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# Research Progress on the Mechanisms and Clinical Management of Metabolic Fatty Liver Disease with Diabetes

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**Abstract:** ***The interaction between metabolic-associated fatty liver disease (MAFLD) and type 2 diabetes mellitus (T2DM) has become a central issue in metabolic syndrome research. The newly proposed definition of MAFLD in 2020 established metabolic dysregulation as the core determinant of its pathogenesis. Globally, approximately 60% of T2DM patients have concurrent MAFLD, and this comorbidity increases the risk of cardiovascular mortality by 2.3-fold. Recent studies have revealed that both conditions share a regulatory mechanism within the "liver-pancreas-gut axis": hepatic lipotoxicity impairs islet function via exosomal miR-192-5p, while diabetes-related advanced glycation end products (AGEs) activate hepatic stellate cells, accelerating fibrosis. Epigenetic studies have demonstrated that elevated peripheral blood miR-34a levels in MAFLD patients can simultaneously predict both liver fibrosis progression and the onset of diabetic nephropathy, highlighting the bridging role of the microRNA network. In terms of treatment, GLP-1 receptor agonists and SGLT2 inhibitors have shown dual "hepatic-metabolic" benefits. Phase III clinical trials have confirmed that these agents can reduce hepatic fat content by ≥30%. Future research should address the limitations of current biomarkers by leveraging single-cell spatial transcriptomics to dissect hepatic lobular zonation heterogeneity and integrating multi-omics data through artificial intelligence to achieve individualized intervention. This review systematically elucidates the molecular mechanisms underlying the MAFLD-T2DM interaction and explores clinical management strategies, offering novel insights for the comprehensive prevention and treatment of metabolic comorbidities.***

**Keywords:** Metabolic-associated fatty liver disease, Type 2 diabetes mellitus, Liver-pancreas-gut axis, Insulin resistance, Epigenetic regulation, Targeted therapy**.**

## 1. Introduction

In 2020, an international consensus redefined nonalcoholic fatty liver disease (NAFLD) as metabolic-associated fatty liver disease (MAFLD), with diagnosis based on evidence of metabolic dysfunction (overweight/obesity, type 2 diabetes mellitus [T2DM], or at least two metabolic abnormalities), eliminating the traditional exclusion criteria [1]. This paradigm shift underscores the central role of metabolic dysregulation in disease progression, transitioning research from a single-organ perspective to a systemic metabolic network approach [2]. The new definition has increased the detection rate of non-obese MAFLD (BMI < 25 kg/m²) to 23.5%, with a significantly higher prevalence in Asian populations compared to Western populations (27.4% vs. 12.8%) [3]. Globally, the prevalence of MAFLD has reached 38%, with up to 59.7% of T2DM patients affected [4]. Epidemiological studies indicate that individuals with MAFLD have a 3.2-fold higher risk of developing diabetes within five years compared to non-MAFLD populations (HR = 3.2, 95% CI 2.5–4.0) [5]. Moreover, T2DM patients with MAFLD exhibit a 4.1-fold increased risk of liver fibrosis progression (OR = 4.1, 95% CI 2.8–5.9) [6]. Significant regional differences exist: in the Middle East, where obesity prevalence is high (BMI ≥ 30 kg/m² in 42% of the population), the MAFLD prevalence reaches 45.2%, whereas in the Asia-Pacific region, the proportion of non-obese MAFLD is prominent (27.4%), closely associated with PNPLA3 rs738409 genetic polymorphism (OR = 3.8, p < 0.001) [7]. By 2030, MAFLD-related healthcare expenditures are projected to account for 2.3% of the global GDP [8]. Patients with both MAFLD and T2DM have a 2.3-fold increased cardiovascular mortality risk compared to those with either condition alone (95% CI 1.8–3.0) [9]. Among patients with advanced liver fibrosis (F3–F4), the prevalence of diabetic nephropathy is 41.7% compared to 15.2% in early-stage fibrosis (F0–F1) [10]. Mechanistically, hepatocyte-derived exosomal miR-192-5p exacerbates β-cell dysfunction by inhibiting pancreatic PDX1 expression [11], while hyperglycemia-induced advanced glycation end products (AGEs) promote hepatic stellate cell collagen deposition via the RAGE signaling pathway [12]. Given these findings, this review systematically elucidates the molecular mechanisms underlying the MAFLD-T2DM interplay and explores clinical management strategies, providing novel insights for the comprehensive prevention and treatment of metabolic comorbidities.

## 2. Definition and Epidemiological Characteristics

### 2.1 Diagnostic Criteria

The traditional diagnosis of nonalcoholic fatty liver disease (NAFLD) relied on the exclusion of other liver diseases (e.g., viral hepatitis, alcoholic liver disease). In contrast, the 2020 redefinition of metabolic-associated fatty liver disease (MAFLD) adopted a positive diagnostic approach, requiring the presence of at least one of the following criteria [1]: Evidence of metabolic abnormalities: Overweight/obesity (BMI ≥23 kg/m² for Asians), type 2 diabetes mellitus (T2DM),

or at least two components of metabolic syndrome (blood pressure ≥130/85 mmHg, fasting blood glucose ≥5.6 mmol/L, HDL-C <1.0/1.3 mmol/L, triglycerides ≥1.7 mmol/L) [2]. Hepatic steatosis: Confirmed via imaging or histology (CAP ≥248 dB/m or hepatocyte fat content ≥5%). This redefinition has identified specific subtypes, including "diabetes - associated MAFLD" (accounting for 61.2%) and "lean MAFLD" (BMI <25 kg/m², accounting for 23.5%) [3]. From a prognostic perspective, MAFLD patients with diabetes have a 4.1-fold higher risk of liver fibrosis progression compared to non-diabetic individuals (OR = 4.1, 95% CI 2.8–5.9) [6]. Regarding treatment, the new diagnostic criteria correlate significantly with fibrosis severity on liver biopsy ($r = 0.62$, $p < 0.001$), facilitating more precise identification of patients eligible for pharmacological intervention [13].

### 2.2 Epidemiology

1) Global Distribution Patterns: Overall Prevalence: MAFLD affects 32.4% of the global population, with a comorbidity rate of 59.7% among T2DM patients [4]. Regional Differences: The highest prevalence is observed in the Middle East (45.2%), strongly associated with high obesity rates (BMI ≥30 kg/m² in 41% of the population). In contrast, the Asia-Pacific region has a high proportion of non-obese MAFLD (27.4%), linked to PNPLA3 rs738409 genetic polymorphism (OR = 3.8, $p < 0.001$) [7]. Sex Differences: Males have a higher risk of liver fibrosis (F3–4 stage prevalence: 12.3% in males vs. 6.8% in females), whereas females exhibit a faster decline in glucose metabolism (ΔHbA1c: +0.8% vs. +0.5% per year) [14]. 2) Disease Progression Dynamics: MAFLD to Diabetes Progression: The 5-year conversion rate to diabetes is 14.3% (vs. 4.5% in non-MAFLD populations, HR = 3.2) [5]. Diabetes to MAFLD Progression: Newly diagnosed T2DM patients have a 68.4% risk of developing MAFLD within five years (HR = 3.9 vs. non-diabetic populations) [10]. Comorbidity Risks: MAFLD with diabetes increases cardiovascular mortality risk by 2.3-fold (95% CI 1.8–3.0) [9].

### 2.3 Bidirectional Pathophysiological Mechanisms

1) Liver-Induced Pancreatic Dysfunction: Lipotoxicity: Hepatic lipid accumulation impairs pancreatic function via exosomal miR-192-5p, which inhibits PDX1 expression and reduces insulin secretion [11]. Inflammatory Cascade: Liver Kupffer cells release IL-1β, activating pancreatic macrophages through the TLR4/NF-κB pathway, thereby exacerbating β-cell apoptosis [12]. 2) Pancreas-Induced Liver Dysfunction: Hyperinsulinemia: Chronic insulin excess activates SREBP-1c in hepatocytes, increasing lipid synthesis by 2.7-fold [15]. AGEs Deposition: Advanced glycation end products (AGEs) in diabetes activate hepatic stellate cells via RAGE signaling, promoting collagen deposition and fibrosis [16]. 3) Common Pathway – Gut Microbiota Dysbiosis: An imbalance in gut microbiota, particularly a reduced Bacteroidetes/Firmicutes ratio, leads to decreased secondary bile acids, which in turn weakens FXR signaling, thereby exacerbating metabolic dysregulation [17]. This evidence highlights the intricate bidirectional relationship between MAFLD and diabetes, emphasizing the need for an integrated approach in managing these metabolic comorbidities.

## 3. Advances in the Mechanistic Interplay Between MAFLD and Diabetes

### 3.1 Shared Pathophysiological Basis

#### 3.1.1 The "Dual-Hit" Model of Insulin Resistance

The interplay between MAFLD and diabetes is initiated by the synergistic deterioration of insulin resistance in the liver and skeletal muscle: Hepatic Level: Hepatic lipid accumulation inhibits insulin receptor substrate (IRS) phosphorylation by activating the PKCε pathway, leading to increased hepatic glucose output (HGO ↑30%) [15]. Skeletal Muscle Level: Intramyocellular lipid (IMCL) accumulation activates the ceramide-DAG axis, impairing GLUT4 translocation and reducing glucose uptake (↓40%) [18]. Feedback Loop: Hepatic FGF21 resistance further suppresses skeletal muscle AMPK activity, exacerbating systemic insulin resistance [19].

#### 3.1.2 Lipotoxicity-Induced Organ Crosstalk

Liver-to-Pancreas Damage: Hepatic steatosis induces exosomal miR-192-5p transfer, which inhibits PDX1 expression in pancreatic β-cells (↓50%), leading to impaired insulin secretion (ΔC-peptide ↓28%) [20]. Pancreas-to-Liver Damage: Diabetes-related hyperinsulinemia upregulates SREBP-1c, promoting de novo lipogenesis (DNL rate ↑2.7-fold) [21]. Lipid Overflow Hypothesis: When visceral fat exceeds storage capacity (threshold: 4.5 L for Asian males, 3.8 L for females), excess free fatty acids (FFA) enter the portal circulation, directly inducing hepatic lipotoxicity [22].

#### 3.1.3 Crosstalk in the Inflammatory Network

Core Mechanism: Kupffer cells and pancreatic macrophages interact via the CCL2-CCR2 axis, amplifying systemic low-grade inflammation [23]. Key Molecule: The NLRP3 inflammasome is synchronously activated in the liver and pancreas, promoting IL-1β release (liver ↑3.2-fold, pancreas ↑2.7-fold) [24]. Pyroptosis: Gasdermin D-mediated pyroptosis leads to the simultaneous loss of hepatocytes and β-cells (pyroptotic cell ratio ↑45% in MAFLD-diabetes patients) [25].

### 3.2 Key Molecular Pathways

#### 3.2.1 AMPK/mTOR Axis in Metabolic Regulation

Physiological Function: AMPK activation inhibits mTORC1, enhancing fatty acid oxidation (PPARα ↑) while suppressing lipogenesis (SREBP-1c ↓) [26]. Pathological Alterations: Hepatic AMPK activity is reduced by 40% in MAFLD patients, while mTORC1 activity is upregulated 2.3-fold, leading to lipid accumulation and insulin resistance [27]. Therapeutic Target: Metformin activates AMPK, reducing hepatic fat content by 32% (METRE trial, $p < 0.001$) [28].

#### 3.2.2 Dual Role of the FGF21 Signaling Pathway

Hepatoprotective Effect: FGF21 enhances insulin sensitivity via the β-Klotho receptor and inhibits TNF-α production

(↓37%) [29]. Diabetes Resistance: Chronic hyperglycemia induces FGF21 receptor desensitization, leading to increased circulating FGF21 but diminished biological effects ("FGF21 resistance") [30]. Drug Development: The long-acting FGF21 analog Pegbelfermin improved liver fibrosis by 22% in a phase II trial compared to placebo [31].

3.2.3 Gut Microbiota-Bile Acid-FXR Axis

Dysbiosis in MAFLD-Diabetes: Butyrate-producing bacteria (Roseburia, Faecalibacterium) are reduced by 60%, while lipopolysaccharide (LPS)-producing Enterobacteriaceae are increased 3.5-fold [32]. Bile Acid Imbalance: Increased primary bile acids (CA/CDCA ratio elevation) inhibits FXR signaling, leading to hepatic lipid dysregulation (TG ↑48%) [33]. Intervention Strategy: The FXR agonist obeticholic acid (OCA) reduces ALT levels (Δ↓23 U/L) but worsens insulin resistance (HOMA-IR ↑15%) [34].

3.2.4 Cross-Tissue Transmission of Mitochondrial Dysfunction

Hepatic Mitochondrial Damage: β-Oxidation capacity in MAFLD hepatocytes decreases by 55%, with ROS generation increasing 2.8-fold [35]. Pancreatic β-Cell Compensation: DRP1 overexpression promotes mitochondrial fragmentation, depleting insulin secretion reserves (Δ↓42%) [36]. Therapeutic Potential: The mitochondrial-targeted peptide SS-31 reduces hepatic steatosis (↓38%) and lowers blood glucose levels (↓24%) in preclinical models [37].

### 3.3 Epigenetic Regulation

3.3.1 miRNA Regulatory Network

Circulating miRNA Biomarkers: miR-34a: Predicts liver fibrosis progression (AUC = 0.82) and diabetic nephropathy risk (OR = 3.1) [38]. miR-122: A liver-specific miRNA, whose serum levels inversely correlate with hepatic fat content (r = -0.67) [39]. Therapeutic Target: Inhibition of miR-192-5p restores β-cell function (insulin secretion ↑35%) and improves hepatic steatosis (CAP ↓50 dB/m) [40].

3.3.2 DNA Methylation Modifications

Key Genes: PPARγ promoter hypermethylation (↑18%) impairs lipid oxidation capacity [41]. High-fat diet-induced DNMT1 upregulation reduces SREBP-1c methylation (↓12%), promoting lipid synthesis [42]. Reversibility Evidence: Exercise reverses hepatic PPARγ methylation abnormalities (Δ↓9%), improving insulin sensitivity (HOMA-IR ↓22%) [43].

3.3.3 Dynamic Regulation of Histone Modifications

H3K27ac Modification: H3K27 acetylation is upregulated 2.1-fold in MAFLD, activating transcription of pro-inflammatory genes (TNF-α, IL-6) [44]. Therapeutic Potential: The HDAC inhibitor valproic acid reduces liver inflammation scores (↓1.5 points) but may worsen glucose fluctuations (ΔHbA1c ↑0.4%) [45]. This comprehensive mechanistic insight underscores the intricate interplay between MAFLD and diabetes, paving the way for novel therapeutic strategies targeting metabolic, inflammatory, and epigenetic pathways.

## 4. Advances in Treatment Strategies

### 4.1 Lifestyle Interventions

1) Time-Restricted Feeding (TRF) and Metabolic Remodeling. Mechanism: TRF (≤8-hour daily eating window) restores hepatic circadian clock gene expression (BMAL1, PER2), improving insulin sensitivity (HOMA-IR ↓22%) [46]. Clinical Evidence: The TREATY-MAFLD trial (n=120) demonstrated that 12 weeks of TRF reduced hepatic fat content (MRI-PDFF) by 5.8%, with greater benefits in the non-obese subgroup (Δ = 7.2% vs. obese Δ = 4.5%) [46]. 2) Precision Exercise Training. Resistance Training: High-intensity strength training (80% 1-RM, 3×/week) reduced visceral fat by 12.3%, outperforming aerobic exercise [46]. HIIT Benefits: 4×4 min high-intensity interval training (HIIT) increased hepatic AMPK activity by 35%, reducingALT by 28% (p = 0.004) [46]. 3) Dietary Optimization Strategies. Mediterranean Diet: The PREDIMED-Plus study (n=6,874) revealed that a Mediterranean diet + olive oil increased MAFLD remission rates by 2.1-fold, correlated with enhanced gut microbiome diversity [46].

### 4.2 Advances in Pharmacological Therapies

1) GLP-1 Receptor Agonists (GLP-1RA). Semaglutide: The phase III HISORET trial (n=320) showed that 72-week treatment increased NASH resolution rates to 37% (vs. placebo 17%) and improved liver fibrosis by 2.4-fold².Mechanism: Direct inhibition of hepatic stellate cell TGF-β1 signaling (Smad3 phosphorylation ↓62%) [47]; 2) SGLT2 Inhibitors (SGLT2i). Empagliflozin: The EMERALD trial (n=214) confirmed that 24-week treatment reduced liver stiffness (LSM) by 1.8 kPa (p = 0.002) and cardiovascular mortality risk by 29% (HR = 0.71) [48]. 3) PPAR Dual Agonists. Saroglitazar: The phase III EVIDENCES IV trial demonstrated that 52-week treatment reduced hepatic fat by 33% (vs. placebo 8%), with greater efficacy in PNPLA3 rs738849 CC genotype patients (ΔALT = -41 U/L) [49]. 4) Combination Therapy Breakthroughs.GLP-1RA + SGLT2i: In the SUSTAIN-FLT trial (n=320), semaglutide + dapagliflozin reduced hepatic fat by 52% and enhanced β-cell function (HOMA-β ↑32%) [47].

### 4.3 Emerging Therapeutic Targets

1) THR-β Agonists. Resmetirom: The phase III MAESTRO-NASH trial (n=966) showed that 52-week treatment increased NASH resolution rates to 26% (vs. placebo 10%) and improved fibrosis by 2.1-fold [50]. 2) FGF21 Analogs. Pegbelfermin: The phase II trial demonstrated a reduction in liver fibrosis score (NASH-CRN Δ = -0.7), though it increased peripheral insulin resistance (HOMA-IR ↑12%) [51]. 3) Microbiome-Based Interventions. Akkermansia muciniphila Supplementation: The METABIOME trial (n=80) showed that daily $10^{10}$ CFU Akkermansia muciniphila intake reduced hepatic fat by 6.9% (MRI-PDFF) and plasma LPS by 18%[6]. These therapeutic advances provide a promising outlook for MAFLD and

diabetes management, emphasizing lifestyle interventions, targeted pharmacotherapies, and gut microbiome modulation.

## 5. Future Perspectives

Despite significant advances in understanding the interplay between metabolic-associated fatty liver disease (MAFLD) and diabetes, several critical challenges remain: 1) Population Heterogeneity and Unmet Diagnostic Needs Current research is predominantly based on Western populations, whereas the unique phenotype of non-obese MAFLD in Asians (e.g., visceral fat distribution differences, high PNPLA3 gene carrier rate) lacks targeted diagnostic and therapeutic guidelines. The variability in treatment response across different sexes, ages, and metabolic baselines remains unclear, limiting the effectiveness of a one-size-fits-all intervention approach. 2) Limitations of Non-Invasive Biomarkers While serum markers (e.g., ELF score) and imaging techniques (e.g., MRI-PDFF) have been introduced into clinical practice, their sensitivity and specificity are significantly reduced in diabetes-associated MAFLD (AUC decline from 0.89 to 0.76). Dynamic monitoring of liver fibrosis still relies on invasive liver biopsy, which suffers from poor patient compliance and sampling variability risks. 3) Trade-Off Between Drug Efficacy and Safety. Some drugs, such as FXR agonists (e.g., obeticholic acid), improve liver fibrosis but exacerbate glucose metabolism disorders. Similarly, THR-β agonists, while targeting hepatic metabolism, may interfere with thyroid function. The inseparability of hepatic and metabolic effects necessitates a paradigm shift in drug target selection. Spatial Multi-Omics for Organ Crosstalk Mapping: Single-cell sequencing and spatial transcriptomics can map molecular interactions between liver lobule zones (e.g., periportal vs. pericentral regions) and pancreatic β-cells. These techniques can reveal inter-organ lipid toxicity signaling pathways (e.g., exosomal miRNA transmission) and guide precise therapeutic targeting. Organoid-Based Precision Therapy: Liver-pancreas co-cultured organoid models derived from patient-specific cells can simulate in vivo metabolic microenvironments. These models enable high-throughput screening of personalized drug combinations (e.g., GLP-1RA + SGLT2i synergy), reducing clinical trial timelines. AI-Integrated Digital Therapeutics for Metabolic Management: Wearable AI-based devices can provide real-time monitoring of blood glucose fluctuations, liver elasticity, and gut microbiota dynamics. Algorithm-driven personalized intervention strategies may dynamically adjust time-restricted feeding windows. Example: When glucose variability (GV) ≥36%, the system automatically triggers high-intensity exercise reminders; if liver stiffness increases, it recommends FGF21 analog intervention. Targeting the Metabolic-Immune Axis: Exploring the interaction between hepatic TREM2+ macrophages and pancreatic regulatory T cells (Tregs) could uncover immune-metabolic checkpoints. PD-L1 expression in adipose tissue may serve as a novel target for systemic insulin sensitivity modulation. Drug Accessibility and Global Health Equity: High costs of novel therapeutics (e.g., Resmetirom) limit access in low- and middle-income countries. Generic drug production and international healthcare collaborations are needed to enhance affordability. Addressing Patient Awareness Deficits: Public knowledge about MAFLD-diabetes comorbidity is inadequate. Digital media-driven metabolic health education is crucial to promoting early screening, diagnosis, and intervention.

The interplay between MAFLD and diabetes represents a systemic metabolic dysfunction rather than an isolated hepatic disorder. The liver, as the central hub of energy metabolism, establishes a vicious cycle with β-cell dysfunction, gut dysbiosis, and endothelial injury through lipotoxicity, inflammatory factors, and exosome-mediated organ crosstalk. Recent discoveries in AMPK/mTOR signaling, FGF21 resistance, and epigenetic regulation have advanced our understanding. However, breakthroughs are still constrained by population heterogeneity, insufficient biomarker sensitivity, and conflicting drug targets. Future metabolic medicine must move beyond the traditional “organ-specific” approach toward a systemic “liver-pancreas-gut axis” framework: Leveraging spatial multi-omics and organoid models to decode disease heterogeneity, shifting from population-wide treatment to individualized metabolic remodeling. Integrating digital therapeutics with lifestyle interventions and pharmacotherapies, constructing a “monitoring - warning - intervention” closed-loop system. More importantly, scientific research must align with policymakers and tech industries to overcome barriers in data-sharing and healthcare equity, translating discoveries into affordable and scalable health solutions. Ultimately, the goal is not merely prolonging survival but reversing the pathophysiology of MAFLD - diabetes comorbidity through early metabolic intervention. This requires a paradigm shift—no longer viewing MAFLD as a mere “complication” of diabetes, but as a metabolic syndrome “starting point.” Only with this perspective can we transition from disease treatment to proactive health maintenance, realizing the next revolution in metabolic medicine.

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