabolic dysfunction–associated steatohepatitis (MASH) represent interconnected metabolic disorders linked bidirectionally through insulin resistance, adipose tissue dysfunction, oxidative stress, chronic inflammation, genetic–epigenetic modulation, and gut microbiota alterations. Adipose dysfunction elevates free fatty acid flux to the liver, promoting hepatic fat accumulation, lipotoxicity, and β-cell damage, while gut–liver axis disruption via increased intestinal permeability translocates proinflammatory mediators, exacerbating progression from NAFLD to MASH and fibrosis in T2DM patients, and elevating prediabetes/T2DM risk in those with NAFLD. This interplay necessitates integrated, multi-layered screening using clinical scores, biomarkers, noninvasive imaging, and metabolic assessments, alongside foundational lifestyle interventions for weight loss and exercise to improve insulin sensitivity, reduce liver fat, and curb inflammation, complemented by novel antidiabetic drugs and liver-targeted therapies. For future research, longitudinal studies should prioritize refining AI-driven screening algorithms that incorporate genetic–epigenetic profiles and microbiota data to personalize combination therapies and optimize outcomes in patients bearing this dual metabolic burden.

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