Research Advances on Peroxisome Proliferator-Activated Receptors in the Pathogenesis and Treatment of Metabolic Dysfunction-Associated Steatotic Liver Disease Complicated by Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is often accompanied by other features of metabolic syndrome, leading to vascular lesions, end-stage organ failure, and cancer. Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the common complications of T2DM, with more than 70% of patients with T2DM also having MASLD. Peroxisome proliferator-activated receptors (PPARs) are involved in the expression of genes related to fatty acid uptake, β-oxidation, lipogenesis, gluconeogenesis, and insulin sensitivity. The pathogenesis of MASLD is closely associated with PPARs dysfunction and is characterized by reduced fatty acid oxidation capacity, adipose tissue dysfunction, decreased insulin sensitivity, and abnormal activation of inflammatory signaling pathways. This review aims to elucidate the important mechanisms and pathophysiological roles of PPARs in T2DM complicated by MASLD, providing a theoretical basis for further research on PPARs-targeted therapy for T2DM complicated by MASLD.

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is one of the common complications of T2DM; more than 70% of patients with T2DM also have MASLD. Peroxisome proliferator-activated receptors (PPARs) participate in the expression of genes related to fatty acid uptake, β-oxidation, lipogenesis, gluconeogenesis, and insulin sensitivity. The pathogenesis of MASLD is closely related to PPAR dysfunction, characterized by decreased fatty acid oxidation capacity, disordered adipose tissue function, and accompanied by reduced insulin sensitivity and abnormal activation of inflammatory signaling pathways. This review aims to clarify the important mechanisms and pathophysiological roles of PPARs in T2DM complicated by MASLD, providing a theoretical basis for further research on PPAR-targeted therapy for T2DM complicated by MASLD.

[**Key words**] Metabolic dysfunction-associated steatotic liver disease; Diabetes mellitus, type 2; Peroxisome proliferator-activated receptors; Pathogenesis; Therapeutic strategies

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Research Advances on PPARs in the Pathogenesis and Treatment of Metabolic Dysfunction-Associated Steatotic Liver Disease and Type 2 Diabetes Mellitus

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Abstract Type 2 diabetes mellitus (T2DM) is frequently accompanied by other features of metabolic syndrome, leading to vascular complications, end-stage organ failure, and cancer. Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the common complications of T2DM, with over 70% of T2DM patients also having MASLD. Peroxisome proliferator-activated receptors (PPARs) participate in gene expression related to fatty acid uptake, β-oxidation, lipogenesis, gluconeogenesis, and insulin sensitivity. The pathogenesis of MASLD is closely associated with PPAR dysfunction, characterized by impaired fatty acid oxidation capacity, disrupted adipose tissue function, reduced insulin sensitivity, and abnormal activation of inflammatory signaling pathways. This review aims to elucidate the key mechanisms and pathophysio-

logical roles of PPARs in T2DM and MASLD, providing a theoretical foundation for further research into PPAR-targeted therapies for this condition.

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Type 2 diabetes mellitus (T2DM) is a chronic state of metabolic dysregulation characterized by persistent hyperglycemia. It is often accompanied by manifestations of metabolic syndrome, life-threatening microvascular and macrovascular complications, end-stage target-organ failure, and certain types of cancer[1]. T2DM accounts for approximately 90% of all diabetes cases and is typically seen in people over 45 years of age. In recent years, the prevalence of this disease has shown a marked upward trend among children, adolescents, and young adults, a trend closely associated with the widespread presence of multiple unhealthy lifestyles and behavioral habits[2]. More than 70% of patients with T2DM have concomitant metabolic dysfunction-associated steatotic liver disease (MASLD)[3–5]. The pathophysiological mechanisms of T2DM combined with MASLD involve complex interactions among insulin resistance, adipose-tissue dysfunction, intestinal dysbiosis, chronic low-grade systemic inflammation, and hepatic inflammation, ultimately leading to excessive lipid accumulation in hepatocytes and subsequent liver injury[6]. Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor superfamily and include three subtypes: PPARα, PPARβ/δ, and PPAR-γ[7]. By regulating the expression of genes involved in fatty-acid uptake,

β-oxidation, lipogenesis, gluconeogenesis, and insulin sensitivity, these receptors play fundamental roles in lipid and glucose homeostasis, inflammation, and energy metabolism[8]. Dysregulation of PPAR signaling is closely related to the molecular pathogenesis of metabolic disorders, including T2DM and MASLD[9]. Studying different PPAR subtypes can provide key insights into the occurrence, progression, and therapeutic intervention of T2DM complicated by MASLD.

1 Bidirectional Association Between T2DM and MASLD

There is a bidirectional relationship between T2DM and MASLD. From a mechanistic perspective, persistent hyperglycemia and elevated free fatty acid levels promote hepatic de novo lipogenesis and aggravate oxidative stress, inflammatory responses, and the progression of fibrosis[10–12]. Antihyperglycemic drugs can not only reduce intrahepatic fat content but may also act on key pathological processes such as inflammatory responses, hepatocellular injury, and fibrosis, thereby demonstrating beneficial effects on metabolic dysfunction-associated steatohepatitis (MASH) in randomized controlled trials[13–15]. Abnormal expression of liver-derived factors driven by energy surplus and hyperglycemia, together with peripheral and hepatic insulin resistance, jointly contributes to the progression of MASLD toward prediabetes and T2DM. Persistent hyperglycemia and elevated free fatty acid levels further promote hepatic de novo lipogenesis and exacerbate oxidative stress, inflammatory responses, and fibrotic progression[16].

1.1 T2DM Accelerates the Progression of MASLD

Patients with T2DM are a high-risk population for MASLD and progressive liver disease. Multiple studies, based on clinical samples from different sources, have used noninvasive testing methods—including hepatic magnetic resonance proton density fat fraction, transient elastography, and magnetic resonance elastography—to evaluate the prevalence of hepatic steatosis and fibrosis and their associated risk factors in this population[17–19]. A noninvasive assessment by AJMER et al.[20] of 501 patients with T2DM aged 50 years or older showed a high prevalence of liver fibrosis and cirrhosis, with obesity and insulin therapy associated with an increased risk of advanced liver fibrosis. The study also found that, among 29 patients with cirrhosis, 2 were detected with hepatocellular carcinoma (HCC) and 1 was diagnosed with gallbladder adenocarcinoma, further indicating that the coexistence of MASLD and T2DM can lead to severe liver disease[21]. The prevalence of MASLD is also significantly increased among patients with T2DM, with reported rates of 55.5%–65.33%. The prevalence is higher in Europe, possibly related to factors such as study methods, ethnic composition, or lifestyle in that region[22–24]. Among patients with T2DM, the prevalence of MASH and advanced fibrosis reaches 31.55%–40.78% and 14.95%–17.0%, respectively[22]. Noninvasive assessment of liver fibrosis likewise suggests a relatively high proportion of progressive lesions in this population: 19.8% of patients with T2DM have elevated liver stiffness measurement

(LSM), which is associated with BMI, age, sex, VCTE, and Asian ethnicity[24]. MASLD and T2DM not only have a high comorbidity rate but also involve mutually reinforcing pathological mechanisms[25]. The pathological mechanisms of MASLD-related liver cancer in patients with T2DM involve increased generation of reactive oxygen species (ROS), endothelial injury, release of proinflammatory cytokines, and activation of the insulin-like growth factor (IGF) pathway[26]. These findings suggest a heavy liver-disease burden among patients with T2DM, making it urgently necessary to strengthen early screening and risk stratification for MASLD and liver fibrosis in clinical practice. Some studies recommend incorporating liver assessment into routine diabetes management, especially by implementing screening strategies based on noninvasive tools in primary care and specialist settings, so as to identify high-risk individuals early and initiate intervention[27].

1.2 T2DM Increases the Risk of Extrahepatic Disease in MASLD

In addition to increasing the risk of fibrosis, cirrhosis, primary liver cancer, and end-stage liver disease, MASLD also gives rise to important extrahepatic clinical manifestations, including cardiovascular disease (CVD), chronic kidney disease (CKD), and certain extrahepatic malignancies[28]. The risk of CVD rises progressively with the severity of MASLD. On the basis of assessing traditional CVD risk factors, liver-specific indicators should be incorporated to optimize risk stratification and to formulate targeted intervention strategies for this high-risk population, thereby reducing the risks of CVD morbidity and mortality. With regard to CKD and end-stage renal disease, T2DM and MASLD have a synergistic effect in aggravating disease progression[29–31]. A population-based longitudinal study showed that, over a median follow-up of 8 years, MASLD combined with T2DM as assessed by the fatty liver index was associated with increased risks of myocardial infarction, ischemic stroke, heart failure, and death[32]. T2DM is associated with increased incidence of multiple cancers; among them, the risks of liver cancer and pancreatic cancer increase by nearly 1-fold, while the risks of gallbladder cancer, kidney cancer, colon cancer, and colorectal cancer increase by 86%, 67%, 64%, and 62%, respectively; the increase in risk for other cancers is less than 50%. The strength of evidence for the association between T2DM and other cancer types is relatively weak because of the possible presence of unmeasured residual confounding factors.

2 PPARs in the Molecular Pathogenesis of T2DM Complicated by MASLD

2.1 Biological Characteristics and Distribution of PPARs

PPARs, as nuclear hormone receptors and transcription factors, play roles in regulating lipid metab-

metabolism, insulin resistance, and adipocyte differentiation. The three subtypes PPARα, PPARβ/δ, and PPAR-γ have different tissue distributions and

functions [33]. Activation of PPARα can alleviate hepatic steatosis and promote fatty-acid oxidation and ketogenesis. PPARβ/δ enhances fatty-acid oxidation and glucose uptake, whereas PPAR-γ promotes adipocyte differentiation and lipid storage and improves insulin sensitivity [34]. PPARα is highly expressed in organs with strong oxidative capacity, such as the liver, heart, and skeletal muscle, and has multiple roles, including adipocyte differentiation, lipid storage, downregulation of leptin, and regulation of insulin sensitivity. Activation of PPARα leads to reduced blood-lipid levels and clearance of plasma triglycerides (TG), thereby increasing levels of high-density lipoprotein cholesterol (HDL-C) [35]. In the liver, PPARα controls lipid metabolism, including fatty-acid uptake, activation and oxidation, lipolysis, ketone-body synthesis, and TG storage [36].

PPARβ/δ is currently regarded as a potential regulator of energy balance and inflammation in T2DM complicated by MASLD. PPARβ/δ is widely expressed in mammalian tissues and can promote the uptake and oxidation of fatty acids by muscle and liver, thereby maintaining whole-body insulin sensitivity and metabolic flexibility. When chronic systemic metabolic stress is present, its protective effect may be weakened [37]. PPAR-γ has been identified as a factor induced during adipocyte differentiation; it is mainly present in adipose tissue but is also found in the liver. PPAR-γ participates in regulating the formation of new adipocytes, lipid storage, and the expression of enzymes required for insulin sensitivity. Under physiological conditions, it coordinates adipose tissue to store lipids effectively, prevents ectopic accumulation in the liver and muscle, and plays an essential role in adipocyte differentiation, lipid storage, and insulin sensitization [38]. In pathological changes closely related to T2DM, such as adipocyte hypertrophy and inflammation, PPAR-γ activity may be disturbed, leading to a reduced capacity of adipose tissue to buffer lipids and to increased ectopic lipid deposition in the liver [39].

2.2 PPARs promote lipid oxidation and phosphorylation

Under physiological conditions, hepatic PPARα is activated and upregulates the expression of β-oxidation genes, helping to clear free fatty acids (FFA) and thereby preventing extensive TG accumulation [40–42]. In T2DM complicated by MASLD, insulin resistance in adipose tissue causes FFA to be released into the blood in amounts exceeding the oxidative capacity of the liver. Because patients with T2DM have hyperinsulinemia, blood glucose levels rise and the amount of lipotoxic substrates increases, such as diacylglycerol (DAG) and ceramide (Cer), which in turn disrupts the normal function of PPARα. Persistently elevated insulin levels stimulate the production of sterol-regulatory-element-binding protein-1c (SREBP-1c), which becomes a potent factor promoting lipogenesis [43]. Mitochondrial processing of the increased lipid-substrate burden in T2DM, as well as crosstalk with transcriptional coactivators such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), is critically important. PPARβ/δ and PGC-1α jointly maintain mitochondrial biogenesis and lipid oxidation, but T2DM-related epigenetic alterations

and dysfunction of coactivators can disrupt this adaptive mechanism, resulting in incomplete fatty-acid oxidation and further aggravating hepatolipotoxicity [44]. Adiponectin can promote the activation of amp-activated protein kinase (AMPK) and PPARα; as an insulin sensitizer, it promotes fatty-acid oxidation while inhibiting hepatic gluconeogenesis [45]. In T2DM, reduced adiponectin levels weaken PPARα signal transduction and aggravate hepatic lipid accumulation. Leptin levels increase in patients with obesity and T2DM; leptin plays roles in regulating appetite and energy expenditure. Leptin levels are markedly elevated in patients with obesity and T2DM, and hyperleptinemia may act through Janus kinase/signal transducer and activator of transcription [46].

2.3 PPARs suppress inflammatory responses

In T2DM complicated by MASLD, insulin resistance leads to excessive influx of free fatty acids into the liver, disrupting lipid homeostasis and activating inflammatory pathways [47]. Dysfunctional adipose tissue releases tumor necrosis factor-α (tumour necrosis factor alpha, TNF-α), along with cellular factors such as interleukins, forming a pro-inflammatory microenvironment, activating signaling cascades that weaken insulin signaling, damaging hepatocytes, and aggravating liver injury. PPARα can exert anti-inflammatory effects by inhibiting the nuclear factor-κB (nuclear factor-kappab, NF-κB) pathway; however, its expression or activity is often reduced in T2DM, weakening the liver' s defense against lipotoxic stress [48]. At the same time, the inflammatory environment also suppresses PPAR-γ activity, aggravating insulin resistance and affecting adipocyte differentiation. Although PPARβ/δ can suppress inflammatory mediators, its signaling pathway is often disrupted in the T2DM state, diminishing its anti-inflammatory and metabolic protective effects [49–51]. Accumulation of lipotoxic lipid intermediates can trigger endoplasmic-reticulum stress and oxidative stress, activate c-Jun N-terminal kinase (c-jun n-terminal kinase, JNK) and inhibitor of κB kinase (ikappab kinase, IKK), interfere with phosphorylation of insulin receptor substrates, suppress downstream insulin signaling, and promote inflammatory-gene expression mediated by activator protein-1 (AP-1). Hyperinsulinemia and hyperglycemia can induce transcriptional changes such as increased SREBP-1c activity and weakened adiponectin signaling, accelerating hepatic steatosis and inflammation. Decreased PPARα-mediated fatty-acid clearance, weakened PPARβ/δ-mediated maintenance of metabolic flexibility, and restriction of the lipid-storage function of PPAR-γ act together to aggravate disease progression and increase the risk of severe liver complications [52]. T2DM complicated by MASLD is not merely a disease of hepatic lipid overload, but a systemic disorder characterized by abnormalities in energy management, insulin resistance, and chronic inflammation, in which PPARs play a central coordinating role [53]. Epigenetic and post-translational modifications in T2DM reduce PPAR availability or ligand affinity, leading to loss of control over chronic inflammation; this is the so-called "metabolic inflammatory response" [54]. As epigenetic and post-translational regulatory mechanisms are revealed, restoration of PPAR function needs to take into account nutritional balance, availability

of coregulators, and inflammatory status.

2.4 PPARs regulate the balance of the intestinal microbiota

PPARs play an important role in host–gut microbiome crosstalk and have been identified as mediators of intestinal epithelial homeostasis. In patients with T2DM complicated by MASLD, the structure of the intestinal microbiota is significantly altered. The abundance of Firmicutes and Proteobacteria increases, whereas that of Bacteroidetes, Lactobacillus, and Para-

the abundance of *Bacteroides* and other genera is reduced [56]. Proteobacteria produce endotoxins that enter the bloodstream, causing endotoxemia and thereby activating systemic inflammatory responses, such as the Toll-like receptor 4 (TLR4), interleukin-6 (IL-6), and TNF-α inflammatory pathways; ultimately, this promotes hepatocellular injury and hepatic steatosis, driving the development of T2DM combined with MASLD. Some bacteria in the phylum Firmicutes, as well as *Akkermansia muciniphila* in the phylum Verrucomicrobiota, can disrupt the intestinal mucus barrier, leading to increased intestinal permeability [57]. Under healthy conditions, short-chain fatty acids (SCFAs) confer many benefits to the body. Butyrate provides the main energy source for intestinal epithelial cells and maintains intestinal barrier integrity. Propionate can enhance satiety, reduce excessive energy intake, and regulate metabolism-related genes by influencing processes such as histone acetylation and methylation through epigenetic modification, thereby improving hepatic lipid metabolism. In addition to accumulating in the intestine, SCFAs can also activate PPARα and reduce hepatic lipid accumulation through the UCP2-AMPK pathway [58]. In patients with T2DM combined with MASLD, intestinal microbiota dysbiosis and reduced abundance of SCFA-producing bacteria lead to markedly decreased SCFA levels, diminishing their beneficial effects on hepatic lipid metabolism and aggravating intrahepatic lipid accumulation [59]. The expression of PPAR-γ can be upregulated by metabolites produced from the fermentation of dietary fiber by the gut microbiota, including SCFAs such as butyrate and propionate, as well as metabolites of *Prevotella* and *Atopobium*. Butyrate-activated PPAR-γ signaling can inhibit the expression of nitric oxide synthase 2 (NOS2), reduce inducible nitric oxide synthesis, and limit luminal nitrate availability, thereby suppressing the overgrowth of Enterobacteriaceae. As key members of the gut microbiome, *Bacteroides* can regulate diseases related to glucose and lipid metabolism [60–62]. Butyrolactone-I (BL-I) can improve blood glucose and insulin resistance in T2DM mice, increase SCFA levels, and activate PPARs expression, which may be related to microbiota regulation. In intestinal inflammation, PPARα deficiency leads to commensal microbiota dysbiosis and aggravated inflammation [63–65].

3 PPARs Agonists for the Treatment of T2DM Combined with MASLD

The pathogenesis of MASLD and MASH involves multiple factors and is highly complex, resulting in limited clinical benefit from single-target intervention strategies. Based on the functional characteristics of different PPAR subtypes, multiple types of PPARs agonists have been developed. PPARα agonists, such as fibrates, mainly activate hepatic fatty acid oxidation and reduce TG; PPAR-γ agonists, such as thiazolidinediones, primarily improve insulin sensitivity and promote adipocyte differentiation as well as glucose and lipid homeostasis. Pioglitazone has been recommended by multiple recent guidelines, including the ADA standards of care for diabetes, as one of the preferred drugs for type 2 diabetes combined with MASLD. In addition, PPARα/γ dual agonists such as saroglitazar, PPARα/δ dual agonists such as elafibranor, and pan-PPAR agonists such as lanifibranor are designed to synergistically regulate multiple metabolic pathways, comprehensively improve hepatic steatosis, inflammation, and fibrosis, and exert overall regulatory effects on systemic glucose and lipid metabolism as well as cardiovascular risk. Several clinical studies have shown that PPARs agonists can improve T2DM combined with MASLD through multiple pathways, including glucose and lipid metabolism and the alleviation of hepatic steatosis and inflammation; however, adverse effects such as cardiovascular lesions, weight gain, and peripheral edema may occur in clinical practice, as shown in Table 1 [66–77].

4 Summary and Outlook

PPARs are key regulators situated at the intersection of energy metabolism, insulin action, and inflammatory responses, and are crucial for maintaining hepatic and systemic metabolic homeostasis. T2DM and MASLD constitute a bidirectionally reinforcing pathological association, one of the key hubs of which is the dysregulation of PPARs function. The metabolic disorder milieu of T2DM suppresses PPARs activity, causing the liver to shift toward lipid accumulation, oxidative stress, and fibrosis, thereby inducing or aggravating MASLD. Meanwhile, the hepatic insulin resistance and chronic inflammation inherent to MASLD further suppress PPARs signaling pathways, exacerbating systemic glucose and lipid metabolic disturbances and promoting the progression of T2DM. Given the ameliorative effects of PPARs on T2DM combined with MASLD, in-depth research on PPARs is expected to bring breakthrough progress in the prevention and treatment of T2DM combined with MASLD.

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tables.

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Table 1 Therapeutic Trials of PPARs Agonists in MASLD

First author	Year	Study design, enrolled patients, treatment duration	Biochemical indicators	Adverse effects
Sany[66]	2010	In a 96-week trial, among 247 randomly assigned participants, 83 were assigned to receive placebo, 84 to receive vitamin E, and 80 to receive pioglitazone.	In the pioglitazone group, steatosis, lobular inflammation, and the activity score of metabolic fatty liver disease were all significantly reduced; ALP and GGT concentrations decreased.	Participants receiving pioglitazone had a similar number of cardiovascular events, and body weight increased.
Cusi[67]	2016	An 18-month RCT followed by an 18-month open-label phase, using pioglitazone ($n = 50$) or placebo ($n = 51$).	Hepatic TG content with pioglitazone decreased from 19% to 7%. The reduction in NAS was associated with resolution of steatosis, inflammation, and hepatocyte ballooning.	Fibrosis in the pioglitazone group did not improve.

First author	Year	Study design, enrolled patients, treatment duration	Biochemical indicators	Adverse effects
Ito[68]	2017	A 24-week open-label, randomized controlled trial enrolled 66 patients with T2DM complicated by MASLD, randomly assigned to the pioglitazone group (15 or 30 mg/d, $n = 34$) or the ipragliflozin group (50 mg/d, $n = 32$).	In the pioglitazone group, hepatic fat content decreased significantly, the liver/spleen CT ratio improved, and ALT and AST levels decreased significantly.	Body weight in the pioglitazone group showed no significant change; both groups were well tolerated.

First author	Year	Study design, enrolled patients, treatment duration	Biochemical indicators	Adverse effects
Kinoshita[69]	2020	A 28-week randomized, open-label, three-arm, parallel-controlled, active-drug controlled study enrolled 90 patients with T2DM complicated by MASLD, randomly assigned to the liraglutide group (1.2 mg/d, $n = 30$), pioglitazone group (30 mg/d, $n = 30$), or glimepiride group (0.5–1 mg/d, $n = 30$).	In the pioglitazone group, hepatic fat content decreased significantly, ALT and GGT levels improved, and HbA_{1c} decreased.	ALT levels increased in the glimepiride group, suggesting possible adverse effects on liver function.

First author	Year	Study design, enrolled patients, treatment duration	Biochemical indicators	Adverse effects
Cho[70]	2021	A 24-week randomized open-label trial enrolled 53 patients with T2DM complicated by NAFLD, randomly assigned to the dapagliflozin group (5 mg/d, $n = 27$) or the pioglitazone group (30 mg/d, $n = 26$).	In the pioglitazone group, HbA_{1c} decreased significantly, ALT and AST levels improved, and hepatic fat content decreased.	Both groups were well tolerated, with no reports of serious adverse events.

First author	Year	Study design, enrolled patients, treatment duration	Biochemical indicators	Adverse effects
Roy[71]	2023	A 12-month randomized controlled trial enrolled 96 patients with T2DM complicated by MASLD, randomly assigned to the pioglitazone group (15 mg/d, $n = 48$) or the saroglitazar group (4 mg/d, $n = 48$).	After 12 months of treatment in the pioglitazone group, liver stiffness measure-ment (LSM) showed no significant change (5.0 kPa vs. 5.0 kPa, $P = 0.83$); CAP decreased by 10.4 dB/m ($P = 0.42$); NFS showed no significant improve-ment (1.06 vs. 1.08, $P = 0.97$).	Both groups were well tolerated, with no reports of serious adverse events.

First author	Year	Study design, enrolled patients, treatment duration	Biochemical indicators	Adverse effects
Ito[72]	2024	A 24-week randomized controlled trial, followed by 5 years of observational follow-up, enrolled 66 patients with type 2 diabetes complicated by MASLD, randomly assigned to the ipragliflozin group ($n = 32$) or the pioglitazone group ($n = 34$).	After 5 years of treatment, the liver/spleen CT ratio in the pioglitazone group increased from 0.76 ± 0.26 to 1.02 ± 0.20 (increase of 0.26), and in the ipragliflozin group from 0.78 ± 0.24 to 0.98 ± 0.20 (increase of 0.20); AST, ALT, HbA_{1c}, and fasting plasma glucose levels in both groups showed sustained improvement over 5 years.	Both groups were well tolerated, with no reports of serious adverse events.

First author	Year	Study design, enrolled patients, treatment duration	Biochemical indicators	Adverse effects
Lee[73]	2025	A 24-week randomized, open-label trial enrolled 50 patients with T2DM complicated by MASLD, randomly assigned in a 1:1:1 ratio to the pioglitazone group (15 mg/d, $n = 15$), empagliflozin group (10 mg/d, $n = 17$), or combination-therapy group ($n = 18$).	After 24 weeks of pioglitazone monotherapy, the proportion of patients with a relative reduction in hepatic fat of $\geq 30\%$ or an absolute reduction of $\geq 5\%$ was 57.1%; those with a relative reduction of $\geq 50\%$ accounted for 35.7%; and those with a relative reduction in LSM of $\geq 20\%$ accounted for 21.4%. In the combination-therapy group, the corresponding proportions were 100.0%, 78.6%, and 50.0%. In the pioglitazone group, HbA_{1c} decreased by 1.3% ($P = 0.003$), HOMA-IR improved	In the pioglitazone group, the BMI z score increased numerically (+0.6 kg/m^2, $P = 0.442$), and subcutaneous fat area increased significantly ($P = 0.042$), whereas the combination-therapy group had a neutral effect on subcutaneous fat. No serious adverse events occurred during pioglitazone treatment. A total of 2 adverse events were reported: 1 case of facial pain and 1 case of mental confusion accompanied by weight lo

First author	Year	Study design, enrolled patients, treatment duration	Biochemical indicators	Adverse effects
Ratzi[74]	2016	Treatment lasted 52 weeks with elafibranor 80 mg ($n = 93$), elafibranor 120 mg ($n = 91$), or placebo ($n = 92$).	Elafibranor 120 mg significantly reduced liver enzymes, lipid and glycemic profiles, and systemic inflammatory markers.	Elafibranor 120 mg caused a mild, reversible increase in serum creatinine.
Gawrieh[75]	2021	A total of 106 patients with MASLD/MASH were randomized in a 1:1:1:1 ratio to receive placebo or saroglitazar 1 mg, 2 mg, or 4 mg for 16 weeks.	Compared with placebo, saroglitazar 4 mg reduced levels of LFC, insulin, and TG; it also improved lipoprotein particle composition and size and reduced lipotoxic lipid species.	The saroglitazar 4 mg group had a mean body-weight increase of 1.5 kg, while the placebo group had a mean increase of 0.3 kg.

First author	Year	Study design, enrolled patients, treatment duration	Biochemical indicators	Adverse effects
Nakajima[76]	2021	A 72-week double-blind, placebo-controlled, randomized multicenter phase 2 trial randomized 118 patients (1:1) to oral pemafibrate 0.2 mg or placebo, twice daily.	In the pemafibrate group, significant reductions in ALT, GGT, and ALP levels were observed; total TC, LDL-C, HDL-C, and TG levels also improved, and FXR agonist and FGF-19 were suppressed.	Six serious events occurred in the pemafibrate group, including obstructive pancreatitis, erysipelas, facial fracture, altered state of consciousness, cerebral infarction, and kidney stone.

First author	Year	Study design, enrolled patients, treatment duration	Biochemical indicators	Adverse effects
Francque[77]	2021	A 24-week RCT used lanifibranor 1 200 mg ($n = 83$), lanifibranor 800 mg ($n = 83$), and placebo ($n = 81$).	The lanifibranor groups showed reduced liver enzyme levels, enhanced lipid metabolism, suppressed inflammatory responses, and improvement in most biomarkers of liver fibrosis; lanifibranor was superior to placebo, with MASH resolution and no worsening of fibrosis.	The incidence of diarrhea, nausea, peripheral edema, anemia, and weight gain in the lanifibranor groups was higher than in the placebo group.

Note: RCT = randomized controlled trial; ALP = alkaline phosphatase; ALT = alanine aminotransferase; GGT = γ-glutamyltransferase; NAS = NAFLD activity score; LFC = liver fat content; FGF-19 = fibroblast growth factor 19; LSM = liver stiffness measurement; CAP = controlled attenuation parameter; NFS = liver fibrosis score; BMI = body mass index; HbA_{1c} = glycated hemoglobin; HOMA-IR = homeostatic model assessment of insulin resistance; FLI = fatty liver index.

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