Thiazolidinediones: Potential Link Between Insulin Resistance and Cardiovascular Disease
Vanita R. Aroda, M D, and Robert R. Henry, M D

Abstract
The thiazolidinediones are a unique class of oral antidiabetic agents that has been shown to directly reduce insulin resistance at sites of insulin action, specifically adipose tissue, skeletal muscle, and the liver. By reducing insulin resistance, these drugs influence many of the modifiable cardiovascular risk factors associated with the insulin resistance syndrome, also known as the cardiovascular dysmetabolic syndrome. Such cardiovascular factors are involved in the development of atherosclerosis and include dyslipidemia, hypertension, microalbuminuria, impaired vascular reactivity, and impaired fibrinolysis. Whether these effects of the thiazolidinediones translate to a reduced incidence of cardiovascular events in people with type 2 diabetes remains to be seen.

Type 2 diabetes is a growing epidemic, affecting an estimated 16 million people in the United States. An additional 16 million people in the United States have the prediabetic condition of impaired glucose tolerance (IGT). In both type 2 diabetes and IGT, cardiovascular disease (CVD) is the leading cause of morbidity and premature death. This increased risk of macrovascular disease in both type 2 diabetes and IGT is intricately associated with the presence of insulin resistance, which refers to an impaired ability for the body to respond appropriately to insulin and utilize glucose (Figure 1).

Insulin resistance is one of the major pathophysiological abnormalities in type 2 diabetes. Insulin resistance and hyperinsulinemia are closely associated with a cluster of metabolic abnormalities termed the insulin resistance syndrome or cardiovascular dysmetabolic syndrome (Figure 2). These metabolic abnormalities not only include hyperglycemia and glucose intolerance, but also other cardiovascular risk factors, including dyslipidemia, hypertension, abnormal fibrinolysis, and vascular abnormalities, ultimately leading to accelerated atherosclerotic disease. The treatment of type 2 diabetes thus not only focuses on optimizing glycemic control, but also on preventing and treating these cardiovascular risk factors to reduce the risk of cardiovascular disease and premature death.

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Figure 1. Insulin resistance, or impaired ability to utilize glucose, in patients with IGT or type 2 diabetes. Adapted from Ref. 55.
Mechanism of Action of Thiazolidinediones

The thiazolidinediones comprise a novel class of antidiabetic agents that may confer beneficial effects on cardiovascular risk factors. Although discovered more than two decades ago, it was not until the mid-1990s that their molecular mechanism of action was elucidated. Thiazolidinediones are synthetic ligands that activate nuclear receptors called peroxisome proliferator-activated receptors (PPARs). Once activated, the PPARs form heterodimers with another nuclear receptor, the 9-cis-retinoic acid receptor (RXR). By binding to specific DNA sequences, these PPAR/RXR heterodimers regulate genetic transcription and translation of proteins involved in glucose and lipid metabolism (Figures 3 and 5).

There are three subtypes of PPARs currently identified: PPARα, PPARβ (also known as PPARδ, NUC-1, and FAAR), and PPARγ. The antidiabetic actions of thiazolidinediones correspond to their ability to activate PPARγ receptors that are found in key target tissues of insulin action: the adipose tissue, skeletal muscle, and liver.

In adipose tissue, where PPARγ is most abundantly expressed, PPARγ activation leads to induction of multiple adipocyte genes involved in fatty acid uptake and delivery, thereby lowering free fatty acid and triglyceride levels. In addition, our group has shown that treatment with troglitazone (Rezulin) for 3 months in humans increases the amount of glucose transport by adipocytes both in the absence of and in the presence of insulin.

Finally, activation of PPARγ is also involved in fat differentiation and redistribution. PPARγ activation may increase the number of small adipocytes, which are thought to take up more glucose than large adipocytes with insulin stimulation.

Thiazolidinediones have also been shown to increase expression of proteins involved in glucose and lipid metabolism in skeletal muscle. PPARγ activation with a thiazolidinedione has been demonstrated to increase insulin stimulation of phosphatidylinositol 3-kinase activity and insulin-stimulated Akt activity, which are key processes in insulin signaling that are defective in skeletal muscle of individuals with type 2 diabetes.

Thiazolidinediones have a less pronounced effect at the level of the liver, but may improve insulin-mediated suppression of hepatic glucose production. These effects, plus others, including probable non-PPARγ-mediated actions, contribute to the ability of thiazolidinediones to increase insulin sensitivity.

Clinical Use of Thiazolidinediones

Clinically, thiazolidinediones have been shown to reduce plasma glucose, insulin levels, and hemoglobin A1C (A1C) in people with type 2 diabetes. As monotherapy, thiazolidinediones have been shown to reduce fasting plasma glucose levels by 60–80 mg/dl and A1C results by 1.2–2.6 percentage points compared to placebo.

They offer an effective, safe means of glycemic control, particularly when used in combination therapy with other antidiabetic agents. They have also been shown to reduce insulin resistance in states of IGT such as obesity and polycystic ovarian syndrome (PCOS). Currently, two structurally diverse PPARγ agonists are used in clinical practice: pioglitazone (Actos) and rosiglitazone (Avandia). Though previously available, troglitazone was removed from the market in March 2000 because of reports of idiosyncratic hepatic
injury.\textsuperscript{19} Pioglitazone and rosiglitazone have not demonstrated a similar increased incidence in hepatic adverse events.\textsuperscript{15,16}

The use of pioglitazone and rosiglitazone are contraindicated in advanced heart failure because they may lead to fluid retention and weight gain, which may worsen or cause heart failure. These effects may be exacerbated in combination therapy with insulin. Pioglitazone is currently approved for use as monotherapy and in combination with insulin, metformin (Glucophage), or sulfonylureas.\textsuperscript{15} Rosiglitazone is currently approved for use as monotherapy or in combination with metformin or sulfonylureas and has recently received approval for use with insulin.\textsuperscript{16}

In addition to improving glycemic control, the thiazolidinediones have potentially favorable effects on other components of the insulin resistance syndrome: dyslipidemia, hypertension and vascular abnormalities, fibrinolysis, and ultimately, atherosclerosis.\textsuperscript{15} As insulin sensitizers, they may modify cardiovascular risk factors and reduce premature cardiovascular mortality in people with type 2 diabetes and insulin resistance. Although most studies have been done with troglitazone, pioglitazone and rosiglitazone appear to have similar effects. Further studies are needed to evaluate the individual differences among the thiazolidinediones. Long-term clinical trials are needed to assess whether these compounds reduce long-term cardiovascular morbidity and mortality by modifying cardiovascular risks. Here, we review the potential cardiovascular benefits of these insulin sensitizers.

**Thiazolidinediones and Dyslipidemia**

Diabetic dyslipidemia is closely related to insulin resistance and may be partly responsible for the increased cardiovascular morbidity and mortality in type 2 diabetes (Table 1).\textsuperscript{20-22}

Diabetic dyslipidemia is characterized by an elevation in triglyceride-rich lipoproteins and a decrease in HDL cholesterol concentrations. Often, the level of LDL cholesterol is similar to that in nondiabetic individuals.\textsuperscript{23} However, people with type 2 diabetes and insulin resistance have an increase in the potentially more atherogenic, small, dense LDL particles.

Both animal models and human clinical trials have demonstrated an improvement in dyslipidemia from thiazolidinediones. Thiazolidinediones improve dyslipidemia primarily by raising HDL cholesterol and decreasing the triglyceride level. This is likely mediated through a combination of PPAR\(\alpha\) and PPAR\(\gamma\) activation. Troglitazone has been shown to lower triglyceride levels ~15–20\% and increase HDL cholesterol levels 5–8\%.\textsuperscript{24} Pioglitazone has also been shown to lower triglycerides by ~9\% and increase HDL levels by ~12–19\%.\textsuperscript{25} Rosiglitazone has been shown to increase HDL levels and has demonstrated variable effects on triglycerides.\textsuperscript{26} More prospective head-to-head studies are required to make adequate comparisons among the different thiazolidinediones.

The effects of thiazolidinediones on LDL cholesterol are more complex. In people with insulin resistance or type 2 diabetes, LDL levels are usually similar to those of nondiabetic individuals. Despite near-normal LDL levels, there are increased levels of the more atherogenic, small, dense LDL particles. Of concern, studies have demonstrated an increase in LDL cholesterol with use of thiazolidinediones compared to placebo. This effect may be due to an increase in the larger, more buoyant, less dense LDL particles, which may be less prone to oxidative modification and thus confer a less atherogenic pattern.\textsuperscript{27}

Despite these findings, it is known that lowering LDL cholesterol is beneficial in significantly decreasing cardiac events, particularly in individuals with increased risk of cardiovascular disease.\textsuperscript{28} Thus, long-term follow-up will be needed to determine whether the rise in LDL cholesterol with the use of thiazolidinediones has an adverse impact on atherosclerosis and cardiovascular mortality or is offset by the potentially favorable effects on particle size.

**Vascular Effects of Thiazolidinediones**

The prevalence of hypertension is 1.5- to 2-fold higher in patients with type 2 diabetes\textsuperscript{29} and, independent of diabetes, is associated with significant insulin resistance and cardiovascular disease. Hypertension is thus an important modifiable cardiovascular risk factor in both people with diabetes and those without diabetes. Thiazolidinediones have been shown to significantly decrease blood pressure in animal models and in diabetic and nondiabetic humans.\textsuperscript{30-32} For example, Ogihara et al.\textsuperscript{31} demonstrated a statistically significant blood-pressure-lowering effect from 164 ± 3/94 ± 2 to 146 ± 3/82 ± 3 mmHg after 8 weeks of treatment with troglitazone.

All three agents have also been shown to decrease urinary albumin excretion in patients with type 2 diabetes with microalbuminuria.\textsuperscript{33-35} Pioglitazone has also been found to reduce excretion of urinary endothelin-1, a urinary protein secreted before the microalbuminuric phase of renal injury.\textsuperscript{35}

The mechanisms of decreased blood pressure and reduced microalbuminuria with thiazolidinediones are not well understood. Their insulin-sensitizing effects may have direct vascular effects or indirect vascular effects via other mediators (e.g., endothelin-1, plasminogen activator inhibitor type 1 [PAI-1], or type-C natriuretic peptide).\textsuperscript{36}

<table>
<thead>
<tr>
<th>Table 1. Summary of Effects of Thiazolidinediones on Lipid Parameters</th>
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<tbody>
<tr>
<td><strong>Diabetic Dyslipidemia</strong></td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
<tr>
<td>Total cholesterol</td>
</tr>
<tr>
<td>LDL cholesterol</td>
</tr>
<tr>
<td>LDL oxidation</td>
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<tr>
<td>LDL particle size</td>
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<td>HDL cholesterol</td>
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acteristic in type 2 diabetes and other insulin-resistant states. Impaired vascular reactivity is associated with endothelial injury and atherogenesis and can be measured noninvasively by brachial artery vasoactivity studies. Thiazolidinediones appear to improve flow-mediated reactivity, perhaps by improving the vasodilator response to insulin or by enhancing nitric oxide production. Murakami et al. demonstrated a beneficial effect not only in brachial artery reactivity, but also in vasospastic angina pectoris in 10 patients with type 2 diabetes treated with 400 mg of troglitazone for 4 months. Long-term studies are needed to evaluate whether a similar effect will be seen with the other thiazolidinediones and whether cardiovascular morbidity is decreased.

### Thiazolidinediones and Left Ventricular Mass

Earlier studies in animals revealed preload-induced cardiac hypertrophy in animals treated with thiazolidinediones. In contrast, Ghazzi et al. evaluated the effect of troglitazone on cardiac mass in patients with type 2 diabetes. They found that troglitazone improved cardiac index and stroke volume without increasing left ventricular mass.

However, despite these intriguing findings, thiazolidinediones can clinically cause increased plasma volume and edema, which may exacerbate or lead to heart failure. Thus, the use of thiazolidinediones in advanced heart failure (New York Heart Association Classification Class III or IV) is contraindicated. While the use of both available thiazolidinediones with insulin is now approved, patients should be observed for signs and symptoms of congestive heart failure while taking a thiazolidinedione, and the thiazolidinedione should be discontinued if there is any deterioration in cardiac status.

### Effect of Thiazolidinediones on Fibrinolysis

Type 2 diabetes and insulin resistance are also associated with abnormalities of the coagulation-fibrinolysis system. Impaired fibrinolysis is primarily due to increased concentrations PAI-1 and is strongly associated with the development and progression of atherosclerosis. Elevated PAI-1 and fibrinogen levels positively correlate with other parameters of the insulin resistance syndrome, including fasting plasma insulin, blood pressure, triglycerides, and body mass index, and may be partly responsible for increased cardiovascular risk in people with type 2 diabetes and in nondiabetic individuals with insulin resistance.

Thiazolidinediones have been shown to decrease PAI-1 activity and increase thrombolysis. In a study by Kubo, 21 patients with type 2 diabetes were randomized to receive 400 mg of troglitazone or a sulfonlurea (40 mg glinazide) for 12 weeks. At the end of treatment, both therapies achieved similar glycemic control. However, only troglitazone therapy resulted in significant reductions in PAI-1 and fibrinogen levels. Similar effects have been shown with the use of troglitazone in PCOS, which is also associated with insulin resistance and impaired fibrinolysis.

### Can Thiazolidinediones Directly Inhibit Atherosclerosis?

The process of atherogenesis is far more complex than simply the accumulation of lipids within the artery wall. Rather, atherosclerosis is an inflammatory process that is initiated by 1) the accumulation of plasma LDL in the arterial wall, 2) its modification by oxidation and glycosylation, and 3) recruitment of circulating monocytes that transform to macrophages. The oxidized LDL is internalized via scavenger receptors, resulting in the formation of foam cells. Complex interactions between the foam cells, the oxidized LDL, and circulating inflammatory and proagulant mediators contribute to injury in the underlying smooth muscle and endothelium, which in turn contributes to atherogenesis.

Thiazolidinediones have been shown to influence many of these factors and mediators of atherosclerosis (Table 2). Thiazolidinediones have been shown to protect LDL from oxidative modification, one of the key initial events in atherogenesis. Cominacini et al. reported in 1998 an increase in resistance of LDL to oxidation in patients with type 2 diabetes treated with troglitazone for 8 weeks. Treatment with troglitazone reduced LDL hydroperoxide, a product of oxidative stress, and increased the LDL lag phase, a measure of resistance to LDL oxidation.

Vascular smooth muscle proliferation from the media to the intima and migration are also crucial events in the progression of atherosclerosis and restenosis. In people both with and without type 2 diabetes, intimal medial thickness correlates with hyperinsulinemia and is a measure of atherosclerosis progression. PPARγ receptors are expressed in vascular smooth muscle cells and are upregulated during injury. Animal models indicate that troglitazone, rosiglitazone, and pioglitazone inhibit intimal hyperplasia and vascular smooth muscle cell proliferation and migration. Furthermore, treatment with both troglitazone and pioglitazone have been associated with decreased carotid intimal- medial complex thickness in patients with type 2 diabetes.

### Table 2. Mechanisms by Which Thiazolidinediones May Decrease Cardiovascular Events

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Beneficial Effect of Thiazolidinediones</th>
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<tbody>
<tr>
<td>Dyslipidemia</td>
<td>Increase HDL</td>
</tr>
<tr>
<td></td>
<td>Decrease LDL oxidation</td>
</tr>
<tr>
<td></td>
<td>Increase LDL particle size</td>
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<tr>
<td></td>
<td>May decrease triglycerides</td>
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<tr>
<td>Blood pressure</td>
<td>Decrease</td>
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<tr>
<td>Microalbuminuria</td>
<td>Decrease</td>
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<tr>
<td>Vascular effects</td>
<td>Decrease vascular smooth muscle proliferation</td>
</tr>
<tr>
<td></td>
<td>Decrease macrophage activation and migration</td>
</tr>
<tr>
<td></td>
<td>Improve vascular reactivity</td>
</tr>
<tr>
<td></td>
<td>Decrease intimal medial thickness</td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td>Decrease PAI-1 activity and fibrinogen</td>
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Similarly, patients with type 2 diabetes tend to have accelerated neointimal proliferation after coronary stent implantation and thus higher rates of restenosis. Takagi et al.\(^5\) studied the effect of 6 months of troglitazone treatment versus placebo in patients with type 2 diabetes who received coronary stent implantation. They demonstrated with serial intravascular ultrasound measurements significantly reduced neointimal tissue proliferation after coronary stent implantation in patients with type 2 diabetes receiving troglitazone.

Macrophage activation also plays a key role in atherosclerosis and plaque rupture.\(^4\) PPAR\(\gamma\) is expressed in macrophages in human atherosclerotic lesions. PPAR\(\gamma\) agonists have been shown to inhibit the production of proinflammatory cytokines (e.g., tumor necrosis factor \(\alpha\), interleukin-6, interleukin-1) in these macrophages.\(^5\) Furthermore, matrix metalloproteinases are key enzymes secreted by macrophages that contribute to plaque rupture by participating in extracellular matrix degradation. Troglitazone has been shown to inhibit the production of matrix metalloproteinase-9 (MMP-9, gelatinase B), implicating a potential for a decrease in plaque rupture.\(^6\)

By protecting LDL from oxidation, inhibiting vascular smooth muscle proliferation, inhibiting macrophage migration, improving fibrinolysis, and reducing endothelial injury, thiazolidinediones may potentially prevent or delay atherosclerosis in people with type 2 diabetes and in nondiabetic people with manifestations of the insulin resistance syndrome.

**Conclusion**

Thiazolidinediones are a unique class of antidiabetic medications that exert multiple effects beyond glycemic control. Clinical trials suggest that they not only decrease insulin resistance, but may also reduce cardiovascular risk by improving various aspects of the insulin resistance or cardiovasculardysmetabolic syndrome. They may reduce accelerated atherosclerosis associated with type 2 diabetes and insulin resistance not only by improving glycemia and decreasing plasma insulin levels, but also by increasing HDL and decreasing triglyceride levels, improving blood pressure, improving fibrinolysis, and reducing vessel wall abnormalities. By influencing these metabolic abnormalities of the insulin resistance syndrome, thiazolidinediones may prevent or delay premature atherosclerotic cardiovascular disease, morbidity, and death. Long-term studies with endpoints such as cardiovascular disease and type 2 diabetes are needed to determine whether these agents are able to fulfill this potential.

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