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Chapter 4

Thiazolidinediones Cause Cardiotoxicity via PPARγ-Independent Mechanism

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Additional information is available at the end of the chapter

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Abstract

Thiazolidinediones (TZDs), peroxisome proliferator-activated receptor gamma (PPARγ) agonists, are highly effective antidiabetic drugs that are widely used to treat type 2 diabetes mellitus (T2DM) due to their unique beneficial actions, such as a renoprotective effect, amelioration of glucose homeostasis, and blood pressure lowering, that other antidiabetic drugs do not have. Those beneficial actions, however, are shadowed by the increased risks of cardiovascular adverse events, including mitochondrial dysfunction, oxidative stress and myocardial energy deficiency, fluid retention, congestive heart failure, and myocardial infarction. Except PPARγ, TZDs also have affinity to numerous non-PPARγ targets in mitochondria, cytosol, and cytoplasm, including MitoNEET, mitochondrial pyruvate carrier, dehydrogenases involved in tricarboxylic acid cycle and electron transport, cytoplasmic ion channels, Na-K-pump, and other unknown enzymes. By binding to these targets, TZDs produce off-target effects and potentially increase cardiotoxicity. In this chapter, we review recent studies, both experimental and clinical, on the myocardial adverse effects associated with TZDs and their underlying mechanisms. We focus our review in large part on the relationship between these myocardial adverse effects and PPARγ.

Keywords: thiazolidinedione, myocardial energy metabolism, mitochondria, oxidative stress, peroxisome proliferator-activated receptors, heart failure, myocardial infarction

1. Introduction

Thiazolidinediones (TZDs) including ciglitazone, pioglitazone, rosiglitazone, and troglitazone, also known as glitazones after the prototypical drug ciglitazone, are a class of

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heterocyclic compounds consisting of a five-membered C3NS ring. Among them, pioglitazone and rosiglitazone were approved for clinical use in the United States and Canada. Through activation of peroxisome proliferator-activated receptor gamma (PPARγ), these compounds improve insulin sensitivity, reduce hyperglycemia, and afford unique beneficial actions, such as a renoprotective effect and blood pressure lowering that other antidiabetic drugs do not have [1]. Therefore, they have been widely used to treat type 2 diabetes mellitus (T2DM) as monotherapy or in combination with other types of oral antidiabetic agents (sulfonylureas, metformin, and acarbose). Their original approvals were based on the ability to reduce insulin resistance, increase peripheral glucose utilization, and decrease hepatic glycogen output, accordingly, lower blood glucose concentration [2]. TZDs provide robust improvement in glycemic control that is comparable to other established agents, such as metformin and the sulfonylureas [3, 4]. More importantly, since the progressive failure and loss of β-cells are ultimately responsible for the onset and progression of T2DM, the potential of TZDs to preserve β-cells is an extremely desirable function in glucose-lowing medicine [5–7]. According to ADOPT (A diabetes Outcome Prevention Study), the rate of monotherapy failure with TZDs is lower than other antidiabetic agents such as metformin and glyburide [8].

The ultimate value of TZDs and any other glucose-lowing drugs should rely on not only the improvement of acute hyperglycemic crises and their serious consequences, but also the reduction of long-term complications associated with diabetes. Theoretically, reducing hyperglycemia over the long term should decrease the possibility of the complications, but this is not the case for rosiglitazone. Instead, its beneficial actions are shadowed by the increased risks of cardiovascular adverse events [9].

The coexistence of heart failure (HF) and T2DM is common and has a strong impact on clinical management and prognosis. The action of any antidiabetic therapy on cardiovascular system is particularly important because more than 70% of deaths in diabetic patients are from cardiovascular causes [10], and clinical courses of cardiovascular events and T2DM frequently progress in parallel [11, 12]. Glucose-lowering drugs, including the TZDs, have complex organ-specific effects on diverse biological processes that may determine the effects on cardiovascular events end point. Unfortunately, the potential for unexpected cardiovascular side effects when rosiglitazone is administered to patients was not fully assessed before the approval from U.S. Food and Drug Administration (FDA) in 1999 and from the European Medicines Evaluation Agency (EMEC) in 2000. According to over 40 clinical trials conducted from 1999 to 2007, rosiglitazone has been reported to increase risks of heart failure [13, 14] and myocardial infarction in T2DM patients [15–17]. Additionally, rosiglitazone was associated with a significant increase in the risk of death from cardiovascular causes that had borderline significance [13, 16, 18, 19]. Rosiglitazone may also worsen the clinical course in patients with pre-existing left ventricular dysfunction [20]. Approximately 10 years after the introduction of rosiglitazone, EMEC required two post-marketing studies on long-term adverse effects and recommended that rosiglitazone be suspended from the European market because the benefits no longer outweighed the risk. Similarly, pioglitazone therapy was also associated with an increased risk of major adverse cardiovascular events in patients with pre-diabetes or insulin resistance and diabetes [21]. In this chapter, we review recent studies, both experimental and clinical, on the myocardial adverse effects associated with TZDs, rosiglitazone in

particular, and discuss their underlying mechanisms. We focus our discussion in large part on the relationship between these myocardial adverse effects and PPARγ.

2. On-target effects of TZDs

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors of nuclear hormone receptor superfamily comprising three subtypes such as PPARα, PPARβ/δ, and PPARγ [22]. PPARα is predominantly expressed in metabolically active tissues such as the adipose tissue, liver, heart, kidney and skeletal muscle [23], and mainly influences fatty acid metabolism and its activation lowers lipid levels [24]. PPARβ/δ is ubiquitously expressed with the highest levels in the intestine, colon, skin, adipose tissue, skeletal muscle and brain and kidney [25] and is involved in fatty acid oxidation in muscle [26]. PPARγ is mostly expressed in adipose tissue, but also found in the skeletal muscle, liver, kidney, colon,

Cells	Target genes	Gene expression	On-target effects	Reference
Adipocyte	Acetyl-CoA synthetase	↑	↑ triglyceride	[31]
Adipocyte	Adipocyte-specific fatty acid binding protein	↑	↑ lipid oxidation	[32]
Adipocyte	Cbl-associated protein	↑	↑ insulin sensitivity	[33]
Adipocyte	Fatty acid translocase	↑	↑ fatty acid uptake	[34]
Hepatocyte, β-cell	Glucokinase	↑	↑ glucose homeostasis	[35, 36]
Hepatocyte, β-cell	Glucose transporter 2	↑	↑ glucose sensing	[35]
Adipocyte	Glucose transporter 4	↑	↑ glucose uptake	[37]
Adipocyte	Glycerol kinase	↑	↓ free fatty acid	[38, 39]
Adipocyte	Insulin receptor substrate 2	↑	↑ insulin sensitivity	[40]
Adipocyte, hepatocyte	Interleukin-6	↓	↑ insulin sensitivity	[41, 42]
Adipocyte	Leptin	↓	↑ insulin sensitivity	[43, 44]
Adipocyte, muscle cell	Lipoprotein lipase	↑	↓ triglyceride	[45, 46]
Adipocyte	Perilipin	↑	↓ free fatty acid	[47, 48]
Adipocyte, hepatocyte	Phosphoenolpyruvate carboxykinase	↑	↑ triglyceride ↓ lipid oxidation	[30, 32, 49]
Adipocyte, hepatocyte	Tumor necrosis factor-α	↓	↑ insulin sensitivity	[41]

Table 1. Selected PPARγ on-target effects of TZDs.

intestine, pancreas, brain, immune cells, and retina and throughout the cardiovascular system at relatively low levels [24, 25, 27]. Activation of PPARγ causes lipogenesis, adipocyte differentiation, and insulin sensitization and enhances glucose metabolism and also decreases plasma free fatty acid level [26]. Functionally, this receptor controls the expression of networks of genes involved in adipogenesis, lipid and glucose metabolism, inflammation and maintenance of metabolic homeostasis. TZDs act by activating PPARγ. When activated, PPARγ and retinoid X receptor (RXR) form heterodimeric complex PPARγ /RXR, which then binds to a specific DNA sequence element termed peroxisome proliferator response element (PPRE), increasing transcription of various involved genes and decreasing transcription of others [28, 29]. The major effects of expression and repression of the aforementioned genes are to increase the storage of fatty acids in adipocytes, thereby decreasing the amount of fatty acids present in circulation. Accordingly, cells become more dependent on the oxidation of carbohydrates, more specifically glucose, in order to yield energy for other cellular processes. Therefore, TZDs improve insulin sensitivity and reduce hyperglycemia [30]. PPARγ on-target effects of TZDs are summarized in **Table 1**.

Besides, TZDs selectively augment or partially mimic certain actions of insulin, causing a slowly generated hypoglycemic effect without increasing pancreatic insulin secretion in non-insulin-dependent diabetic patients via the activation of PPARγ, which increases transcription of certain insulin-sensitive genes [2]. Thus, the action of TZDs is often accompanied by a reduction in circulating concentrations of insulin, triglycerides and non-esterified fatty acids while the β-cell function is largely restored. The PPARγ on-target effects of TZDs, however, are still not completely clear.

3. Off-target effects of TZDs

Drugs exert desired and undesired effects based on their binding interactions with protein target(s) and off-target(s), providing evidence for its efficacy and toxicity. Many different and seemingly unrelated side effects have emerged during the development of TZDs, such as fatal hepatotoxicity, rhabdomyolysis, nephrotoxicity, multisystem organ failure, etc. In isolated hearts [50] or in vivo [25], rosiglitazone suppressed Jun NH_2-terminal kinase and activated the adenosine monophosphate-activated protein kinase and protein kinase B (AKT) pathways, and these effects could not be fully blocked by a PPARγ antagonist [51]. Similarly, studies in the pig demonstrated rapid effects of troglitazone in the recovery of left ventricular function after ischemia/reperfusion injury [52, 53]. The effect of troglitazone in this model was found to be imparted not by the TZD moiety but by its tocopherol moiety, which does not activate PPARγ [53]. Together these data suggest that in addition to PPARγ-dependent (on-target) effects, TZDs also exert PPARγ-independent (off-target) effects.

Using [^{3}H]pioglitazone, a structurally related iodinated photoaffinity probe, mass spectrometry analysis and amino-terminal sequencing, a 17-kDa mitochondrial protein mitoNEET has been identified as a saturable and specific binding site for [^{3}H]pioglitazone [54]. MitoNEET is broadly expressed in insulin-sensitive tissues including the liver, muscle, adipose, and heart [55]. MitoNEET is an integral iron-sulfur-cluster transfer protein in the outer mitochondrial

membrane that has been shown to inhibit mitochondrial iron transport, which may in turn decrease mitochondrial respiratory activity [56, 57], oxidative capacity [55] and redox-sensitive signaling [58]. Overexpressing mitoNEET in adipocytes decreased the levels of reactive oxygen species [57]. In contrast, knocking down mitoNEET in adipocytes increased reactive oxygen species-induced protein damage [57].

Similarly, the mitochondrial pyruvate carrier 2 (Mpc-2) has also been identified as a direct mitochondrial target of the TZDs (mTOT) using photoaffinity and mass spectrometry-based proteomics approaches [59]. Two mTOT-binding TZDs with little effect on PPARγ (MSDC-0160 and MSDC-0602) were shown to enhance brown adipose tissue formation and improve insulin sensitivity in mice, whereas the deletion of the Mpc-2/mTOT gene resulted in a loss of brown adipose tissue formation [59]. A phase IIb study in patients with diabetes suggested that MSDC-0160 may have similar glucose-lowering efficacy to pioglitazone, with preliminary hints of fewer side effects [60]. MSDC-0160 was associated with a lower level of fluid retention [60]. These data suggest that specifically targeting Mpc-2/mTOT may have potential as a therapy for diabetes, and that both on-target and off-target effects may contribute to efficacy of the drugs, but off-target effects potentially increase cardiotoxicity.

Pioglitazone and rosiglitazone possess a common functional core, glitazone, which is considered a privileged scaffold upon which to build a drug selective for a given target-in this case, PPARγ. A retrospective analysis of pioglitazone and rosiglitazone has identified numerous non-PPARγ proteins as high affinity binders of TZDs in the rat heart, including mitochondrial and cytoplasmic dehydrogenases, ion channels, modulators and enzymes involved in glucose homeostasis, mitochondrial energy production and synaptic transduction [61].

Defining the off-target effects of TZDs and determining whether their cardiovascular adverse effects are mediated through PPARγ-dependent or -independent mechanisms will be critical in developing new therapeutic agents. From this point of view, we discuss recent studies, both experimental and clinical, on the myocardial adverse effects associated with TZDs, particularly rosiglitazone and their underlying mechanisms, focusing in large part on PPARγ-independent (off-target) mechanism in the following context.

4. Rosiglitazone causes myocardial energy deficiency and mitochondrial dysfunction via PPARγ-independent mechanism

Using ^{31}P-nuclear magnetic resonance (NMR) spectroscopy, we measured intracellular phosphocreatine (PCr), adenosine triphosphate (ATP), and calculated free energy of ATP hydrolysis (ΔG_{ATP}) in isolated beating hearts perfused in Langendorff mode with regular Krebs-Henseleit buffer containing 10 mM glucose and 0.5 mM pyruvate. At baseline, all hearts from cardiomyocyte-specific PPARγ deficient (PPARγ$^{-/-}$) mice and their littermate control (PPARγ$^{+/+}$) mice showed similar PCr and ATP resonance areas, and PCr/ATP ratio, indicating the loss of regulatory action of cardiomyocyte PPARγ on myocardial energy metabolism can be compensated in vivo. At the human therapeutic concentrations of 1 and 3 μM, rosiglitazone showed no marked effects on the resonance areas and concentrations of intracellular PCr

([PCr]) and ATP ([ATP]). At the supratherapeutic concentrations of 10 and 30 μM, however, rosiglitazone decreased myocardial [PCr], [ATP], and ΔG_{ATP} in both PPARγ$^{-/-}$ and PPARγ$^{+/+}$ mice in parallel compared with their vehicle controls [62]. To confirm the results from ^{31}P-NMR spectroscopy, we freeze-clamped hearts from those mice at the end of each experiment and then measured total ATP, ADP, AMP content using HPLC and calculated energy charge. Consistent with the abovementioned results, total ATP content, ATP to ADP ratio and energy charge decreased following acute treatment with rosiglitazone at 10 and 30 μM in hearts from both PPARγ$^{-/-}$ and PPARγ$^{+/+}$ mice compared with vehicle control [62].

Since mitochondrial oxidation of fatty acid and glucose is a major source of ATP in cardiomyocytes, we measured glucose and palmitate oxidation rates in fresh tissue homogenates using [1-^{14}C]-glucose and [1-^{14}C]-palmitic acid, respectively. At the therapeutic concentrations of 1 and 3 μM, incubation of rosiglitazone with myocardial homogenates for 60 min did not change glucose and palmate oxidation rates. At the supratherapeutic concentrations of 10 and 30 μM, however, it decreased oxidation rates of glucose and palmitate in myocardial homogenate from both PPARγ$^{-/-}$ and PPARγ$^{+/+}$ mice to the same extent. Consistently, rosiglitazone decreased also mitochondrial respiration rate at these supratherapeutic concentrations in both homogenates [62].

We then determined the effects of rosiglitazone on both mitochondrial and cytosolic rate-limiting enzymes controlling ATP synthesis. When incubated with fresh tissue homogenate or isolated mitochondria for 60 min, rosiglitazone at 1 and 3 μM did not affect the activities of cytosolic and mitochondrial enzymes tested as compared with vehicle treatment. At the supratherapeutic concentrations of 10 and 30 μM, however, rosiglitazone decreased the activities of myocardial mitochondrial complexes I and IV in both PPARγ$^{-/-}$ and PPARγ$^{+/+}$ mice to the same extent, but did not alter the activities of other mitochondrial enzymes citrate synthase, creatine kinase, Complexes II, III, V and cytosolic enzymes phosphofructokinase, lactate dehydrogenase and glyceraldehyde 3-phosphate dehydrogenase [62]. These results indicate that the higher concentrations of rosiglitazone caused myocardial energy deficiency and mitochondrial dysfunction in the cardiomyocytes in a PPARγ-independent manner. Consistent with our study, Brunmair et al. reported that 10–100 μM TZDs rosiglitazone, troglitazone and pioglitazone inhibited mitochondrial complex I activity, respiratory control and glucose oxidation in the rat liver and skeletal muscles [63]; Rachek et al. found that troglitazone induced mitochondrial dysfunction and cell death in human hepatocytes [64]; results from Scatena et al. also suggested that TZDs induced a non-PPARγ-mediated effect: mitochondrial respiratory chain dysfunction [65].

The PPARγ-independence of rosiglitazone-induced energy deficiency and mitochondrial dysfunction are also supported by the following evidences: (1) Treatment with PPARγ agonist medium-chain triglyceride decanoic acid improved mitochondrial function as evidenced by increases in mitochondrial number, activities of mitochondrial enzyme citrate synthase, complex I, and catalase [66], whereas treatment with PPARγ agonist rosiglitazone induced mitochondrial dysfunction, suggesting rosiglitazone likely induces the mitochondrial dysfunction via PPARγ-independent mechanism [62]. (2) PPARγ-dependent effects are based upon altered transcription of genes involved in energy metabolism and usually require hours

to days to take into effect. The myocardial energy deficiency was observed after short time (30–60 min) exposure to rosiglitazone in our study [62]. Such an acute treatment generally does not allow gene expression to change after transcriptional activation of PPARγ, indicating rosiglitazone likely induced myocardial energy deficiency via PPARγ-independent mechanism.

To rule out the possibility that rosiglitazone caused myocardial energy deficiency and mitochondrial dysfunction through activation of PPARγ in other cardiac cells including fibroblast, smooth muscle cells and endothelial cells, we examined the effects of GW9662, a specific PPARγ antagonist on the detrimental actions of rosiglitazone on myocardial energy metabolism and mitochondrial function. We found that perfusion of hearts from C57BL/6 mice with 10 μM GW9662 for 60 min affected neither total ATP content, nor ATP/ADP ratio, nor energy charge. This antagonist did not reverse the decreases in total ATP content, ATP/ADP ratio and energy charge induced by rosiglitazone at 10 μM in those hearts. Furthermore, 10 μM GW9662 showed no effects on the oxidation rates of glucose and palmitate, mitochondrial respiration rate, or the activities of mitochondrial complexes I and IV, it did not antagonize the downregulations of those parameters by rosiglitazone at the supratherapeutic concentration of 10 μM, either [62]. Additionally, treatments with rosiglitazone at the supratherapeutic concentrations of 10 and 30 μM for 60 min significantly decreased intracellular ATP content in cultured mouse cardiomyocytes. In contrast, treatment with 10 μM rosiglitazone showed no effect on intracellular ATP content in cultured mouse cardiac fibroblasts, treatment with 30 μM rosiglitazone only slightly decreased intracellular ATP content in these fibroblasts. Interestingly, pretreatment with 30 μM GW9662 did not prevent the decreases in intracellular ATP content induced by rosiglitazone in these cultured cardiomyocytes or cardiac fibroblasts [62]. These results further support that rosiglitazone induces myocardial energy deficiency via PPARγ-independent mechanism.

To maintain energy homeostasis, the capacities of ATP synthesis by mitochondrial oxidative phosphorylation, glycolysis, and phosphotransferase (i.e., creatine kinase, CK) reactions must match the demand for ATP utilization by the sarcomere, ion pumps, etc. [67]. Therefore, increased ATP utilization and decreased ATP synthesis, singly or in combination, can cause energy deficiency. The free energy of ATP hydrolysis ΔGATP decreased following rosiglitazone treatment. Furthermore, heart mechanical work (assessed by rate pressure product, an indirect index of calcium cycling, metabolic demand, and ATP utilization) also decreased following acute treatment with rosiglitazone at 10–30 μM. These results suggest that decreased ATP synthesis may be responsible for myocardial energy deficiency induced by rosiglitazone. The main pathways for ATP synthesis in hearts are glycolysis, phosphoryltransfer reactions, and substrate oxidative phosphorylation. Rosiglitazone showed no effect on glycolytic rate-limiting enzymes and the product of CK activity and total creatine content [62], indicating that neither glycolysis nor phosphoryltransfer reaction is likely to be involved in rosiglitazone-induced myocardial energy deficiency.

The inhibition of complex I by rosiglitazone caused impaired oxidation of NADH and in turn decreased NAD content. As a result, NADH/NAD ratio increased. The impaired oxidation of NADH leads to decreased substrate oxidation and in turn decreased ATP synthesis. Complex

IV acts as the terminus of mitochondrial electron transport by accepting four electrons to reduce a single oxygen molecule. The reaction is coupled with the transfer of four protons across the mitochondrial membrane, driving ATP synthesis. Thus, the inhibition of both complexes I and IV by rosiglitazone reduces ATP synthesis, which manifests as the myocardial energy deficiency induced by rosiglitazone.

5. Rosiglitazone induces myocardial mitochondrial oxidative stress via PPARγ-independent mechanism

To assess the in vitro effects of rosiglitazone on redox homeostasis, we determined enzyme (NADPH oxidase, xanthine oxidase and mitochondrial complexes I and III)-dependent reactive oxygen species (ROS) O_2^- production, the capacity of ROS elimination systems including superoxide dismutase (SOD), reduced glutathione (GSH), glutathione peroxidase and catalase, and biomarkers malondialdehyde (MDA), protein carbonyl and 8-hydroxy-2′-deoxyguanosine (8HOdG) of oxidative damage to lipids, proteins and DNAs, respectively, in isolated mitochondria and nuclei. We found that at 1 and 3 μM, rosiglitazone showed no effects on any of the aforementioned parameters. At 10 and 30 μM, however, rosiglitazone increased mitochondrial complexes I- and III-dependent O_2^- production, decreased the level of mitochondrial GSH and SOD activity, and increased the levels of mitochondrial MDA, protein carbonyl and 8-OHdG [62]. Interestingly, pretreatment with 30 μM GW9662 did not prevent rosiglitazone-induced changes in the above redox parameters. Furthermore, even at the supratherapeutic concentrations of 10 and 30 μM, rosiglitazone did not affect the activities of catalase and glutathione peroxidase, and changed neither the level of nuclear protein carbonyl nor the level of nuclear 8-OHdG [62]. Similar to our study, rosiglitazone at 50 and 60 μM induced apoptosis via oxidative stress in cultured H9c2 cells [68].

We also assessed the acute effects of rosiglitazone on mitochondrial oxidative stress in vivo. At 1 mg/kg, injection of rosiglitazone into mouse tail vein showed no effect on the levels of myocardial mitochondrial MDA, protein carbonyl and 8-OHdG. At 10 mg/kg, however, rosiglitazone increased the levels of these mitochondrial oxidative stress markers. Importantly, injection of antioxidant N-acetyl-L-cysteine 600 mg/kg into mouse tail vein prevented the above rosiglitazone-induced changes of mitochondrial oxidative stress markers in vivo [62]. Furthermore, intravenous injection of GW9662 at 1 mg/kg, previously demonstrated to interact selectively with PPARγ, acting as a potent and full PPARγ antagonist, did not prevent 10 mg/kg rosiglitazone induced myocardial oxidative stress [62]. Taken together, our in vitro and in vivo data support that rosiglitazone induces myocardial mitochondrial oxidative stress via PPARγ-independent mechanism, possibly by decreasing mitochondrial ROS-scavenging capacity.

6. Rosiglitazone causes cardiac dysfunction via PPARγ-independent mechanism

Normal cardiac contractile function requires energy homeostasis. As we found that rosiglitazone caused energy deficiency, we therefore further determined the effects of rosiglitazone

on cardiac function. In ex vivo Langendorff-perfused hearts, treatment with rosiglitazone at 1 and 3 μM for 24–30 min showed no obvious effects on cardiac systolic function as assessed by left ventricular systolic pressure (LVSP) and the rate of tension development (+dP/dt). Treatment with rosiglitazone at 10 and 30 μM for 24–30 min, however, decreased LVSP and + dP/dt in hearts from C57BL/6, PPARγ−/− and PPARγ+/+ mice, indicating acute treatment with rosiglitazone at the supratherapeutic concentrations causes cardiac systolic dysfunction [62]. Similarly, treatment with rosiglitazone at 1 and 3 μM for 24–30 min showed no obvious effects on cardiac diastolic function as assessed by left ventricular end diastolic pressure (EDP) and the rate of relaxation (–dP/dt). Treatment with rosiglitazone at 10 and 30 μM for 24–30 min, however, increased EDP and decreased –dP/dt in all hearts from the above three genotypes, indicating acute treatment with rosiglitazone at the supratherapeutic concentrations also causes cardiac diastolic dysfunction [62]. Interestingly, rosiglitazone-induced cardiac dysfunction was not distinguishable among C57BL/6, PPARγ−/− and PPARγ+/+ mice, indicating acute rosiglitazone treatment caused cardiac dysfunction independently of cardiomyocyte PPARγ [62]. Additionally, treatment of hearts with 10 μM GW9662 for 60 min, affected neither cardiac function, nor rosiglitazone-induced cardiac dysfunction. In contrast, treatment of hearts with 20 mM N-acetyl-L-cysteine (NAC) for 60 min did not affect baseline cardiac function, but prevented cardiac dysfunction induced by rosiglitazone at the supratherapeutic concentration of 10 μM [62]. These data further support that rosiglitazone induced cardiac dysfunction via a mechanism related to oxidative stress and independent of PPARγ.

We also evaluated the side effects of rosiglitazone on cardiac function in vivo setting by using echocardiography. Injection of rosiglitazone at the dose of 1 mg/kg into mouse tail vein showed no effect on cardiac function as assessed by fraction shorting [29] and ejection fraction EF). At 10 mg/kg, however, rosiglitazone decreased FS and EF, indicating rosiglitazone caused cardiac dysfunction at a higher dose. NAC at 600 mg/kg alone showed no effect on cardiac function. In combination with 10 mg/kg rosiglitazone, however, this antioxidant prevented rosiglitazone-induced cardiac dysfunction. In contrast, intravenous injection of PPARγ selective antagonist GW9662 at 1 mg/kg did not prevent 10 mg/kg rosiglitazone-induced cardiac dysfunction [62]. These in vivo studies also support that rosiglitazone induces cardiac dysfunction via a mechanism related to oxidative stress and independent of PPARγ.

7. TZDs induce cardiac hypertrophy via PPARγ-independent mechanism

TZDs are expected to inhibit cardiomyocyte growth in vitro and in pressure overload models via activation of PPARγ. Paradoxically, TZDs have also been reported to induce cardiac hypertrophy in mice, rats and dogs [69, 70]. This side effect may occur because TZDs expand blood volume. However, an essential question is whether or not this effect is directly attributable to cardiac PPARγ activation. Treatment with TZD rosiglitazone 10 mg/kg per day for 4 weeks induced cardiac hypertrophy in both PPARγ−/− and PPARγ+/+ mice. Rosiglitazone treatment increased cardiac phosphorylation of p38 mitogen-activated protein kinase (p38-MAPK), a MAPK pathway essential for cardiac hypertrophy, in PPARγ−/− mice. The effect of rosiglitazone on p38-MAPK persisted in PPARγ−/− mouse hearts indicated that activation

of p38-MAPK by TZDs is independent of cardiomyocyte PPARγ [70]. Furthermore, phosphorylation of c-Jun N-terminal kinases was not affected by rosiglitazone or cardiomyocyte PPARγ deletion. Surprisingly, despite hypertrophy, AKT phosphorylation was suppressed in PPARγ−/− mouse hearts [70]. These data demonstrate that cardiomyocyte PPARγ suppresses cardiac growth and embryonic gene expression and inhibits nuclear factor κB activity in vivo, and that rosiglitazone causes cardiac hypertrophy at least partially independent of PPAR-γ in cardiomyocytes [70].

8. TZDs increase risks of heart failure

Congestive heart failure (CHF) is a major complication of diabetes and occurs as a result of both atherosclerotic coronary disease and non-ischemic diabetic cardiomyopathy. TZDs improve glycemic control and afford beneficial effects on many markers of cardiovascular risk including blood pressure, waist to hip ratio, HDL levels, endothelial reactivity, C-reactive protein, fibrinolysis, and microalbuminuria by improving peripheral insulin sensitivity. These antidiabetic agents, however, have been reported to worsen the existing CHF or precipitate new-onset failure in several reviews and meta-analyses of placebo-controlled randomized clinical trials (RCTs).

Bolen et al. found that the risk for CHF was higher with TZDs as either monotherapy or combination therapy than with metformin or sulfonylureas, with a range of 0.8–3.6% for TZDS and 0–2.6% for non-TZDs [4]. Lago et al. found an increased risk of CHF in use of TZDs in patients with diabetes and prediabetes compared with placebo and active-controls: relative risk 1.72, 95% confidence interval (CI) 1.21–2.42. The overall event rate for CHF with TZDs was 2.3% and with the comparison drugs 1.4% [14]. Singh et al. reported that the relative risk of CHF in use of rosiglitazone in patients with diabetes or prediabetes compared with various other antidiabetic drugs was 2.09 (95% CI 1.52–2.88) [17]. They also examined onset of CHF in both pioglitazone and rosiglitazone compared with placebo in three randomized controlled trials with subjects with either type 2 diabetes or prediabetes. The odds ratio (OR) for all heart failure adverse events was 2.10 (95% CI 1.08–4.08). Four observational studies produced an OR 1.55 (95% CI 1.33–1.80). These authors also examined case reports, including 162 case subjects with 99 analyzable cases. Among these cases, the median time to onset of CHF was 24 weeks, although failure could occur early and did not appear to relate to dosage. CHF was not limited to the elderly; 26% of cases were in subjects less than 60 years of age [71]. Hernandez et al. found that the TZD therapy was significantly and consistently associated with a higher risk of CHF: TZDs 360/6807 [5.3%] versus placebo 234/6328 [3.7%], OR 1.59; 95% CI 1.34–1.89; $p < 0.00001$. The risk of CHF was higher with rosiglitazone than with pioglitazone (OR 2.73; 95% CI 1.46–5.10) versus (OR 1.51; 95% CI 1.26–1.81; $p = 0.06$). Rosiglitazone and pioglitazone were associated with a similar risk of serious/severe CHF (OR 1.47; 95% CI 1.16–1.87; $p = 0.002$). The use of TZDs was also associated with edema (OR 2.04; 95% CI 1.85–2.26; $p < 0.00001$) [72]. The above increased risk of CHF was largely confirmed in other meta-analyses: the use of rosiglitazone for >4 weeks in 132 trials involving 41,743 patients with or without T2DM was associated with a 69% higher relative risk of serious CHF [73]; and

the combined short- and long-term use of pioglitazone in 19 RCTs involving 16,390 patients with T2DM found a 41% higher relative risk of serious CHF [74]. Another meta-analysis of 26 RCTs found 126% higher odds of peripheral edema in 15,332 diabetics with short- and long-term use of TZDs [75].

One of the potential mechanisms responsible for increased risk in CHF with TZD treatment may be the fluid accumulation observed in large-scale studies on antidiabetic medications [74–76]. In spite of a weak beneficial effect on blood pressure [77], volume overload beyond a certain threshold induced by TZDs increases the myocardial energy demand of the left ventricular and triggers metabolic disorder. As a compensatory mechanism, the contractile function of myocardia is temporarily restored via cardiac hypertrophy, overtaking the growing amount of mitochondrial respiration and ATP production gradually.

In susceptible individuals, these pathophysiological responses likely explain why rosiglitazone precipitate clinical heart failure, and why ischemic events are easily provoked. Notably, the sodium-retentive actions of rosiglitazone within the renal tubules are dose and duration-dependent and insulin-independent, accordingly, it is likely that concurrent treatment with insulin and rosiglitazone mutually reinforces the risk of each agent, thus markedly increases the possibility of worsening heart failure. The reasons for fluid retention and peripheral edema with TZD use are not fully understood and are likely to be multifactorial. One possibility is the reduction in renal excretion of sodium and an increase in sodium and free water retention. Whether these actions are PPARγ-dependent or not warrants further study.

The other potential mechanism responsible for increased risk in CHF with TZDs treatment may be related to their direct adverse effects on myocardial energy deficiency, mitochondrial function and cardiac function observed in our previous study [62]. It is well known that altered energy metabolism and cardiac dysfunction are common features of heart failure resulted from different causes, including diabetes. We demonstrated that rosiglitazone induced myocardial energy deficiency, mitochondrial dysfunction and cardiac dysfunction in perfused mouse hearts at the supratherapeutic concentrations of 10 and 30 μM and induced cardiac dysfunction in vivo at a high dose of 10 mg/kg [62]. TZDs might be accumulated over a longer period of time in the cell or their effects are in some other way "cumulative" in some patients who need increased doses due to the tolerance during a long period of therapeutic time, and in diabetic patients with renal dysfunction. Therefore, it is likely that TZDs increase the risk of heart failure in T2DM patients through their PPARγ-independent adverse effects on the heart.

9. TZDs increase risks of myocardial infarction

Muraglitazar, an investigational dual PPARα and PPARγ agonist, was the first TZD agent halted because of increased adverse cardiovascular events, including myocardial infarction, transient ischemic attack, and stroke, during phase 2 and 3 trials [78]. In 2007, Nissen and Wolski performed the first large meta-analysis of 42 trials involving 27,847 patients with

randomized control group not receiving rosiglitazone and found that rosiglitazone was associated with a significant increase in the risk of myocardial infarction (OR 1.43, 95% CI 1.03–1.98, P = 0.03) and with an increase in the risk of cardiovascular death (OR 1.64, 95% CI 0.98–2.74, P = 0.06) [16]. In 2010, Nissen and Wolski published an update including 56 trials with 35,531 randomized patients: 19,509 who received rosiglitazone and 16,022 who received control therapy. They continued to demonstrate that rosiglitazone therapy significantly increased the risk of myocardial infarction (OR 1.28, 95% CI 1.02–1.63, P = 0.04) [79]. Consistent with above analyses, Ontario study [80] and Taiwan study [81] also reported the increased risks in both myocardial infarction and cardiovascular death following the treatment with rosiglitazone. Several other meta-analyses by Psaty and Furberg, GlaxoSmithKline, U.S. FDA and Singh et al. found the increased risks in myocardial infarction but uncertainty in cardiovascular death in patients with rosiglitazone treatment [17, 82, 83], whereas meta-analysis by Shuster et al. reported the increased risk in cardiovascular death but uncertainty in myocardial infarction in subjects treated with rosiglitazone [84].

In contrast, the meta-analysis by Diamond et al. and Lago et al. reported that rosiglitazone was not associated with an increase in the risk of myocardial infarction and cardiovascular death [14, 85].

These discrepancies can be ascribed to the inconsistencies in trial design, eligibility, follow-up, sample size, analytical methodology, and endpoint criteria among analyses and studies.

The mechanisms responsible for increased risks in myocardial infarction and cardiovascular death related to TZDs are not fully characterized. Several contributing factors are possible: first, the reduction in hemoglobin. TZDs, including rosiglitazone, may produce a modest reduction in the hemoglobin level. In susceptible patients, a reduced hemoglobin level may result in increased physiological stress, thereby provoking myocardial ischemia [16]. The second is adverse effects on serum lipids. TZDs may produce detrimental influences on serum lipids. Rosiglitazone increased low-density lipoprotein cholesterol (LDL-C) concentration of 18.6% among T2DM patients treated for 26 weeks with an 8-mg daily dose via increasing serum paraoxonase activity, which protects LDL-C against lipid peroxidation. This TZD also significantly increased triglyceride levels in 50 patients who were given at 4 mg/day for 3 months in addition to their usual treatment compared to baseline levels [86, 87]. Higher LDL-C level was consistently and independently associated with higher incidences of major adverse cardiovascular events after controlling for conventional risk factors [88]. Third, overload of intravascular volume. TZDs may induce fluid retention and peripheral edema likely via the reduction in renal excretion of sodium and an increase in sodium and free water retention [13]. The volume overload increases stress on the left ventricular wall, a factor that determines myocardial oxygen demand. In susceptible patients, an increase in myocardial oxygen demand could theoretically provoke ischemic events.

10. Summary

There are two TZDs approved for prescription use in the United States: rosiglitazone maleate (Avandia) and pioglitazone hydrochloride (Actos). Both have been widely used to treat adult patients with T2DM, either as monotherapy or in combination with insulin, metformin,

or sulfonylurea when diet, exercise, and a single agent does not result in adequate glycemic control. The mechanisms of action of TZDs in lowering plasma glucose among patients with T2DM are thought to include the following: increase insulin sensitivity, decrease endogenous glucose production and postprandial gluconeogenesis, increase fasting and postprandial glucose clearance, and have beneficial effects on beta-cell function. The glycemic effects of these agents are thought to be mediated by binding to PPARγ (**Figure 1**).

Their efficacy and beneficial effects, however, are shadowed by the increased risks of cardiovascular adverse events. Evidences are accumulating that TZDs, particularly rosiglitazone, cause cardiotoxicity including myocardial energy deficiency, mitochondrial dysfunction, and oxidative stress with concomitant cardiac dysfunction in ex vivo perfused hearts. TZDs may also cause cardiac hypertrophy in whole animal model. Additionally, TZDs increase the risks of heart failure and myocardial infarction in patients with T2DM. Understanding whether the cardiotoxicity induced by TZDs is PPARγ independent or not is an important issue for designing more specific PPARγ agonists with fewer side effects. TZDs also have affinity to numerous non-PPARγ targets in mitochondria, cytosol and cytoplasm, including

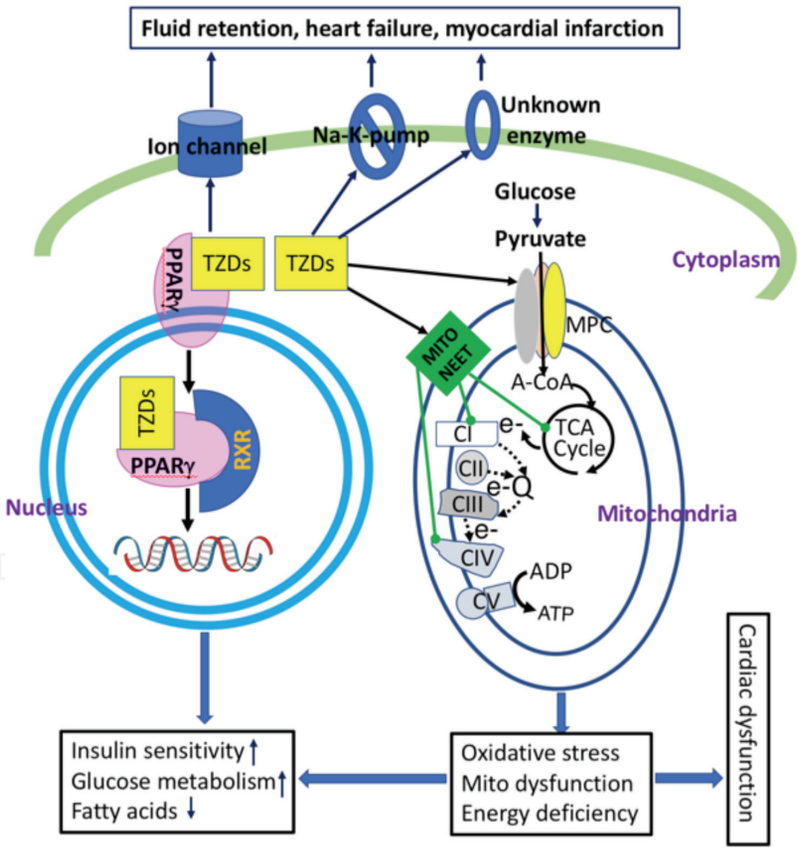

Figure 1. PPARγ-dependent (on-target) and -independent (off-target) effects of thiazolidinediones (TZDs). TZDs produce on-target effects by binding to nucleus PPARγ, increasing insulin sensitivity and glucose oxidation and contributing to efficacy of the drugs. They produce off-target effects by binding to numerous non-PPARγ targets including MitoNEET, mitochondrial pyruvate carrier (MCP), dehydrogenases involved in TCA cycle and electron transport chain complexes, cytoplasmic ion channels, Na-K-pump and other unknown enzymes. Off-target effects potentially increase cardiotoxicity including mitochondrial (Mito) dysfunction, oxidative stress and myocardial energy deficiency, fluid retention, congestive heart failure and myocardial infarction. Paradoxically, Mito dysfunction and energy deficiency may also stimulate insulin sensitivity and glucose uptake in the heart and indirectly contributing to efficacy of the drugs. A-CoA, acetyl-coenzyme A; TCA, tricarboxylic acid; e–, electron; CI, CII, CIII, CIV and CV, mitochondrial respiratory chain complexes I, II, III, IV and V, respectively; Q, coenzyme Q.

MitoNEET, mitochondrial pyruvate carrier (MCP), dehydrogenases involved in TCA cycle and electron transport, cytoplasmic ion channels, Na-K-pump and other unknown enzymes. By binding to these non-PPARγ targets, TZDs produce off-target effects and potentially increase cardiotoxicity including mitochondrial dysfunction, oxidative stress and myocardial energy deficiency, fluid retention, congestive heart failure and myocardial infarction. Paradoxically, mitochondrial dysfunction and energy deficiency may also stimulate insulin sensitivity and glucose uptake in the heart and indirectly contributing to efficacy of TZDs. Therefore, TZDs may produce antidiabetic effects via both PPARγ-dependent and PPARγ-independent mechanisms, and they may induce cardiotoxicity solely via PPARγ-independent mechanism (**Figure 1**). This chapter also raised concerns that the use of TZDs may lead to a significant increase in adverse cardiovascular effects. The benefit/risk profile of TZDs should be considered when treating diabetic patients with or without prior cardiovascular diseases.

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Conflict of interest

Authors declare no conflict of interest.

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