

Pioglitazone in Type 2 Diabetes Mellitus: A Comprehensive Review of Mechanisms and Efficacy: In vitro and In vivo Studies

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ABSTRACT

Type 2 diabetes mellitus is a long-lasting metabolic disease featuring mitigated insulin sensitivity, compromised beta-cell performance, and elevated circulating glucose concentrations. By 2030, T2DM is anticipated to rank as the seventh primary cause of death. Pioglitazone is a thiazolidinedione (TZD) class medication used to treat T2DM. It can be used alone or in combination with other glycemic-lowering medications. This study aims to elucidate the mechanisms underlying pioglitazone's effects and its efficacy in T2DM by means of in vitro and in vivo analyses. Clinical studies have reported pioglitazone's efficacy in lowering glycated hemoglobin (HbA1c), fasting blood glucose (FBS), and homeostasis model assessment-insulin resistance (HOMA-IR). Pioglitazone functions as an insulin-sensitizing agent and improves blood glucose control by increasing peripheral glucose uptake, lowering hepatic glucose release, and gluconeogenesis. Furthermore, the betterment in insulin secretion and sensitivity by pioglitazone is partly attributable to the anti-inflammatory and antioxidant functions of peroxisome proliferator-activated receptor-gamma (PPAR- γ) and PPAR- α . Also, the pioglitazone contributes to improving lipid profiles, reducing blood pressure, and helps to prevent atherosclerosis and liver diseases that are associated with decreased diabetic complications. However, studies have shown that pioglitazone may activate mechanisms associated with β -cell apoptosis, heart failure, fracture risk, and weight gain. Therefore, physicians should anticipate the possibility of these side effects at high doses.

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Introduction

Type 2 diabetes mellitus (T2DM) is a lasting metabolic abnormality defined by insulin resistance, mitigated beta-cell functionality, and enhanced blood glucose values. It contributes significantly to global mortality rates. T2DM accounts for more than 90% of diabetic patients. By 2030, T2DM is expected to become the seventh major contributor to global mortality (1-3). It may involve damage to the kidneys, liver, eyes, peripheral nerves, heart, and vascular system, leading to greater incidences of renal failure, diabetic retinopathy, heart attacks, and strokes (4, 5). With the increasing global spread of obesity and the aging population, the need for effective antidiabetic treatments, control glycemic indices, and address the long-term complications of diabetes remains critical (6). Pioglitazone is a thiazolidinedione (TZD) class

drug. It took a long time from its initial discovery to become a widely used treatment for T2DM. Pioglitazone can be utilized alone or alongside other drugs that attenuate glycemic indexes. Takeda Pharmaceutical Company was produced pioglitazone. It received Food and Drug Administration (FDA) approval on 1999 under the brand name Actos. Then, in 2000, pioglitazone was approved by the European Medicines Agency (EMA). Currently, pioglitazone is commonly given either by itself or together with other oral hypoglycemic agents for overweight patients with T2DM who are unresponsive to metformin (2, 7). Clinical studies have declared pioglitazone's efficacy in attenuation of glycated hemoglobin (HbA1c), fasting blood glucose (FBS), homeostasis model assessment-insulin resistance (HOMA-IR) with some evidence suggesting superiority

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over other oral agents in certain patient subgroups, particularly those with decreased insulin sensitivity and dyslipidemia (8). In this study, we aim to elucidate the underlying mechanisms and therapeutic potential of pioglitazone in T2DM through in vitro and in vivo analyses

Methods

This study took the form of a narrative review. We conducted a search of PubMed, Scopus, and Google Scholar to retrieve relevant studies for the evaluation. The bulk of the studies examined were released between 2010 and 2026. The keywords included T2DM, Pioglitazone, FBS, HOMA-IR, PPAR- α , PPAR- γ , GLUT4, Adiponectin, AMPK, NF- κ B, TNF- α , IL-1 β , NLRP3, CRP, ICAM-1, PAI-1, MCP-1, NRF2, Triglyceride, Cholesterol, HDL-C, LDL-C, Blood pressure, Atherosclerosis, NAFLD, NASH, ALT, AST, GGT, HOMA- β . In vitro and In vivo studies as well as review studies related to the mechanism of action of pioglitazone in T2DM patients were collected.

Mechanisms of Action

Pioglitazone acts as an insulin sensitizer and improves blood glucose control by increasing peripheral glucose uptake, decreasing hepatic glucose release, and gluconeogenesis (9).

Peroxisome proliferator-activated receptor (PPAR) Activation

Activation of peroxisome proliferator-activated receptor (PPAR) is the principal pathway through which pioglitazone exerts its antidiabetic activity. Because PPAR is fundamentally involved in glucose and lipid regulation, it is a key therapeutic target in T2DM (10). The PPAR family includes three subtypes: PPAR- α , PPAR- δ , and PPAR- γ . These are all ligand-inducible transcription factors that fall within the nuclear hormone receptor superfamily. Pioglitazone specifically targets PPAR- α and PPAR- γ . PPARs associate with retinoid X receptor (RXR) to create heterodimers, binding to peroxisome proliferator-activated response elements (PPREs) and modifying the transcription of specific target genes. Pioglitazone interacts to the ligand binding domain (LBD) of PPAR- γ , stimulating peculiar conformational changes that enable transcriptional regulation. Hydrogen bonds are established between the head group of pioglitazone and the polar residues of the AF-2 pocket and helix 12, serving to stabilize the active state of the LBD (11).

PPAR- γ

The stimulation of PPAR- γ by pioglitazone modulates multiple genes related to metabolic homeostasis. PPAR- γ interacts to PPREs in the promoter region of the glucose transporter 4 (GLUT4) gene, upregulating its expression. Higher expression of GLUT4 at both the mRNA and protein levels result in a higher presence of GLUT4 storage vesicles (GSVs) within the cell (12). The PI3K/AKT pathway mediates PPAR- γ 's beneficial effects on insulin signaling, leading to increased GLUT4

translocation to the membrane (13).

Adiponectin: PPAR- γ increases adiponectin secretion (14). In a randomized controlled trial (RCT) conducted by Esteghamati et al., the serum levels of adiponectin were significantly enhanced by the intake of pioglitazone at 30 mg per day over a period of three months (15). Ciaraldi et al. reported that consumption pioglitazone (45 mg/day) for 6 months in polycystic ovary syndrome (PCOS) patients improved serum adiponectin levels that was more effective than metformin (16). Furthermore, in a RCT conducted by Yoneda et al., the combination of pioglitazone (15-30 mg) and tofogliflozin over a period of six months in patients with NAFLD significantly increased the levels of adiponectin (17). The hormone stimulates glucose uptake by activating AMP activated protein kinase (AMPK), which facilitates the redistribution of GLUT4 to the plasma membrane. It prohibits gluconeogenesis in the liver by inhibiting main enzymes like phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). In a study published by Yadollah et al., induction of HepG2 cells with pioglitazone (10 μ M) downregulated PEPCK and G6Pase (18). de Mendonça et al. showed that pioglitazone at a dose of 35 mg/kg/day attenuated the expression of hepatic PEPCK in adipoWT mice suffering from nonalcoholic fatty liver disease (NAFLD) (19). Furthermore, adiponectin drives fatty acid oxidation and attenuates lipolysis, decreasing circulating free fatty acids (FFAs) that enhance insulin resistance (20, 21). Adiponectin exerts anti-inflammatory effects that help attenuates insulin resistance. In a study by Dikmen and colleagues, administration of recombinant adiponectin to rats with acute pancreatitis resulted in reduced nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activity and lower levels of interleukin-1 β (IL-1 β) and tumor necrosis factor alpha (TNF- α). IL-1 β and TNF- α exacerbate insulin resistance (22). I κ B α keeps NF- κ B in an inactive state in the cytoplasm. A further observation from Ciaraldi et al.'s study was that pioglitazone treatment elevated I κ B α protein levels in muscle, suggesting a decrease in inflammation (16). Guo et al. showed that the administration of pioglitazone-metformin complex (75 mg of pioglitazone and 1500 mg of metformin per day) for 12 weeks in PCOS patients resulted in a further downregulation of IL-1 β and TNF- α compared to the metformin group. Additionally, the treatment complex downregulated the NLR family pyrin domain containing 3 (NLRP3) and caspase-1 (23). Caspase-1 is a component of the NLRP3 inflammasome that participates in the secretion of IL-1 β (23, 24). Adiponectin helps protect beta-cell function by attenuating both oxidative stress and inflammatory processes, which facilitates adequate insulin secretion. Therefore, low levels of adiponectin are linked to obesity, T2DM, and metabolic syndrome (25). NF- κ B: PPAR- γ is capable of interacting to the p65 subunit of NF- κ B, which halts NF- κ B from attaching to DNA, thereby hindering the transcription of genes that promote inflammation (26). Furthermore, PPAR- γ prohibits I κ B kinase (IKK) activation, thus blocks NF- κ B translocation to the nucleus (27). The relationship between pioglitazone and NF- κ B-associated inflammatory markers has been the

subject of multiple studies.

Liu et al. showed that the level of high-sensitivity C-reactive protein (hs-CRP) declined after 6 months of pioglitazone (30 mg/day) intake in patients with T2DM (28). In another finding from the study by Esteghamati et al., metformin and pioglitazone significantly mitigated hs-CRP concentrations in T2DM patients, but pioglitazone reduced intercellular adhesion molecule-1 (ICAM-1) levels compared to metformin in male T2DM patients (15). Erem et al. reported that after 12 months of treatment with pioglitazone (15-45 mg/day) in patients with T2DM, the levels of homocysteine and E-selectin were significantly diminished. As an amino acid, homocysteine can activate the NF- κ B signaling pathway. NF- κ B mediates the upregulation of E-selectin in endothelial cells during inflammation (29). In a study by Tripathy et al., obese T2DM patients exhibited considerable declines in hs-CRP, plasminogen activator inhibitor type-1 (PAI-1), and monocyte chemoattractant protein-1 (MCP-1) following six months of treatment with pioglitazone at 15 mg per day (30).

Nuclear factor erythroid 2-related factor 2 (NRF2): NRF2 functions as a central regulator of antioxidant pathways that increases the expression of antioxidant compounds. The binding of NRF2 to the antioxidant response element (ARE) is necessary for its regulatory activity. NRF2 and PPAR- γ influence each other in opposing ways. PPAR- γ has the ability to activate NRF2, while the activation of NRF2 may lead to an increase in the expression of PPAR- γ (31). In a study

reported by Zakaria et al., receiving pioglitazone 30 mg/kg for 7 days in lipopolysaccharide (LPS)-stimulated mice upregulated heme oxygenase-1 (HO-1) (antioxidant agent) mRNA and activity, and NRF2 mRNA. Meanwhile, it downregulated p65 mRNA (32). Zhao et al. showed that pioglitazone upregulated NRF2 and HO-1 in the ischemic brain tissue. Furthermore, pioglitazone (5 and 10 μ M) enhanced the activation of the ARE in neuronal PC12 cells. These effects were dependent on PPAR- γ activation (33).

PPAR- α

PPAR- α upregulates enzymes involved in fatty acid oxidation, such as carnitine palmitoyltransferase I (CPT1) and acyl-CoA oxidase 1 (ACOX1). This process prevents fat accumulation in tissues and mitigates the insulin resistance and inflammation-related effects of free fatty acids (FFAs) and triglyceride synthesis intermediates, including diacylglycerol (DAG) (34, 35). Like PPAR- γ , PPAR- α hinders NF- κ B activity by regulating p65, IKK, and I κ B activity (36, 37). Hsiao et al. stated that pioglitazone (100 mg/kg/day) intake in mice fed with high fat diet (HFD) upregulated hepatic expression of CPT-1A, adipose triglyceride lipase (ATGL), and hormone-sensitive lipase (HSL), thereby promoting lipolysis and beta-oxidation. Furthermore, the examination on alpha mouse liver 12 (AML12) cells showed that these regulatory roles in lipolysis and beta-oxidation were dependent on PPAR- α and PPAR- γ (38) [Table1](#).

Table1. Effects of pioglitazone in improving diabetic conditions through the involvement of PPAR- α and PPAR- γ

Study	Dosage	Study duration	Effects on variables	In vitro/in vivo study
Esteghamati et al. (15)	30 mg/day	3 months	Adiponectin hs-CRP and ICAM-1	Patients with newly diagnosed type 2 diabetes
Ciaraldi et al. (16)	45 mg/day	6 months	Adiponectin and I κ B α	PCOS patients
Yoneda et al. (17)	15-30 mg/day	6 months	Adiponectin	Patients with NAFLD
Yadollah et al. (18)	10 μ M	-	PEPCK and G6Pase	HepG2 cells
de Mendonça et al. (19)	35 mg/kg/day	8 weeks	PEPCK	adipoWT mice suffering from NAFLD
Guo et al. (23)	75 mg/day	12 weeks	IL-1 β , NLRP3, Caspase-1, and TNF- α	PCOS patients
Liu et al. (28)	30 mg/day	6 months	hs-CRP	Patients with T2DM
Erem et al. (29)	15-45 mg/day	12 months	E-selectin and Homocysteine	Patients with T2DM

Tripathy et al. (30)	15 mg/day	6 months	hs-CRP, PAI-1, and MCP-1	↓	Obese patients with T2DM
Zakaria et al. (32)	30 mg/day	One week	HO-1, NRF2 p65	↑ ↓	LPS stimulated mice
Hsiao et al. (38)	100 mg/kg/day	-	CPT-1A, ATGL, HSL	↑	Mice fed with HFD

PCOS: Polycystic ovary syndrome, IkBα: IkappaB alpha, PEPCK: Phosphoenolpyruvate carboxykinase, NAFLD: Nonalcoholic fatty liver disease, HO-1: Heme oxygenase-1, CPT-1: Carnitine palmitoyltransferase I, ATGL: Adipose triglyceride lipase, HSL: Hormone-sensitive lipase, HFD: High fat diet.

Metabolic and Cardiovascular Effects

Some of the metabolic and cardiovascular effects of pioglitazone that were related to PPAR-γ and PPAR-α were mentioned.

Lipid Indices

Lipid profiles are abnormal in T2DM patients. Due to the mechanisms associated with pioglitazone, it can lead to improvements in lipid indices. Cusi et al. stated that pioglitazone 45 mg/day consumption for 18 months in nonalcoholic steatohepatitis (NASH), prediabetes or T2DM patients lowered hepatic triglyceride levels. So, pioglitazone can reduce fatty liver (39). In a RCT conducted by Clark et al., a substantial lowering in serum triglyceride and cholesterol concentrations was observed in obese cats after a 7-week treatment with pioglitazone at doses of 1 or 3 mg/kg/day (40). In a clinical trial by Heo et al., the addition of pioglitazone (15 mg/day) to metformin and dapagliflozin for six months in T2DM patients led to substantial improvement in triglyceride levels and high-density lipoprotein cholesterol (HDL-C) concentrations (41). Other findings from Yoneda et al.'s study revealed that a combination therapy of pioglitazone (15-30 mg) and tofogliflozin over 6 months in NAFLD patients enhanced HDL-C levels but led to a reduction in triglyceride concentration (17). According to Skochko and colleagues, a 6-month course of pioglitazone (15 mg/day) as an adjunct to standard treatment in coronary heart disease (CHD) patients, mitigated total cholesterol and low-density lipoprotein cholesterol (LDL-C) and elevated HDL-C concentrations (42).

Blood Pressure Modulation

Pioglitazone substantially impacts blood pressure regulation, mainly by acting on PPAR-γ and affecting vascular function, inflammation, and insulin sensitivity (43). The activation of PPAR-γ enhances endothelial function by increasing nitric oxide (NO) availability through reduced oxidative stress, leading to improved vasodilation (44). Kvandova et al. showed that pioglitazone (10 mg/kg/day) intake for 10 days resulted in a reduction of blood pressure in borderline hypertensive (BHR) rats and delayed the rise in blood pressure in young spontaneously hypertensive (SHR) rats. Additionally, the treatment enhanced the activity and expression of nitric oxide synthase (NOS) in BHR and SHR rats (45). Grešová et al. showed that intake of pioglitazone 10 mg/kg/day for 10 days in both young

and adult BHR rats resulted in improvement in blood pressure and upregulation of endothelial NOS expression and activities (46). Endothelin-1 (ET-1) and cyclooxygenase-2 (COX-2) are inflammatory mediators produced by NF-κB and contributed to decreased vascular endothelial function. Palacios-Ramírez et al. reported that pioglitazone (2.5 mg/Kg/day) intake for 4 weeks in SHR rats altered the balance from vasoconstrictive ETA receptors to vasodilatory ETB receptors, suppressed COX-2 expression and activation, and increased NO availability, resulting in a reduction of vascular resistance (44). Majka et al. reported that treating esophagogastrroduodenal anastomosis (EGDA) rats with pioglitazone (10 mg/kg) over a 12-week period, attenuated mucosal COX-2 expression (47). Human studies on pioglitazone's anti-inflammatory effects linked to NF-κB have shown that the drug enhances vascular relaxation and reduces blood pressure via decreased production of pro-inflammatory molecules.

The influence of pioglitazone on blood pressure has been the subject of multiple human studies. In a study by Gerber et al., T2DM patients receiving pioglitazone (30 mg and 45 mg) for 20 weeks experienced a 10-mmHg drop in systolic and an 8-mmHg drop in diastolic blood pressure (48). In a study published by Kroese et al., treatment with pioglitazone 45 mg over 16 weeks, attenuated blood pressure in congenital adrenal hyperplasia (CAH) patients (49).

Atherosclerosis Prevention

As previously stated, pioglitazone contributes to the prevention of atherosclerosis because of its anti-inflammatory and antioxidant properties. It was shown, pioglitazone slowed carotid intima-media thickness (CIMT) progression and attenuated coronary plaque burden. Saremi et al. carried out a randomized controlled trial showing that pioglitazone substantially mitigated the annual progression of carotid intima-media thickness in individuals with prediabetes. This effect was not dependent on improvements in conventional risk factors, indicating a direct benefit to vascular health (50). Polonsky et al. demonstrated that pioglitazone (15-45 mg/day) was more effective than glimepiride (1-4 mg/day) in slowing the progression of carotid intima-media thickness (CIMT). This effect was partially related to a 14% increase in HDL-C concentration with pioglitazone, which was associated with a reduction in atherosclerosis progression (51).

Effects of NAFLD/NASH

The liver is the organ where most biochemical reactions occur and is therefore closely related to oxidative and inflammatory conditions (52). There is growing interest in pioglitazone as a therapeutic agent for non-alcoholic fatty liver disease (NAFLD) and its more aggressive variant, non-alcoholic steatohepatitis (NASH). Its benefits mostly stem from its role as a PPAR- γ agonist, lowering insulin resistance and regulating metabolic pathways associated with liver fat buildup and inflammation (53). Pioglitazone has demonstrated effectiveness in attenuation of liver steatosis, inflammation, and hepatocellular ballooning. Some research indicated it might also slow down fibrosis progression. Furthermore, various meta-analyses showed that pioglitazone substantially alleviated alanine transaminase (ALT), aspartate transferase (AST), and gamma-glutamyl transferase (GGT) levels, signifying diminished liver damage (54, 55). Based on this information, pioglitazone reduces NAFLD and NASH by decreasing triglyceride, cholesterol, and LDL-C levels, while increasing adiponectin and HDL-C levels. Zhao et al. reported findings from 15 RCTs revealed that pioglitazone improved liver enzymes, insulin resistance and metabolic measures in patients with NASH (54). Wang et al. indicated that pioglitazone could have a positive impact on ameliorating NAFLD, showing consistent results in both non-diabetic and diabetic NAFLD patients by improving histopathology, liver enzymes, and HOMA-IR, while also mitigating blood lipid levels (55).

Beta-Cell Preservation

Pioglitazone has demonstrated the ability to improve basal beta-cell function, as indicated by enhances in the homeostasis model assessment of beta-cell function (HOMA- β) (56). Part of the actions of pioglitazone in beta-cell preservation is due to its roles as antioxidant, anti-inflammatory, or anti-apoptotic factor. In a study published by Wallace et al. administer of pioglitazone at doses of 30 and 45 mg per day for 12 weeks in patients with T2DM resulted in an 11.5% enhance in HOMA- β . This enhancement was related to a decrease in the proinsulin/insulin ratio, indicating decreased stress on beta-cells (57). In a study published by Xiang et al., a comparison was conducted regarding the adjustments in beta-cell compensation for insulin resistance between the Troglitazone in Prevention of Diabetes (TRIPOD) and Pioglitazone in Prevention of Diabetes (PIPOD) studies. Pioglitazone hindered the decline in beta-cell function that was showed during placebo treatment in the previous TRIPOD study. The disposition index, which reflects beta-cell compensation for insulin resistance, remained stable, and the annual rate of diabetes development was low (4.6%) in women who demonstrated the most substantial reduction in demands for insulin secretion. In this study, participants started treatment with 30 mg/day of pioglitazone for two months. After

observing no symptoms of fluid retention at this dosage, the dose was enhanced to 45 mg per day for the remaining three years of the study (58). Fatty acids, triglycerides, and cholesterol are toxic to beta cells. pioglitazone is associated with preventing the toxicity in these cells by lowering their levels (59). Furthermore, Jin et al. reported that a daily dosage of 30 mg of pioglitazone for four months increased the Δ insulin/ Δ glucose (DI/DG) ratio in impaired glucose tolerance (IGT) patients, which was positively correlated with the enhancement of the glucose disposal rate (GDR) (59). Lu et al. reported that pioglitazone monotherapy led to a 16.06% increase in HOMA- β (95% CI: 9.67–22.44%), comparable to metformin's increase of 18.01%, but substantially higher than the 11.29% increase observed with sitagliptin (60). Pioglitazone can affect beta-cell apoptosis. Lamounier et al. showed that pioglitazone (10 μ M) transiently diminished apoptosis in adult rat islets at normal glucose (5.6 mM), suggesting protective effects under physiological conditions (61).

Adverse Effects

Pioglitazone promotes insulin secretion and hinders beta-cell apoptosis through its antioxidant, anti-inflammatory, and lipid-lowering properties. However, in cellular studies, exposure of beta-cells to high glucose levels may lead to alterations in the function of pioglitazone. As noted in the study by Lamounier et al., pioglitazone (10 μ M) diminished apoptosis under physiological conditions. However, Other results of the study were that at elevated glucose levels (23 mM), pioglitazone enhanced apoptosis and attenuated the expression of pro-survival genes such as Bcl2, increasing concerns about possible adverse effects during uncontrolled hyperglycemia. The dual mechanism highlights the necessity of maintaining glycemic control when administering pioglitazone (61).

Pioglitazone activates PPAR- γ , enhancing renal sodium reabsorption and vascular permeability, resulting in an increase in plasma volume, fluid retention, and heart failure. In a case report published by Jearath et al., hospital admissions due to heart failure were substantially higher in patients on pioglitazone compared to those on placebo (5.7% versus 4.1%). However, the rate of death from heart failure was lower in the pioglitazone group. The decreased all-cause mortality, despite a higher risk of heart failure, is associated with improved glycemic control and a reduced incidence of myocardial infarction and stroke (62). In a study published by Guidance et al., patients with moderate-to-severe heart failure and poorly controlled type 2 diabetes who received pioglitazone had a 9.9% hospitalization rate for heart failure, compared to 4.7% among those treated with glibenclamide. Hospitalization was more prevalent in older patients and those using insulin. In addition, other findings of this study were that when pioglitazone is consumed alongside insulin or sulfonylureas, edema usually ranges from mild to moderate, but in some instances, it can

become severe (63).

Other side effects have been reported with pioglitazone. Azhari et al. demonstrated a connection between pioglitazone and a significant rise in fracture risk (risk ratio RR 1.21; 95% CI 1.01–1.45; $P = 0.04$) (64). Furthermore, taking pioglitazone may cause weight gain. In a meta-analysis reported by Filipova and colleagues, pioglitazone treatment resulted in an enhancement in both weight and Body Mass Index (BMI) in patients with T2DM (65). It was shown that there is a relationship between taking different doses of pioglitazone and weight gain. The results from the study by Clar et al. and the study by Yanai et al. found that higher doses (30–45 mg/day) were associated with increased weight gain compared to lower doses (7.5–15 mg/day) (66, 67).

Conclusion

Various studies have been conducted on the effects of pioglitazone in preclinical and clinical settings. Pioglitazone is a medication utilized for managing patients with T2DM. The various functions of pioglitazone are mediated by PPAR- γ , PPAR- α . Pioglitazone acts as an insulin sensitizer and improves blood glucose control by increasing peripheral glucose uptake, decreasing hepatic glucose release, and gluconeogenesis. Furthermore, the improvement of insulin secretion and sensitivity by pioglitazone is partly attributable to the anti-inflammatory and antioxidant functions of PPAR- γ and PPAR- α . Also, pioglitazone contributes to improving lipid profiles, reducing blood pressure, and helping to prevent atherosclerosis and liver diseases. However, studies have shown that pioglitazone may activate mechanisms associated with beta-cell apoptosis, heart failure, fracture risk, and weight gain. Therefore, physicians should anticipate the possibility of these side effects at high doses. Given that pioglitazone has been widely used to treat patients with T2DM in recent years, clinical studies have comprised the majority of studies related to the effects of this drug. However, for further investigation into the precise mechanisms of action of pioglitazone, the results of preclinical studies (in vitro and in vivo) were very useful. In the future, it would be better to conduct more studies on the anti-inflammatory and antioxidant effects of this drug, as well as its side effects.

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N.A

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