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Pioglitazone-Mediated Reduction of Ectopic Fat in Metabolic Dysfunction-Associated Steatotic Liver Disease

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Abstract

Ectopic fat accumulation is a significant metabolic disorder that contributes to insulin resistance, inflammation, and organ dysfunction. Pioglitazone, a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist, improves insulin sensitivity and promotes the redistribution of ectopic fat from visceral and non-adipose tissues to subcutaneous adipose tissue. Pioglitazone has been shown to reduce ectopic fat, improve liver histology in metabolic dysfunction-associated steatotic liver disease (MASLD)/metabolic dysfunction-associated steatohepatitis (MASH), and improve glucose and lipid metabolism. Its effects on hepatic, visceral, pancreatic, intramyocellular, and cardiac fat suggest potential benefits across multiple metabolic conditions. Combination therapy with sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), or other metabolic agents may provide complementary benefits while mitigating pioglitazone-associated weight gain. However, concerns regarding fluid retention, weight gain, and other adverse effects require careful patient selection and monitoring. This narrative review examines the mechanisms by which pioglitazone influences ectopic fat distribution, summarizes evidence across different organ-specific fat depots, and discusses its potential role in combination therapeutic strategies. Further research is needed to clarify its long-term effects on organ-specific fat depots and clinical outcomes and to identify patients most likely to benefit from therapy.

Categories: Therapeutics, Cardiology, Internal Medicine
Keywords: ectopic fat, glp-1 receptor agonists, masld, nafld, pioglitazone, sglt2 inhibitors

Introduction And Background

Ectopic fat deposition, defined as the accumulation of triglycerides in non-adipose tissues such as the liver, skeletal muscle, pancreas, and heart, is a major feature of metabolic disorders including obesity, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD) [1]. Under conditions of energy surplus and insulin resistance, the storage capacity of subcutaneous adipose tissue may be exceeded, leading to lipid spillover and deposition in ectopic sites [2]. This can result in organ-specific dysfunction, including hepatic steatosis that may progress to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, and cirrhosis; intramyocellular lipid accumulation; pancreatic steatosis; and cardiac dysfunction [3-6]. Metabolic dysfunction-associated steatotic liver disease (MASLD) affects approximately one-third of adults globally, with a substantially higher burden among individuals with type 2 diabetes mellitus (T2DM) [7]. A large meta-analysis involving approximately 1.8 million individuals with T2DM reported a pooled MASLD prevalence of approximately 65% (95% CI: 62%-68%) [7]. In South Asian populations, a systematic review and meta-analysis estimated MASLD prevalence at 34.7% (95% CI: 29.0%-40.5%) in populations not selected for T2DM and 60.0% (95% CI: 48.9%-71.1%) among individuals with T2DM, although substantial between-study heterogeneity was observed [8].

MASLD, the hepatic manifestation of metabolic dysfunction, is associated with inflammation, insulin resistance, and dyslipidemia, all of which contribute to hyperglycemia and cardiovascular risk [9]. Beyond its hepatic manifestations, MASLD is associated with an increased burden of cardiovascular disease, including coronary artery disease, atrial fibrillation, and heart failure with preserved ejection fraction (HFpEF) [10,11]. Ectopic lipid accumulation, insulin resistance, and chronic low-grade inflammation contribute to endothelial dysfunction, oxidative stress, and atherogenic dyslipidemia, promoting subclinical atherosclerosis and arterial stiffness [11,12]. In addition, myocardial and epicardial fat accumulation may contribute to myocardial inflammation, fibrosis, and impaired ventricular relaxation, providing potential mechanistic links between MASLD and HFpEF [10]. These overlapping metabolic and inflammatory

pathways highlight the importance of cardiovascular risk assessment in individuals with MASLD [11,12]. Pancreatic steatosis has also been associated with impaired insulin secretion and β-cell dysfunction, contributing to the development of T2DM [13,14]. Hepatic and pancreatic fat may therefore contribute collectively to worsening glycemic control and insulin resistance.

Pioglitazone, a thiazolidinedione and peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist, improves insulin sensitivity in adipose tissue and skeletal muscle and promotes redistribution of fat from ectopic to subcutaneous depots [15,16]. It also has anti-inflammatory effects. Evidence suggests that pioglitazone can reduce hepatic fat and improve hepatic glucose metabolism, lipid profiles, and histological features of MASH [15,16]. Its effects on pancreatic fat and β-cell function have also been explored, although the evidence is less consistent and should be interpreted cautiously [13,14]. However, its clinical use is limited by adverse effects, including weight gain, fluid retention, worsening heart failure, and increased fracture risk. A possible association between prolonged pioglitazone exposure, particularly at higher cumulative doses, and bladder cancer has also been reported, although the evidence remains inconclusive; these concerns warrant individualized assessment of treatment dose, duration, and safety [17,18].

Although existing studies support the role of pioglitazone in improving metabolic parameters and reducing selected ectopic fat depots, evidence varies according to the organ studied, patient population, and assessment method. This review therefore examines ectopic fat deposition in metabolic disease, with particular emphasis on MASLD and other organ-specific fat depots, and evaluates the therapeutic role of pioglitazone in modifying ectopic fat and related metabolic outcomes.

Review

Methods

This article was developed as a narrative review to examine the role of pioglitazone in ectopic fat deposition and related metabolic disorders. Relevant literature was identified through searches of PubMed, MEDLINE, and the Cochrane Library, supplemented by reference-list screening of relevant articles. The narrative synthesis included mechanistic studies, clinical studies, randomized controlled trials (RCTs), systematic reviews, and meta-analyses relevant to ectopic fat distribution, insulin resistance, MASLD, and the metabolic effects of pioglitazone.

To strengthen and update the evidence presented in this review, additional structured literature searches were conducted in July 2026 using PubMed, MEDLINE, and the Cochrane Library. Search terms included combinations of terms related to pioglitazone, ectopic fat, visceral adipose tissue, hepatic fat, pancreatic fat, intramyocellular lipid, epicardial or pericardial fat, MASLD/MASH, combination therapy, and PPAR-targeted therapies. The detailed search strategies used for each evidence table are provided in the Appendices. The literature search and study selection were conducted by a single researcher. Titles and abstracts were screened for relevance to the review objectives, and potentially relevant articles were assessed for inclusion in the narrative synthesis. Independent duplicate screening and formal inter-reviewer disagreement resolution were not undertaken.

For the tabulated evidence, priority was given to RCTs and other relevant clinical studies that directly evaluated changes in ectopic fat depots, hepatic steatosis or fibrosis, metabolic outcomes, or related imaging and histological measures. Systematic reviews and meta-analyses were included where they provided clinically relevant synthesis of the available evidence. Studies were selected based on their relevance to the specific therapeutic or organ-specific domains represented in each table. Where sufficiently relevant evidence was not identified for a particular domain, no study was included solely to populate the table. Articles that did not address pioglitazone, ectopic fat deposition, or the relevant metabolic and therapeutic outcomes were excluded from the tabulated evidence synthesis.

As the objective of this article was narrative rather than quantitative evidence synthesis, no formal meta-analysis was performed. Findings were summarized descriptively, with emphasis on the direction and magnitude of reported effects, clinical relevance, and limitations of the available evidence. The included literature was evaluated narratively, considering study design, population characteristics, sample size, clinical relevance, and consistency of findings across studies. No formal risk-of-bias scoring or quantitative publication-bias assessment was performed, consistent with the narrative rather than systematic-review design.

Pioglitazone: mechanism of action and metabolic effects

Pharmacokinetics and PPAR-γ Activation

Pioglitazone, a thiazolidinedione (TZD), acts primarily by activating the nuclear receptor PPAR-γ, which is widely expressed in adipose tissue. When activated, PPAR-γ regulates the transcription of genes involved in glucose and lipid metabolism, adipogenesis, and energy homeostasis. Important upregulated genes include GLUT4, glucokinase, and lipoprotein lipase, all of which contribute to improved glucose uptake and lipid storage [19].

Pharmacokinetically, pioglitazone is well absorbed after oral administration, reaching peak plasma concentrations within 2-4 hours. It is more than 99% protein-bound, has a volume of distribution of approximately 0.63 L/kg, and has a half-life of 3-7 hours, allowing once-daily administration [20]. The drug undergoes extensive hepatic metabolism by CYP2C8 and CYP3A4 to produce active metabolites, particularly metabolites II, III, and IV, which contribute to its therapeutic effects [20]. Concomitant use of drugs that modulate CYP2C8 activity may alter plasma pioglitazone concentrations and require dose adjustment. Pioglitazone also has partial agonist activity at PPAR-α, which is expressed primarily in the liver, heart, and vascular tissue and plays a role in fatty acid oxidation, potentially contributing to its lipid-modifying and anti-inflammatory effects [20].

Effects on Insulin Sensitivity and Lipid Metabolism

Endoplasmic reticulum (ER) stress, oxidative stress, and disturbances in the unfolded protein response have emerged as important research themes in obesity-associated metabolic dysfunction, with potential relevance to insulin resistance and ectopic lipid accumulation [21].

Pioglitazone increases insulin sensitivity in several tissues, including skeletal muscle, adipose tissue, and the liver. It decreases hepatic glucose production and facilitates peripheral glucose uptake, thereby improving glycemic control in T2DM [19]. In adipocytes, pioglitazone inhibits lipolysis, leading to a substantial reduction in plasma free fatty acid (FFA) levels and thereby reducing the lipotoxic burden on other organs [22].

By modulating adipokines, bioactive molecules secreted by adipose tissue, pioglitazone has secondary effects on hepatic and skeletal muscle insulin sensitivity [20]. Additionally, its PPAR-γ/α activity may modulate lipid metabolism by improving lipid profiles, lowering triglyceride levels, and altering adipocyte lipid composition, including reductions in pro-inflammatory arachidonic acid-rich glycerophospholipids [23]. These effects may contribute to improved metabolic homeostasis and insulin signaling in insulin-resistant states.

Adipose Tissue Redistribution and Ectopic Fat Modulation

Pioglitazone, a thiazolidinedione, promotes fat redistribution from visceral to subcutaneous depots and enhances adipogenesis. White et al. found that pioglitazone increased adipogenesis by 3.3% in the femoral subcutaneous fat (scFEM) depot in women with obesity ($p = 0.04$), with improved insulin sensitivity indicated by a significant increase in the Matsuda index ($p = 0.04$) [24]. Although visceral fat decreased (VAT abdominal AT reduced by 9%, $p = 0.002$), no significant changes were observed in abdominal subcutaneous fat (scABD; $p = 0.32$), suggesting that pioglitazone may improve metabolic health by redistributing fat and promoting adipocyte formation [24].

Moody et al. reported that pioglitazone reduced epicardial adipose tissue (EAT) and paracardial adipose tissue (PAT) areas by 9% ($p = 0.03$) and 9% ($p = 0.09$), respectively, in patients with T2D, while improving insulin sensitivity, with whole-body glucose uptake increasing by 71% ($p < 0.01$). Reductions in EAT and PAT were associated with improved metabolic outcomes, supporting the effects of pioglitazone on ectopic fat and cardiometabolic function [25].

Palavicini et al. used shotgun lipidomics to investigate the effects of pioglitazone (45 mg/day for 6 months) in individuals with obesity and T2DM. Despite an average weight gain of 3.6 kg, no significant changes were observed in the overall triglyceride, ceramide, or diacylglycerol content of subcutaneous adipose tissue [23]. However, pioglitazone induced qualitative remodeling of adipose-tissue glycerophospholipids, including reductions in arachidonic acid-enriched lipid species. These findings suggest that the metabolic effects of pioglitazone may involve qualitative remodeling of adipose-tissue lipid composition rather than simply changes in total lipid content, potentially contributing to improved adipose-tissue metabolic function.

The effects of pioglitazone on body composition and muscle function during intentional weight loss, with or without resistance training, were evaluated in a 2 × 2 factorial RCT in older adults. Shea et al. found that, over 16 weeks of hypocaloric weight loss, men receiving pioglitazone experienced significantly greater visceral fat loss than controls (-1,160 vs. -647 cm^3; $p = 0.007$) [26]. In women, pioglitazone was associated with a significant difference in thigh subcutaneous fat compared with controls (-104 vs. -298 cm^3; $p = 0.002$), with no significant effect on lean mass [26]. In a related analysis, Marsh et al. showed that, despite reductions in lean and appendicular lean mass, muscle power and strength were largely preserved. Women assigned to resistance training showed significant improvements in leg press power ($p < 0.001$), and a significant pioglitazone-by-resistance training interaction was observed for leg power ($p = 0.006$), suggesting that pioglitazone may potentiate the effect of resistance training on muscle power in women [27].

Pioglitazone and MASLD

Pioglitazone has demonstrated clinical benefits in patients with MASLD, particularly in improving hepatic

steatosis, inflammation, and hepatocellular ballooning, along with metabolic parameters such as insulin sensitivity and lipid profiles [17,28,29]. Evidence for improvement in liver fibrosis, however, remains less consistent [28,29]. Clinical evidence from RCTs and meta-analyses [17,28-30] evaluating the hepatic and metabolic effects of pioglitazone is summarized in Table *1*. Although these findings support a potential therapeutic role for pioglitazone in appropriately selected patients with MASLD, its benefits should be considered alongside its established adverse-effect profile [17].

Outcomes	Evidence base	Key findings	Clinical interpretation	Reference study
Cardiovascular outcomes	Systematic review and meta-analysis of 9 RCTs (12,026 participants)	Reduced MACE in prediabetes/insulin resistance (RR 0.77, 95% CI 0.64-0.93) and T2DM (RR 0.83, 95% CI 0.72-0.97); increased heart failure, edema, weight gain, and fractures	Reduces cardiovascular events in selected high-risk patients; careful patient selection is required because of fluid retention and heart failure risk	Liao et al. (2017) [17]
Hepatic and metabolic outcomes in NASH	Systematic review and meta-analysis of 15 RCTs	Improved fasting glucose, HbA1c, HOMA-IR, triglycerides, ALT, AST, GGT, and fasting insulin versus control	Demonstrates consistent metabolic and liver biochemical benefits; evidence does not establish fibrosis regression	Zhao et al. (2022) [28]
Liver histology in NAFLD with prediabetes or T2DM	Meta-analysis of 4 studies	Improved steatosis, inflammation, hepatocellular ballooning, insulin sensitivity, liver enzymes, and glycemic control; no significant improvement in fibrosis stage	Supports histological improvement in disease activity, while evidence for fibrosis improvement remains limited	Lian and Fu (2021) [29]
Effect according to diabetes status	Meta-analysis of 7 RCT reports (614 participants)	Similar hepatic and metabolic responses in patients with and without T2DM; edema occurred more frequently in patients with diabetes receiving pioglitazone	Benefits appear independent of diabetes status, although additional high-quality RCTs are needed	Wang et al. (2023) [30]

TABLE 1: Summary of clinical evidence on pioglitazone in metabolic and hepatic disease

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma-glutamyl transferase, HbA1c: glycated hemoglobin, HOMA-IR: homeostatic model assessment of insulin resistance, MACE: major adverse cardiovascular events, NAFLD: nonalcoholic fatty liver disease, NASH: nonalcoholic steatohepatitis, RCT: randomized controlled trial, RR: relative risk, T2D: type 2 diabetes.

Organ-Specific Mechanisms of Lipotoxicity

In cardiomyocytes, excessive fatty acid uptake and impaired lipid oxidation can promote the accumulation of lipotoxic intermediates, particularly diacylglycerols (DAGs) and ceramides. DAG-mediated activation of protein kinase C (PKC) isoforms can interfere with insulin signaling, while ceramide accumulation contributes to mitochondrial dysfunction, oxidative stress, and apoptosis. These processes may promote myocardial metabolic dysfunction and impaired contractile performance [31,32]. Pioglitazone may indirectly attenuate these pathways through PPAR-γ-mediated improvements in adipose tissue lipid storage, reduced circulating free fatty acid availability, and improved systemic insulin sensitivity. However, direct evidence demonstrating pioglitazone-induced reductions in myocardial DAG or ceramide concentrations in humans remains limited.

In pancreatic β-cells, chronic exposure to excess fatty acids and glucose can promote intracellular DAG and ceramide accumulation, PKC-related signaling disturbances, endoplasmic reticulum stress, mitochondrial dysfunction, and impaired glucose-stimulated insulin secretion. Ceramide-associated apoptotic signaling may further contribute to progressive β-cell dysfunction [33,34]. By reducing systemic lipotoxic exposure and improving insulin sensitivity, pioglitazone may alleviate metabolic stress on pancreatic β-cells and support preservation of β-cell function. Nevertheless, these proposed benefits should not be interpreted as direct evidence that pioglitazone reverses pancreatic ceramide accumulation or mitochondrial injury in humans.

Clinical Applications and Future Perspectives

Pioglitazone appears to provide the greatest clinical benefit in individuals with metabolic dysfunction, particularly those with T2D, insulin resistance, or nonalcoholic steatohepatitis (NASH/MASH). These populations commonly exhibit increased ectopic fat accumulation, which contributes to impaired glucose metabolism and heightened cardiometabolic risk. Clinical and mechanistic studies indicate that pioglitazone can reduce hepatic, visceral, and intramyocellular fat and improve insulin sensitivity and β-cell

function [35-41]. Its effects on pancreatic fat have also been investigated, although the available evidence is less consistent [13,14].

Importantly, although weight gain is commonly observed with pioglitazone, this may reflect a redistribution of adipose tissue toward subcutaneous depots rather than an increase in visceral adiposity [24,40]. Patients with coexisting obesity, metabolic syndrome, or prediabetes may also derive metabolic and hepatic benefits, particularly with respect to insulin sensitivity, glycemic control, and selected histological outcomes [17,28-30,35,36]. Table *2* summarizes representative clinical studies evaluating the effects of pioglitazone on different ectopic fat depots and overall body-fat distribution.

Fat depot/outcome	Patient population	Study design	Dosage and duration	Key findings	Reference study
Hepatic fat	Adults with biopsy-proven NASH	Randomized placebo-controlled trial	Pioglitazone 45 mg/day for 6 months	Improved hepatic steatosis, hepatocellular ballooning, histological activity, and insulin sensitivity	Belfort et al. (2006) [35]
Hepatic fat	Adults with prediabetes/T2DM and biopsy-proven NASH	Randomized placebo-controlled trial	Pioglitazone 45 mg/day for 18 months	NASH resolution in 58% of patients with significant reductions in NAS and improved fibrosis	Cusi et al. (2016) [36]
Hepatic fat	Patients with T2DM (n = 21)	Comparative clinical trial using ^{1}H-MRS	Pioglitazone for 6 months	Hepatic lipid content decreased from 12.0 ± 6.1 to 8.4 ± 3.7 AU (P < 0.01)	Teranishi et al. (2007) [37]
Intramyocellular fat	Patients with T2DM (n = 24)	Clinical intervention using ^{1}H-MRS, muscle biopsy, and hyperinsulinemic-euglycemic clamp	Pioglitazone 45 mg/day for 4 months	IMCL decreased from 1.5% to 0.9% (p < 0.05); insulin-stimulated glucose disposal increased by 25%-56%; long-chain fatty acyl-CoA decreased from 12.5 to 8.1 nmol/g (p < 0.05)	Bajaj et al. (2010) [38]
Intramyocellular fat	Patients with metabolic syndrome (n = 14)	Clinical intervention using ^{1}H-MRS and ^{31}P-MRS	Pioglitazone 15 mg/day for 4 months	IMCL decreased by 26%; peak VO_2 increased from 25.1 ± 4.9 to 27.2 ± 3.9 mL/kg/min; anaerobic threshold improved (p < 0.05).	Yokota et al. (2017) [39]
Intramyocellular fat	Patients with T2DM (n = 21)	Comparative clinical trial using ^{1}H-MRS	Pioglitazone for 6 months	IMCL decreased from 8.4 ± 3.6 to 6.3 ± 2.4 AU/creatine (p < 0.01).	Teranishi et al. (2007) [37]
Visceral fat/body fat redistribution	Patients with T2DM	Randomized clinical trial using MRI	Pioglitazone	Reduced visceral adiposity with redistribution toward subcutaneous adipose tissue and improved insulin sensitivity	Miyazaki et al. (2002) [40]
Visceral fat/body fat redistribution	Patients with T2DM (n = 21)	Comparative clinical trial using MRI	Pioglitazone for 6 months	No significant change in absolute VAT or SAT; VAT/SAT ratio decreased from 0.92 ± 0.41 to 0.85 ± 0.41 (p < 0.05); adiponectin increased from 5.6 ± 4.1 to 16.2 ± 9.9 µg/mL (p < 0.0001)	Teranishi et al. (2007) [37]
Visceral fat/body fat redistribution	Patients with familial combined hyperlipidemia (n = 22)	Randomized, double-blind, placebo-controlled trial using MRI and ^{1}H-MRS	Pioglitazone 30 mg/day for 4 weeks, then 45 mg/day for 12 weeks	Total adipose tissue increased by 5.3% (p = 0.02); subcutaneous adipose tissue increased by 7.1% (p = 0.003); adiponectin increased by 130% (p = 0.001); no significant change in visceral fat or intrahepatic lipid content	Thomas et al. (2007) [41]

TABLE 2: Clinical intervention studies evaluating the effects of pioglitazone on ectopic fat depots and body fat redistribution

AU: arbitrary units, IMCL: intramyocellular lipid, MRI: magnetic resonance imaging, MRS: magnetic resonance spectroscopy, NAFLD: nonalcoholic fatty liver disease, NAS: NAFLD Activity Score, NASH: nonalcoholic steatohepatitis, SAT: subcutaneous adipose tissue, T2DM: type 2 diabetes mellitus, VAT: visceral adipose tissue, VO_2: oxygen consumption, ^{1}H-MRS: proton magnetic resonance spectroscopy, ^{31}P-MRS: phosphorus-31 magnetic resonance spectroscopy.

Combination strategies involving pioglitazone have been investigated to enhance metabolic and hepatic benefits while potentially mitigating adverse effects such as weight gain. In patients with T2DM, the addition of agents with complementary mechanisms of action may improve glycemic control, body weight,

lipid parameters, and markers of hepatic steatosis compared with pioglitazone-based therapy alone [42-47].

Clinical studies evaluating pioglitazone in combination with glucagon-like peptide-1 receptor agonists (GLP-1RAs), sodium-glucose cotransporter-2 (SGLT2) inhibitors, and other glucose-lowering therapies are summarized in Table *3* [42-47]. The available evidence suggests that these combinations may provide complementary metabolic benefits, although the magnitude and nature of the effects vary according to the therapeutic combination, study population, and outcomes assessed. These findings support further evaluation of combination strategies in MASLD/MASH and T2D, particularly where complementary metabolic effects may improve efficacy or offset treatment-associated weight gain.

Reference study	Study design/intervention	Liver/ectopic-fat assessment	Key findings
Sathyanarayana et al. (2011) [42]	T2DM (n = 21); pioglitazone (PIO) vs PIO + exenatide for 12 months	Hepatic fat by MRS	Combination reduced hepatic fat more than PIO alone (61% vs 41%, p < 0.05), with greater improvements in adiponectin, triglycerides, and ALT, and minimal weight change
Yoneda et al. (2022) [43]	Combination phase (n = 32); PIO or tofogliflozin (TOFO) for 24 weeks followed by PIO + TOFO for 24 weeks	MRI-PDFF; MRE	Combination therapy improved hepatic and metabolic outcomes, further reduced steatosis and ALT, and attenuated PIO-associated weight gain
Lee et al. (2025) [44]	Randomized controlled trial (n = 50); PIO vs empagliflozin (EMPA) vs PIO + EMPA for 24 weeks	MRI-PDFF, MRE, visceral/SAT	Combination therapy achieved the greatest reduction in liver fat and stiffness; liver-fat response 100% vs 57.1% (PIO) vs 87.5% (EMPA) (p = 0.010), with the largest reduction in visceral fat
Abdul-Ghani et al. (2025) [45]	Patients with T2DM (n = 55); metformin + PIO + exenatide vs sequential metformin → glipizide → insulin	Six-year assessment of liver fat and fibrosis	Triple therapy was associated with lower hepatic fat and fibrosis despite comparable glycemic control
Fu et al. (2023) [46]	Multicenter double-blind RCT (n = 120); PIO + metformin vs metformin for 24 weeks	Fatty liver severity	Combination therapy produced greater improvement in fatty liver severity, particularly in moderate-to-severe NAFLD
Hooshmand Gharabagh et al. (2024) [47]	Randomized prospective open-label trial (n = 60); EMPA 10 mg + metformin vs PIO 30 mg + metformin for 6 months	NAFLD grade; FibroScan/liver stiffness	Both regimens improved fibrosis stage, liver stiffness, and liver biochemistry. Weight and BMI decreased only with EMPA, whereas PIO was associated with modest weight gain

TABLE 3: Pioglitazone in Combination Therapies and Their Effects on Ectopic Fat and Metabolic Health

ALT: alanine aminotransferase, BMI: body mass index, EMPA: empagliflozin, MET: metformin, MRI-PDFF: magnetic resonance imaging-proton density fat fraction, MRE: magnetic resonance elastography, MRS: magnetic resonance spectroscopy, NAFLD: nonalcoholic fatty liver disease, PIO: pioglitazone, RCT: randomized controlled trial, SAT: subcutaneous adipose tissue, T2DM: type 2 diabetes mellitus, TG: triglycerides, TOFO: tofogliflozin.

Cardiovascular outcomes of pioglitazone

Coronary Artery Disease and Myocardial Infarction

Pioglitazone may confer cardiovascular benefits through improvements in insulin sensitivity, adipose tissue lipid handling, and inflammatory and atherogenic metabolic pathways. In the PROactive randomized trial involving 5,238 patients with type 2 diabetes and established macrovascular disease, the broad primary composite cardiovascular endpoint was not significantly reduced (HR 0.90, 95% CI 0.80-1.02; p = 0.095). However, the main secondary composite endpoint of all-cause mortality, nonfatal myocardial infarction, and stroke was significantly reduced (HR 0.84, 95% CI 0.72-0.98; p = 0.027) [48]. In a prespecified analysis of 2,445 participants with previous myocardial infarction, pioglitazone was associated with a lower risk of recurrent fatal or nonfatal myocardial infarction (HR 0.72, 95% CI 0.52-0.99; p = 0.045) and acute coronary syndrome (HR 0.63, 95% CI 0.41-0.97; p = 0.035) [49]. These findings suggest potential benefits in selected patients with established coronary disease, although the overall trial findings and increased heart failure risk require balanced interpretation.

Atrial Fibrillation

The potential effects of pioglitazone on atrial fibrillation may involve improved insulin sensitivity and attenuation of inflammatory and oxidative pathways associated with atrial remodeling. A meta-analysis involving 130,854 patients with diabetes reported a lower incidence of atrial fibrillation among thiazolidinedione users (OR 0.73, 95% CI 0.62-0.87), including an association with pioglitazone (OR 0.56, 95% CI 0.32-0.98). However, the pooled analysis of RCTs did not demonstrate a statistically significant reduction in atrial fibrillation (OR 0.77, 95% CI 0.53-1.12), indicating that the apparent benefit was largely driven by observational evidence [50]. Furthermore, a small randomized study found no significant reduction in atrial fibrillation recurrence after electrical cardioversion despite improvements in inflammatory markers [51]. Therefore, the evidence remains insufficient to establish pioglitazone as an effective intervention for atrial fibrillation prevention.

Stroke and Cerebrovascular Outcomes

Evidence for the cerebrovascular benefits of pioglitazone is supported by the IRIS randomized trial, which enrolled 3,876 insulin-resistant patients without diabetes who had experienced a recent ischemic stroke or transient ischemic attack. Over a median follow-up of 4.8 years, the composite endpoint of fatal or nonfatal stroke or myocardial infarction occurred in 9.0% of pioglitazone-treated participants compared with 11.8% receiving placebo (HR 0.76, 95% CI 0.62-0.93; p = 0.007) [52]. A subgroup analysis of PROactive also reported a reduction in recurrent fatal or nonfatal stroke among participants with previous stroke (HR 0.53, 95% CI 0.34-0.85; p = 0.0085), although this finding arose from a subgroup analysis [53]. A meta-analysis of randomized trials in patients with established cardiovascular disease subsequently reported reductions in recurrent myocardial infarction (RR 0.77, 95% CI 0.64-0.93) and stroke (RR 0.81, 95% CI 0.68-0.96), alongside an increased risk of heart failure (RR 1.33, 95% CI 1.14-1.54) [54]. These findings support a potential role in secondary cardiovascular prevention among appropriately selected patients, while emphasizing the importance of individual risk assessment.

Clinical safety and risk stratification for pioglitazone

Recent evaluations of pioglitazone's safety profile highlight weight gain and fluid retention as common adverse effects, with the latter potentially worsening heart failure in predisposed individuals [17]. An increased risk of fractures has also been reported [17]. Although some studies suggest a potential association between pioglitazone and bladder cancer, particularly with prolonged and high-dose use, the evidence remains inconclusive. Pioglitazone should not be used in patients with active bladder cancer, while in those with a prior history of bladder cancer, the potential benefits and risks should be carefully considered [18]. Despite these risks, pioglitazone has demonstrated cardiovascular benefits, including a reduction in major adverse cardiovascular events in patients with T2DM [17]. These risks should be weighed against its metabolic and hepatic benefits, particularly in patients with advanced insulin resistance or NASH. Efforts to develop newer PPAR modulators aim to improve the efficacy and safety of treatment for metabolic disorders such as T2DM, NASH, and obesity.

Fluid retention and peripheral edema are recognized adverse effects of pioglitazone and may result from increased renal sodium and water retention associated with PPAR-γ activation. Although peripheral edema does not necessarily indicate cardiac dysfunction, pioglitazone can precipitate or exacerbate congestive heart failure, particularly in susceptible patients or when combined with insulin. The cardiovascular benefits reported in selected populations must therefore be balanced against the increased risk of heart failure and edema [17,52].

Pioglitazone is also associated with an increased risk of fractures, particularly among women and individuals with additional skeletal risk factors. Potential mechanisms include PPAR-γ-mediated promotion of adipocyte differentiation at the expense of osteoblast formation, which may adversely affect bone remodeling. Although reductions in bone mineral density have been reported, fracture risk should not be interpreted solely in terms of bone mineral density changes [55,56].

A practical approach to risk stratification involves three stages. Before treatment, clinicians should assess heart failure history and symptoms, volume status, concomitant insulin therapy, previous fragility fractures, osteoporosis risk, and other relevant contraindications. Pioglitazone should not be initiated in patients with New York Heart Association class III or IV heart failure, and symptomatic heart failure warrants particular caution or avoidance. During treatment, clinicians should monitor body weight, peripheral edema, dyspnea, and other signs of fluid retention, especially following treatment initiation or dose escalation. Bone health assessment should be individualized according to age, fracture history, and established osteoporosis risk factors. If clinically significant edema, new or worsening heart failure symptoms, or other serious adverse effects develop, treatment should be reassessed promptly, with dose reduction or discontinuation considered according to clinical circumstances. These measures represent a practical risk-assessment framework rather than a formally validated pioglitazone-specific risk-stratification algorithm.

PPAR-γ signaling has also attracted interest in oncology because of its involvement in pathways related to cancer cell metabolism, apoptosis, and tumor biology. A recent bibliometric analysis of PPAR-γ research in breast cancer identified growing interest in cancer-metabolism-immunity interactions, while highlighting the limited clinical efficacy of conventional PPAR-γ agonists in oncology and the need for more selective

modulators [57]. However, these findings do not establish a causal relationship between pioglitazone exposure and cancer risk.

Development of PPAR-γ modulators with improved efficacy and safety

PPAR-γ regulates glucose metabolism, adipogenesis, and insulin sensitivity. Although full agonists such as pioglitazone improve insulin sensitivity and reduce ectopic fat, their use is associated with adverse effects including weight gain, fluid retention, and fracture risk [17]. Newer PPAR-targeted therapies aim to retain metabolic benefits while improving tolerability and addressing specific metabolic and hepatic pathways (Table *4*).

Therapeutic strategy	Agent	Key clinical evidence	Main findings	Clinical considerations	Reference study
Pan-PPAR-α/δ/γ agonism	Lanifibranor	Phase 2b NATIVE RCT (n = 247) in noncirrhotic NASH; phase 2 RCT (n = 38) in T2DM with MASLD	Lanifibranor 1200 mg improved disease activity without worsening fibrosis (55% vs 33%, P = 0.007). Reduced intrahepatic triglycerides and improved hepatic/peripheral insulin sensitivity and cardiometabolic parameters	Promising histologic and metabolic efficacy. Adverse effects include gastrointestinal symptoms, edema, anemia, and modest weight gain. Phase 3 validation and long-term outcome data are required	Francque et al. (2021) [58]; Barb et al. (2025) [59]
Dual PPAR-α/γ agonism	Saroglitazar	Randomized double-blind phase 2 trial (n = 106) in NAFLD/NASH	Reduced ALT, liver fat, insulin resistance, and triglycerides versus placebo. Benefits on non-invasive steatosis and fibrosis measures remain inconsistent across studies	Demonstrates metabolic and biochemical benefits, but evidence for histologic fibrosis regression and long-term liver outcomes remains limited	Gawrieh et al. (2021) [60]
Mitochondrial pyruvate carrier-targeted insulin sensitization	MSDC-0602K	52-week randomized, double-blind, placebo-controlled phase IIb trial (n = 392) in biopsy-confirmed NASH with F1-F3 fibrosis	Did not significantly improve primary histologic endpoints. Higher doses improved glucose, HbA1c, insulin, liver enzymes, and selected markers of disease activity	Demonstrates metabolic benefits without established histologic efficacy; remains investigational	Harrison et al. (2020) [61]
Selective PPAR-α modulation (SPPARMα)	Pemafibrate	Randomized MASLD/T2DM study with supportive PEMA-FL analyses and observational MRE studies	Consistently improved triglycerides and liver enzymes. CAP and liver stiffness were not significantly improved in randomized studies, although exploratory analyses suggested favorable changes in non-invasive fibrosis markers	Antifibrotic efficacy remains unproven. Further prospective studies are required to confirm effects on liver stiffness and fibrosis	Kato et al. (2025) [62]; Tanigawa et al. (2026) [63]; Ichikawa et al. (2023) [64]

TABLE 4: Emerging PPAR-targeted and insulin-sensitizing therapies for MASLD/MASH

ALT: alanine aminotransferase, CAP: controlled attenuation parameter, HbA1c: glycated hemoglobin, LSM: liver stiffness measurement, MASLD: metabolic dysfunction-associated steatotic liver disease, MASH: metabolic dysfunction-associated steatohepatitis, MRE: magnetic resonance elastography, NAFLD: nonalcoholic fatty liver disease, NASH: nonalcoholic steatohepatitis, PPAR: peroxisome proliferator-activated receptor, RCT: randomized controlled trial, SPPARMα: selective peroxisome proliferator-activated receptor-alpha modulator, T2D: type 2 diabetes.

Challenges and future directions

The development of safer, more targeted PPAR-γ modulators continues to face important challenges. A key consideration is achieving therapeutic efficacy while minimizing adverse effects. PPAR-γ activation influences multiple physiological systems; therefore, adverse effects such as fluid retention and effects on bone metabolism can be difficult to avoid. Designing compounds that selectively modulate specific pathways or co-regulators may help reduce these risks. Another limitation is the variability in patient response, which complicates the determination of appropriate dosing and treatment duration. This highlights the need for a more individualized treatment approach based on patient-specific characteristics.

Conclusions

Pioglitazone, a PPAR-γ agonist, has demonstrated metabolic and hepatic benefits in conditions

characterized by ectopic fat accumulation, particularly T2DM and MASLD/MASH. Evidence supports improvements in insulin sensitivity, glycemic control, lipid metabolism, hepatic steatosis, and selected histological outcomes, although the magnitude of benefit varies across outcomes and patient populations. Its clinical use requires careful consideration of established adverse effects, including weight gain and fluid retention. Further research is needed to clarify its long-term effects on organ-specific ectopic fat depots and clinical outcomes and to identify patients most likely to benefit from therapy.

Appendices

Evidence table	Search focus	Suggested PubMed/MEDLINE search terms
Table 1	Overall clinical, hepatic, metabolic, and cardiovascular evidence for pioglitazone	("pioglitazone" OR "thiazolidinedione") AND ("NAFLD" OR "NASH" OR "MASLD" OR "MASH" OR "insulin resistance" OR "cardiovascular outcomes") AND ("randomized controlled trial" OR "clinical trial" OR "systematic review" OR "meta-analysis")
Table 2	Pioglitazone and specific ectopic fat depots	("pioglitazone" OR "thiazolidinedione") AND ("ectopic fat" OR "liver fat" OR "hepatic fat" OR "visceral adipose tissue" OR "subcutaneous adipose tissue" OR "intramyocellular lipid" OR "skeletal muscle fat" OR "epicardial fat" OR "cardiac fat" OR "pancreatic fat")
Table 3	Pioglitazone combination therapy and hepatic/metabolic outcomes	("pioglitazone") AND ("combination therapy" OR "metformin" OR "SGLT2 inhibitor" OR "empagliflozin" OR "tofogliflozin" OR "GLP-1 receptor agonist" OR "exenatide" OR "insulin") AND ("NAFLD" OR "NASH" OR "MASLD" OR "MASH" OR "liver fat" OR "hepatic steatosis")
Table 4	Emerging PPAR-targeted and insulin-sensitizing therapies	("PPAR agonist" OR "pan-PPAR" OR "dual PPAR" OR "selective PPAR modulator" OR "insulin sensitizer" OR "lanifibranor" OR "saroglitazar" OR "pemafibrate" OR "elafibranor" OR "MSDC-0602K") AND ("NAFLD" OR "NASH" OR "MASLD" OR "MASH")

TABLE 5: Search strategy used to identify evidence for Tables 1-4

Databases: PubMed, MEDLINE, and the Cochrane Library. Search coverage: Evidence available up to July 2026.

Searches that did not yield sufficiently relevant clinical evidence did not contribute studies to the corresponding evidence table.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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