ABSTRACT

Many people with diabetes will die as a result of cardiovascular complications that often begin to develop long before the patient is ever diagnosed. A growing body of evidence suggests that rather than being an inert tissue, visceral fat is metabolically active and secretes a variety of potentially atherogenic substances, including adipokines and cytokines, which contribute to the cardiovascular risks and complications of diabetes. Peroxisome proliferator-activated receptors play a role in metabolic regulation by helping facilitate glucose and fat metabolism. This article reviews the mechanism of action of drugs targeted to peroxisome proliferator-activated receptors and the role of the thiazolidinediones in diabetes management. The potential role of inflammation and dyslipidemia in the pathogenesis of diabetes is also discussed. (Adv Stud Pharm. 2006;3(6):220-228)

PROCEEDINGS

TYPE 2 DIABETES: THE ROLE OF THE THIAZOLIDINEDIONES*

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Cardiovascular disease is the leading cause of death and disability in people with diabetes. Complications from atherosclerosis account for approximately 80% of deaths and 75% of hospitalizations in patients with diabetes. Additionally, patients with diabetes are 2 to 4 times more likely to experience myocardial infarction or stroke than nondiabetics.1 Thus, the management of cardiovascular risks in these patients is just as critical as the management of blood glucose in reducing complications and improving outcomes.

Patients with type 2 diabetes mellitus (T2DM) almost always have insulin resistance accompanied by varying degrees of insulin deficiency. Most patients with T2DM are obese, which, along with increasing age and lack of physical activity, increases insulin resistance.2 Obese patients with T2DM have a high percentage of body fat in the abdominal cavity, which is called intra-abdominal or visceral fat. Visceral fat is a metabolically active substance responsible for producing a variety of hormones, vasoactive substances, and inflammatory mediators that lead to the metabolic syndrome (central obesity, hypertension, lipid abnormalities, and abnormal glucose metabolism) and contribute to the progression of cardiovascular disease.3

Many people with diabetes will die as a result of cardiovascular complications that often begin to develop long before the patient is ever diagnosed with diabetes. Patients with impaired glucose tolerance due to insulin resistance, referred to as “prediabetes,” are not only at risk of progressing to diabetes, but they are also at risk for cardiovascular disease as a result of the elevated blood pressure, lipid abnormalities, and abnormal clotting associated with insulin resistance.4 Patients with T2DM have a 3-fold increased risk of coronary artery disease, and those with prediabetes, without chronic hyperglycemia, have a 2-fold increased risk compared with nondiabetic persons.
Insulin resistance has also been implicated as a cause of atherosclerosis. In addition, evidence suggests that insulin resistance and hyperglycemia may contribute to endothelial dysfunction and ultimately lead to accelerated atherogenesis. This continuum of cardiovascular risk in diabetes is illustrated in Figure 1.\(^7\)\(^8\)\(^9\)

A study by Nievas et al. sought to determine the relationship between intra-abdominal fat, insulin sensitivity, and the lipoprotein profile.\(^10\) The study divided 196 healthy subjects (with no known history of diabetes or coronary disease) into 3 groups: lean insulin sensitive, lean insulin resistant, and obese insulin resistant. The study reported that intra-abdominal fat contributed to insulin resistance, although subcutaneous fat did not. Insulin-resistant groups had increased central adiposity, even among individuals of comparable weights. Although the lean groups had similar body mass indexes, insulin-resistant subjects had more visceral fat. These findings add to a growing body of evidence showing that rather than being an inert storage tissue, visceral fat is metabolically active and secretes atherogenic substances that contribute to the cardiovascular risks and complications of diabetes. These substances include: free fatty acids, which contribute to lipid abnormalities; adipokines (cytokines secreted by adipose tissue) such as angiotensinogen, which contributes to hypertension; interleukins and tumor necrosis factor, which contribute to vascular inflammation; and leptin, which contributes to obesity (Figure 2).\(^11\)\(^12\) Together, these substances mediate the decreased insulin sensitivity, increased insulin resistance, and, eventually, vascular inflammation, endothelial dysfunction, and atherosclerosis typical of patients with diabetes.

**The Role of Peroxisome Proliferator-Activated Receptor Agonists**

Similar to adipokines, peroxisome proliferator-activated receptors (PPARs) are involved in regulating metabolism. PPARs are a group of 3 nuclear receptor isoforms that act as transcription factors to control gene expression. PPARs play a crucial role in the regulation of cellular metabolism, including glucose ho-
meostasis, fatty acid oxidation, and adipocyte differentiation.\textsuperscript{13,15} **Troglitazone** (no longer on the market), pioglitazone, and rosiglitazone belong to a class of drugs known as thiazolidinediones (TZDs). The TZDs are 1 class among many therapeutic options for patients with T2DM. TZDs are the first group of drugs targeted to activate PPAR\(\gamma\), the most prevalent PPAR isoform in human tissue. These drugs reduce insulin resistance by sensitizing muscle and fat to the actions of insulin.\textsuperscript{13,16}

The proposed mechanism of action of TZDs is shown in Figure 3. TZDs cross the plasma membrane and pass through the cytoplasm to the nucleus, where they bind with PPAR\(\gamma\) that are in conformation with retinoic X receptors. This activated complex binds to specific DNA sequences located in the promoter region of responsive genes and activates gene transcription. Once insulin binds to its receptor, it also sends a signal into the nucleus to activate transcription factors that regulate the transcription of insulin-responsive genes. Although their precise mechanism of action is unknown, TZDs enhance the action of insulin and decrease insulin secretion. These agents help to normalize glucose levels by increasing peripheral glucose utilization and decreasing hepatic glucose production.\textsuperscript{16,17} PPAR\(\gamma\) receptor agonists have been shown to decrease insulin resistance and preserve pancreatic beta cell function.\textsuperscript{18} Importantly, these agents also improve the cardiovascular risk profile by improving dyslipidemia, and decreasing renal microalbumin excretion, blood pressure, free fatty acid, and C-reactive protein levels. Activators of PPAR\(\gamma\) also increase adiponectin levels.\textsuperscript{18}

**The Importance of Adiponectin**

Adiponectin is a protein hormone that modulates several metabolic processes, including glucose regulation and fatty acid catabolism. Adiponectin, secreted from adipose tissue into the bloodstream, plays a role in metabolic disorders such as T2DM, obesity, and atherosclerosis. Serum levels of the protein correlate with systemic insulin sensitivity. Unlike other adipokines that are secreted at higher-than-normal levels in obesity and the metabolic syndrome, adiponectin secretion is decreased in these states.\textsuperscript{19}

Researchers have found that adiponectin functions differently in obese patients with diabetes than in people without diabetes or lean people with diabetes. Obese patients with diabetes have significantly lower adiponectin levels as compared with lean diabetics, lean nondiabetics, and obese nondiabetics (\(P < .025\)).\textsuperscript{20} Pajvani et al measured adiponectin levels in a subgroup of 40 women with gestational diabetes treated with troglitazone for 3 months.\textsuperscript{21} Over this short period of time, insulin sensitivity increased, and this increase was associated with increased serum adiponectin levels.

In a case-control study of data from the Health Professionals Follow-Up Study, the relationship between adiponectin and cardiovascular risk was assessed in 18 225 men over a 6-year period. Patients with adiponectin levels in the highest quintile demonstrated a significantly lower risk of myocardial infarction compared with those whose adiponectin levels were in the lowest quintile (relative risk, 0.39; 95% confidence interval, 0.23–0.64; \(P < .001\)).\textsuperscript{22}

The TZDs appear to compensate for the adiponectin deficit seen in obese patients with diabetes. Through the mechanism of action previously discussed, TZDs cross the cell membrane and combine with the PPAR\(\gamma\) receptors. Through the activation of gene transcription, PPAR\(\gamma\) receptors and their ligands have been reported to increase adiponectin

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**Figure 3. Thiazolidinediones: Mechanism of Insulin Sensitization**

![Diagram](https://example.com/diagram.png)

PPAR = peroxisome proliferator-activated receptor; RXR = retinoid X receptor; TF = transcription factors; TZD = thiazolidinedione.

Adapted with permission from Saltiel et al.
mRNA levels. A recent study demonstrated that rosiglitazone can increase plasma levels of adiponectin more than 2-fold as compared with placebo (P <.0005) after just 3 months of use. This may account for the reduced cardiovascular risk reported in TZD-treated patients.

**INFLAMMATION AND DIABETES**

Researchers are also exploring inflammation as a contributing mechanism in diabetes development and the associated cardiovascular risk. Ridker et al explored observational data from the Women’s Health Study to assess whether C-reactive protein levels added prognostic information to the metabolic syndrome. In this study, metabolic syndrome was diagnosed using modified National Cholesterol Education Program Adult Treatment Panel III criteria that substituted body mass index >26.7 kg/m² for waist circumference >35 to define obesity in women. Women without diabetes at baseline (14,719) were followed for 8 years. The study found a relationship between the number of metabolic syndrome markers (e.g., central obesity, high triglycerides, low high-density lipoprotein, high blood pressure, and glucose abnormalities) and C-reactive protein levels: as the number of markers increased, so too did C-reactive protein. Women with all 5 markers were found to have the highest C-reactive protein levels. At all levels of severity of the metabolic syndrome, C-reactive protein added prognostic information on subsequent cardiovascular risk.

Further supporting the hypothesis that inflammation may play an important role in the pathogenesis of diabetes was a study that followed 1047 nondiabetic individuals for 5 years. Concentrations of C-reactive protein, fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) in study subjects were recorded. Subjects who developed diabetes during the study had significantly higher baseline levels of C-reactive protein (median [interquartile range]; 2.40 [1.29, 5.87] vs 1.67 mg/L [0.75, 3.41]; P = .0001) and PAI-1 (24 [15, 37.5] vs 16 mg/mL [9, 27]; P = .0001); a smaller trend was observed for fibrinogen (mean ± SD; 287.8 ± 58.8 vs 275.1 ± 56.0 mg/dL; P = .013).

Strategies to reduce C-reactive protein are an active area of study in the treatment of diabetes. One such study of 357 T2DM patients taking rosiglitazone (4 mg or 8 mg) reported a significant reduction in C-reactive protein levels over 26 weeks (P <.05). Another study, which was conducted in endothelial cells, demonstrated that the inflammatory adipokine tumor necrosis factor-α promotes secretion of PAI-1. As discussed earlier, this plays a role in the development of atherosclerosis in patients with diabetes. This effect was blunted with troglitazone treatment.

Similar effects have also been demonstrated with metformin, but to a lesser extent. Nage et al randomized 27 persons with T2DM to metformin 2.5 g or placebo for 12 weeks to investigate the effects of metformin on glycemic control, insulin resistance, and risk factors for cardiovascular disease. At study end, PAI-1 activity was significantly lower in the metformin group than in the placebo group (difference of 5.3 U/mL, P = .001). A significant improvement in glucose control was also reported: A1c was reduced by 1.3%, and fasting glucose by 55 mg/dL.

Given the evidence surrounding cardiovascular risk reduction with troglitazone and metformin, combination therapy with 2 insulin-sensitizing agents has been studied to determine whether there might be cumulative effects. In one such study, Weissman et al treated patients with T2DM with open-label metformin 500 mg twice a day for at least 3 weeks. The patients were then randomized to receive rosiglitazone in combination with metformin or to continue metformin alone, but at an increased dose. Combined insulin-sensitizer therapy was associated with significantly greater reductions in C-reactive protein and PAI-1 levels as compared with treatment with metformin alone. Thus, combining insulin-sensitizers seems to have a much more pronounced effect than using metformin alone. The theoretical model these studies suggest is that the anti-inflammatory effects of PPAR activation may form the basis of a new approach to blunting atherosclerosis. Direct effects on the vascular wall, in addition to indirect effects of improving glucose and lipid metabolism, are mediated via adipocytes and other peripheral tissue (Figure 4).

**DYSLIPIDEMIA IN PATIENTS WITH DIABETES**

Several studies have demonstrated that people with diabetes and insulin resistance are more likely to experience dyslipidemia than nondiabetics. Patients with diabetes have elevated triglycerides and low-density lipoprotein cholesterol (LDL-C) levels, in addition to low high-density lipoprotein cholesterol (HDL-C). In patients with insulin resistance, LDL-C levels are similar.
to or only slightly elevated compared with the general population.\(^9\) However, it is important to look beyond the numbers to assess global risk in these individuals.

In patients with insulin resistance, LDL particles are more atherogenic than LDL particles in the general population because of a shift toward a greater proportion of small, dense particles.\(^9\) These particles are more susceptible to oxidation and, therefore, bind to and penetrate into the arterial walls more readily. They are toxic to endothelial cells, where they promote PAI-1 and thromboxane production, in addition to binding to LDL scavenger receptors, inhibiting their beneficial effects.\(^9\)

The relationship between LDL particle size and health outcomes was the subject of a recent clinical trial. In this study, 2072 men who were free from ischemic heart disease were classified as having large (260 Å in diameter) or small (<255 Å in diameter) LDL particles. The study confirmed a strong association between small LDL particles and the risk of ischemic heart disease in men, particularly over the first 7 years of follow-up. In contrast, large LDL particles were not associated with an increased risk of ischemic heart disease over the 13-year follow-up (RR = 0.76; \(P = .07\)).\(^{40}\)

In patients who are not treated with statins, studies suggest that pioglitazone and rosiglitazone have differing effects on particle size and lipid levels.\(^{41}\) In patients receiving statin therapy, some studies suggest these differences are eliminated, whereas other studies suggest they persist.\(^{42,43}\) Thus, the degree and clinical significance of differences among PPAR\(_\gamma\) activators with regard to their effects on lipids in patients with diabetes remains controversial. One study assessed the differences between the lipid effects of these 2 agents in patients with T2DM who were not taking statins. The study randomized 802 patients to use pioglitazone or rosiglitazone over a 6-month period with dose escalation to maximum 45 mg once a day pioglitazone or 4 mg twice a day rosiglitazone. At study end, both treatment groups achieved comparable glucose control (6.9% \(\Delta_1\)), but the lipid profiles between groups varied substantially. Whereas pioglitazone produced a 12% reduction in triglycerides, rosiglitazone increased triglycerides by nearly 15%. LDL-C levels increased with both drugs, but to a greater extent with pioglitazone (5.2 +/- 0.5 vs 2.4 +/- 0.5 mg/dl; \(P < .001\)); non-HDL increase with pioglitazone was smaller than with rosiglitazone (12.3 +/- 1.6 vs 21.3 +/- 1.6 mg/dl; \(P < .001\)). Triglyceride levels were reduced by 51.9 +/- 7.8 mg/dl with pioglitazone, but were increased by 13.1 +/- 7.8 mg/dl with rosiglitazone (\(P < .001\) between treatments). At baseline, mean LDL particle size was 20.0 nm in the pioglitazone group and 20.1 nm in the rosiglitazone group (\(P = \text{ns}\)). At week 24, a larger increase was observed in the pioglitazone group than in the rosiglitazone group for mean

![Figure 4. PPAR Activation and Atherosclerosis: A Hypothesis](image)

**Figure 4.** PPAR Activation and Atherosclerosis: A Hypothesis

| FFA = free fatty acid; HDL = high-density lipoprotein; PPAR = peroxisome proliferator-activated receptor |
| Adapted with permission from Plutzky\(^8\) |

![Figure 5. Head-to-Head Clinical Trial: Fasting Triglyceride, HDL-C, and Non-HDL-C Results](image)

**Figure 5.** Head-to-Head Clinical Trial: Fasting Triglyceride, HDL-C, and Non-HDL-C Results

\(*P < .01\) between treatment groups; \(\dagger P < .001\) vs baseline; \(\ddagger P < .05\) vs baseline; \(\ddagger P = \text{ns}\) vs baseline; HDL-C = high-density lipoprotein cholesterol |

Adapted with permission from Goldberg et al.\(^{44}\)
LDL particle size; mean percent change from baseline was 2.4% (P .001) (+0.5 nm) and 1.7% (P .001) (+0.3 nm), respectively (Figure 5).61 PPARγ activation has also been associated with modest, but sustained blood pressure reduction.61

Atherosclerosis and Myocardial Infarction Outcomes

Multiple studies have provided evidence that PPARγ activation reduces the important clinical endpoint of atherosclerosis. All 3 TZDs—troglitazone, pioglitazone, and rosiglitazone—have demonstrated an ability to reduce intimal medial thickness, suggesting that these agents mitigate the inflammatory process in addition to controlling blood glucose.45-48 Animal studies have shown this effect is additive when PPARγ activators are added to statin therapy.69 Accumulated data in human studies confirm that TZDs blunt neointimal proliferation in patients with T2DM who undergo stenting. A series of 3 reports from a Japanese group evaluated troglitazone added to diet or conventional glucose-lowering therapy, or pioglitazone added to conventional glucose-lowering therapy.70-72 A fourth, smaller trial found a trend toward benefit with rosiglitazone added to metformin or other glucose-lowering therapy. However, in this trial, the TZD was added after stenting (in contrast with the other trials, which added the drug prior to stenting). In addition, a low dose of rosiglitazone (4 mg) was given in the first month, with a full dose (8 mg) given for the remainder of the trial.73 Preliminary data also suggest that PPARγ activators reduce myocardial infarction (MI), with the greatest relative risk reduction (49%) observed with TZD treatment.74 Additional research in this area is needed.

A prospective study of 5238 patients with T2DM was conducted to assess whether pioglitazone could reduce cardiovascular events in patients at high risk because of atherosclerotic disease.26,27 Subjects were randomized to pioglitazone (initial dose 15 mg, with forced titration to 30 mg or 45 mg, depending on tolerability) or placebo. At baseline, study subjects were taking several drugs known to reduce cardiovascular risk, including antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors and beta blockers, antiplatelet drugs such as aspirin, and lipid-modifying drugs such as statins and fibrates.27 The primary outcome (all-cause mortality, nonfatal MI, stroke, acute coronary syndromes, leg amputation, and coronary or peripheral revascularization) was reduced an insignificant 10% over 36 months in pioglitazone patients (compared with placebo, P = .095). The main secondary outcome of all-cause mortality, MI, or stroke was significantly reduced 16% in pioglitazone patients compared with placebo (P = .027), although divergence in the survival curves suggests that even greater risk reduction might have been achieved with longer treatment duration.27 Notably, treated patients did experience a higher rate of edema and heart failure, suggesting that cardiovascular benefits and risks should be weighed on a patient-by-patient basis. Additional studies are needed to confirm the benefit of TZDs in patients with T2DM and to more fully characterize the mechanism and prognosis of treatment-related heart failure.74 Several outcome-based studies are currently under way to further assess whether intensive treatment with TZDs, insulin, and ACE inhibitors can reduce cardiovascular events in the setting of T2DM.

Discussion

Dr Malone: What we learned from Dr Bartel’s presentation was that more complex therapy and more complex science do not necessarily lead to better outcomes. The pharmacist has the role of responsible, evidence-based, conscientious review of prescribed medication. I think it is important for hospital and retail pharmacists to stay focused on the basics: glucose control and blood pressure control, with medications best suited to the individual patient. We can stray from the basics when you emphasize science without proven outcome.

Dr Holaway: In terms of PPAR activators, their mechanism of action involves G-protein coupled receptors. Some pharmacogenomic research suggests that response to PPAR agonists may be dependent on patient genotype. However, the big question is how we keep patients with diabetes from dying early. The overwhelming evidence shows that we can do that by lowering LDL levels to <70 mg/dL to reduce cardiovascular risk. With regard to the importance of C-reactive protein effects, nearly every cardiologist will question the value of those lab tests because the evidence to support a connection between C-reactive protein and cardiovascular outcomes is not yet conclusive. Other markers, such as adiponectin and ApoB...
[apolipoprotein B] levels, are also believed to contribute to particle size and atherogeneity, but that has not been absolutely proven. From my point of view, I think we need to stay focused on the basics.

**Dr Cornell:** Going back to the basics, if the pharmacist can simply provide patients with a diabetes checklist and ask them to discuss it with their physician or refer them to a certified diabetes educator, that can make a significant difference in outcomes.

Regarding TZDs, these drugs are attempting to target the actual cause of the disease instead of treating its symptoms; therefore, they represent a dramatic improvement over the older medications. However, some managed care organizations will not include TZDs on their formularies because of cost. I advise patients to try the natural TZDs: you can transcribe GLUT-4 [glucose 4] transporters quicker and faster, and better with exercise.

**Dr Bartels:** I agree. However, if we are looking at trying to develop a medication management scheme, how do we do that? There is not agreement among the endocrinology specialists on what treatment is first- or second-line therapy. For obese patients, many specialists will agree that metformin is first line but do you add a sulfonylurea or glitazone next? Where does insulin fit into the medication regimen?

**Dr Triplitt:** Several algorithms are available to address this, including the algorithm the American Diabetes Association recently published. The algorithm I have personally worked on and used is the Glycemic Control Algorithm published by the Texas Diabetes Council (available at: http://www.dshs.state.tx.us/diabetes/hcstand.shtm), which is substantially evidence based and referenced. It includes information related to combination therapy and even includes several insulin therapy algorithms and teaching tools. I highly recommend the use of these algorithms as a starting point for offering pharmacists some insight into how evidenced-based diabetes therapy could be prescribed.

**Dr Holaway:** Dr Bartels presented some interesting data regarding reduction of cardiovascular risk with TZDs. One recent trial presented at the American College of Cardiology annual conference found that sulfonylureas actually increased cardiovascular risk.²⁵

**Dr Bartels:** There has also been other evidence to support that. But still, managed care organizations will frequently recommend use of sulfonylureas as second-line agents despite the evidence that TZDs, particularly in combination with metformin, are a better therapeutic option.

**Dr Cornell:** The prescribing habits of primary care physicians not trained in diabetes management come into play here. How many pharmacists feel confident enough to ask the physician to consider another therapeutic approach? It is important to provide pharmacists with tools for how to undertake such communications and interventions with healthcare providers.

**Dr Johnson:** Medication management—looking at a patient’s profile, making sure he is on the right medicine, taking the right dose, and that he is actually taking the medicine—is something the pharmacist can easily accomplish by looking at the medication records. A 2-minute consult with patients who are not taking blood pressure medication will help assess whether they have checked their blood pressure recently and whether they should be on medication.

**Dr Cornell:** By advising patients to have a blood pressure and blood glucose monitor at home, we can put them in the driver’s seat of managing their disease.

**Dr Malone:** What we do know is that 1 therapeutic approach is not going to fix anything. If you take out lifestyle interventions, you are looking at basically 6 different types of medication that a patient with diabetes needs to take, and the pharmacist needs to know that. For T2DM, these medications include: a statin, an aspirin, an ACE/angiotensin receptor blocker (ARB), hydrochlorothiazide combined with an ACE/ARB to reach blood pressure goals, and combination agents based on patient specifics (first-tier metformin and sulfonylureas, second-tier insulin, exenatide, and TZD).

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