Nonhypoglycemic Effects of Thiazolidinediones

Akhil A. Parulkar, MD; Merri L. Pendergrass, MD, PhD; Ramona Granda-Ayala, MD; Tri Richard Lee, MD; and Vivian A. Fonseca, MD

The thiazolidinediones are a new class of compounds for treatment of type 2 diabetes. Troglitazone became available in the United States in 1997 but was withdrawn from the market in March 2000 because it caused severe idiosyncratic liver injury. Rosiglitazone and pioglitazone have been available since 1999. Because these drugs directly improve insulin resistance and decrease plasma insulin levels (a risk factor for coronary artery disease), they may decrease risk for cardiovascular disease in patients with type 2 diabetes. Research on the non–glucose lowering effects of troglitazone and, to a lesser extent, of rosiglitazone and pioglitazone have demonstrated changes in several cardiovascular risk factors associated with the insulin resistance syndrome. These beneficial effects include a decrease in blood pressure, correction of diabetic dyslipidemia, improvement of fibrinolysis, and decrease in carotid artery intima–media thickness. Other in vitro effects related to the ability of these agents to bind a newly described class of receptors (peroxisome proliferator–activated receptors) may also have implications for atherosclerosis. However, these drugs increase low-density lipoprotein (LDL) cholesterol levels and may favorably change LDL particle size and susceptibility to oxidation (although the implications of the latter changes are not clear). Furthermore, these drugs tend to cause weight gain. The authors' enthusiasm for these drugs has diminished somewhat because of reported adverse events, including rare liver failure. Nevertheless, because of the mechanism of action of the thiazolidinediones, clinical trials designed to determine whether they (or similar "insulin sensitizers") decrease cardiovascular events in people with type 2 diabetes will be of interest.

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For author affiliations and current addresses, see end of text.

The thiazolidinediones are a new class of compounds for treatment of type 2 diabetes mellitus. The efficacy of these drugs in decreasing plasma glucose levels is well established (1–6). Troglitazone, a member of this class, became available for clinical use in the United States in 1997 but was withdrawn in March 2000 because of reports of severe hepatic injury. Rosiglitazone and pioglitazone became available in 1999 and are approved as monotherapy and in combination with other oral hypoglycemic agents; pioglitazone is also approved in combination with insulin. The glucose-lowering effects of the thiazolidinediones are mediated primarily by decreasing insulin resistance at the level of the muscle and thereby increasing glucose uptake. To a lesser extent, they decrease insulin resistance in the liver and thereby decrease hepatic glucose production (1). The mechanisms of action of the thiazolidinediones are still being investigated; however, some of their actions are mediated through binding and activation of the peroxisome proliferator–activated receptor-γ (PPAR-γ), a nuclear receptor that has a regulatory role in differentiation of cells, particularly adipocytes (7). This receptor is also expressed in several other tissues, including vascular tissue (7). The thiazolidinediones also decrease plasma concentrations of free fatty acids and in doing so may indirectly improve insulin sensitivity (8). Thiazolidinediones may also activate other members of the PPAR family of receptors (such as PPAR-α and PPAR-δ), which along with PPAR serve as gene transcription factors (9). These receptors are present in many tissues, and although their functions are still being elucidated, the data suggest that they have many important effects. Thus, the thiazolidinediones may affect many organ systems and disease processes (9).

Substantial evidence indicates that insulin resistance, along with compensatory hyperinsulinemia, not only contributes to hyperglycemia in type 2 diabetes but also may play a pathophysiologic role in other metabolic abnormalities. These include high levels of plasma triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, hypertension, abnormal fibrinolysis, and coronary heart disease (10–13). This cluster of abnormalities is called the insulin resistance syndrome, syndrome X, or the metabolic syndrome (14). Since thiazolidinediones directly improve insulin resistance (2), it has been proposed that they may correct other abnormalities of the insulin resistance syndrome, as well as improve hyperglycemia. Thus, use of these agents to treat patients with type 2 diabetes may confer benefits beyond decreases in glucose level. Because of the effects of thiazolidinediones on hyperinsulinemia and insulin resistance, their vascular effect is a subject of considerable research interest (**Table 1**).

We discuss the nonhypoglycemic effects of the thia-

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zolidinediones that have been described in the literature. We emphasize their potential to improve other components of the insulin resistance syndrome, such as dyslipidemia, hypertension, impaired fibrinolysis, and atherosclerosis. We discuss their effects in other insulin-resistant states, such as the polycystic ovary syndrome; examine their effects on body weight and composition; and draw attention to other potential effects currently being investigated. Much of the data presented relates to troglitazone (the most extensively studied thiazolidinedione) but may be relevant to the other thiazolidinediones. In vitro data support the possibility of a class effect, although proof from currently ongoing clinical trials (Freed M, SmithKline Beecham; Wishner W, Takeda Pharmaceuticals. Personal communication) is needed. Long-term clinical trials are also needed to determine whether such reduction in risk factors will prevent cardiovascular disease.

Cardiovascular Effects

Epidemiologic studies have demonstrated that hyperinsulinemia, a marker for insulin resistance, is an independent risk factor for cardiovascular disease (47). Correction of insulin resistance may be clinically important in type 2 diabetes and may decrease risk for cardiovascular disease. In the United Kingdom Prospective Diabetes Study, treatment with metformin (another drug that decreases hyperinsulinemia and insulin resistance) was shown to produce greater reduction in cardiovascular disease events and mortality than sulfonylureas and insulin (48). The latter drugs decreased blood glucose level to a similar degree as metformin but did not decrease plasma insulin concentrations. This effect may have been mediated through a decrease in insulin resistance, although other effects of metformin, such as improvement in lipid profile, improved fibrinolysis, and prevention of weight gain, may be important (48). Further clinical trials are needed to determine whether treatment of diabetes with agents that reduce insulin resistance (such as the thiazolidinediones and metformin) is superior to use of agents that stimulate insulin secretion (such as sulfonylureas). The National Institutes of Health recently initiated such a clinical trial (49).

Cardiac Output and Left Ventricular Mass

Initial studies of cardiac function with thiazolidinedione therapy were performed because of reported cardiac enlargement in animals treated with drugs of this class (3). Ghazzi and colleagues (3) investigated whether patients with type 2 diabetes treated with troglitazone, 800 mg/d (a dosage higher than that used in clinical practice), or glyburide experienced an increase in cardiac mass or functional impairment. Two-dimensional echocardiography and pulsed Doppler ultrasonography demonstrated that neither troglitazone nor glyburide changed left ventricular mass index significantly over 48 weeks. However, substantial increases in stroke volume index and cardiac index and a statistically significant decrease in diastolic pressure and estimated peripheral resistance were observed in troglitazone-treated patients but not glyburide-treated patients, who experienced no change (3). These findings are reassuring and contrast with those of animal studies. Similar studies of rosigli-

Table 1. **Effects of the Thiazolidinediones on Cardiovascular Risk Factors***

Risk Factor	Effect	Reference
Lipids	Decrease in triglyceride levels; increase in HDL cholesterol and LDL cholesterol levels	3, 15–19
	Decrease in LDL cholesterol oxidation	20–24
	Increase in size of LDL cholesterol particles	20
Coagulation and fibrinolysis	Decrease in PAI-1 and fibrinogen levels	25–27
Platelet aggregation†	Decrease in platelet aggregation	28
Body weight and fat distribution	Decrease in intra-abdominal fat mass; no change in total body fat or weight	29
Microalbuminuria	Decrease in microalbuminuria	30–33
Direct vascular effects	Decrease in intima–media compact thickness	34
	Decreases in blood pressure	3, 35, 36
	Increase in cardiac output, stroke volume, and peripheral vascular resistance	3
	Coronary artery relaxation by decrease in cytosolic calcium; regulation of monocyte and macrophage function in atherosclerotic lesions	37–40
	Decrease in brachial artery vasoactivity	41, 42
	Vasorelaxant effect on human small arteries‡	43
	Increase in forearm blood flow	42
	Decrease in migration of vascular smooth-muscle cells	44–46
	Decrease in calcium influx and attenuation of vascular contraction	37, 38

* HDL = high-density lipoprotein; LDL = low-density lipoprotein; PAI-1 = plasminogen activator inhibitor type 1.
† This effect has been noted with troglitazone but not pioglitazone; may be an effect of vitamin E.
‡ This effect has been demonstrated by troglitazone and not rosiglitazone.

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tazone and pioglitazone have also demonstrated no adverse effect on cardiac mass or function (4, 5, 50). Nevertheless, thiazolidinediones are currently contraindicated in patients with advanced heart failure because of their effect on plasma volume (43).

Lipid Metabolism and Oxidation

Insulin resistance and type 2 diabetes are associated with a characteristic pattern of lipid abnormalities, including an elevated plasma triglyceride level and a low plasma high-density lipoprotein (HDL) cholesterol level. Plasma levels of low-density lipoprotein (LDL) cholesterol do not differ from those in nondiabetic persons, but qualitative changes in LDL cholesterol, with an increase in small, dense LDL cholesterol, are common (15, 51–55). In several clinical trials, troglitazone therapy significantly lowered triglyceride levels (3, 16, 17) and increased HDL cholesterol levels in persons with type 2 diabetes (3, 16). A modest increase in LDL cholesterol level was observed, but the ratio of LDL cholesterol to HDL cholesterol and apolipoprotein B levels did not change. Data published to date indicate that all of the thiazolidinediones increase HDL cholesterol levels and that troglitazone and pioglitazone decrease triglyceride levels (3–5, 16–18). A recent small study (19) demonstrated a possible difference in the lipid-lowering effects of thiazolidinediones: Compared with rosiglitazone, pioglitazone seemed to produce a greater decrease in the triglyceride level and a lesser increase in the LDL cholesterol level. However, the study was neither randomized nor double-blind. Further studies on such possible differences are therefore needed.

Similar changes in lipid levels have been observed in nondiabetic persons with insulin resistance. Like troglitazone, pioglitazone significantly reduced fasting serum levels of triglycerides and increased fasting levels of HDL cholesterol in 20 patients with type 2 diabetes (56). The effects of the thiazolidinediones on LDL cholesterol are more complex. Persons with insulin resistance or type 2 diabetes are more likely than nondiabetic persons to have small, dense, triglyceride-rich LDL cholesterol particles (51). These characteristics may make LDL cholesterol susceptible to oxidation. Oxidative modification confers atherogenic properties on LDL cholesterol particles; this may be a key initial event in the progression of atherosclerosis (15) and is a measurable risk factor (52–55). Evidence suggests that PPAR-γ may be an important regulator of foam-cell gene expression and that oxidized LDL cholesterol regulates macrophage gene expression through activation of PPAR-γ (57). Furthermore, PPAR-γ promotes uptake of oxidized LDL cholesterol by macrophages (58). Thus, an interaction between PPAR-γ and oxidized LDL cholesterol may be important in the development of atherosclerosis in diabetes.

Thiazolidinediones have been shown to substantially increase levels of total cholesterol and LDL cholesterol (4, 5). However, the increase is predominantly in the larger buoyant particles of LDL cholesterol, which may be less atherogenic than small, dense LDL cholesterol particles. Levels of the latter have been shown to decrease with troglitazone therapy (20). These data were confirmed in other studies demonstrating that troglitazone increased the resistance of LDL cholesterol to oxidation (20–24). Whether these effects are produced by the other thiazolidinediones or were related to vitamin E moiety in the troglitazone molecule is unclear and warrants further study. Although the effects of the thiazolidinediones on LDL cholesterol oxidation are in theory appealing, their role in preventing cardiovascular events is unclear. Of note, vitamin E, which also has antioxidant and free radical–scavenging properties, did not reduce cardiovascular outcomes in the Heart Outcomes and Prevention Evaluation study (59).

In summary, all of the thiazolidinediones appear to substantially increase HDL cholesterol levels. Troglitazone and pioglitazone have been shown to decrease triglyceride levels. All of the thiazolidinediones increase LDL cholesterol levels, although changes in the size of LDL cholesterol particles may make the cholesterol less susceptible to oxidation. The differences between the thiazolidinediones in their lipid effects may reflect the fact that different populations have been studied; a randomized comparative trial is needed to determine whether a true difference exists.

Effects on Blood Pressure and Vascular Resistance

The prevalence of hypertension is 1.5-fold to 2-fold higher in patients with type 2 diabetes than in patients without diabetes (60, 61). This is not surprising; hypertension is associated with substantial insulin resistance, even in patients without diabetes. If insulin resistance is etiologically related to hypertension, the thiazolidinedi-

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ones, which decrease resistance, may also decrease blood pressure. Troglitazone and rosiglitazone have been found to decrease blood pressure substantially (4). This effect has been observed in patients with type 2 diabetes and hypertension (35), nonhypertensive persons with type 2 diabetes (3), and obese persons without diabetes (62, 63). Sung and associates (36) found that during the stress of a mental arithmetic test, patients with type 2 diabetes had a significant increase in systolic blood pressure compared with controls. Treatment with troglitazone but not glyburide attenuated this stress-induced increase in blood pressure (36). In another study, decreases in mean blood pressure correlated significantly with reductions in plasma insulin level (35).

These findings are consistent with the hypothesis that troglitazone decreases blood pressure by improving insulin resistance (35). Potential mechanisms for the hypotensive effects of these drugs (other than improvement of insulin resistance) include improved endothelium-dependent vasodilatation, decrease in calcium influx and calcium sensitivity of the contractile apparatus (37, 38), and inhibition of endothelin-1 expression and secretion in bovine vascular endothelial cells through activation of PPAR-γ (64).

Pioglitazone therapy decreased arterial pressure in rat models of hypertension (65–67). These data were confirmed in other animal and in vitro studies, but data in humans are lacking. Although rosiglitazone may cause vasoconstriction in preconstricted human arteries in vitro, clinical trial data suggest a trend toward a decrease in blood pressure in patients treated with rosiglitazone (4). In insulin-resistant Zucker rats, rosiglitazone treatment was shown to prevent the development of hypertension and also partially protected against impaired endothelial function (68).

Effects on Vascular Reactivity and Endothelial Function

In healthy persons, insulin dilates the arterioles that supply skeletal muscle, probably through enhancement of nitric oxide production (36, 69). Although the clinical significance of this observation is unclear, defects in nitric oxide synthesis are thought to be important in the pathogenesis of cardiovascular disease in persons with type 2 diabetes (11, 69, 70). In obese persons with insulin resistance and patients with type 2 diabetes, this vasodilatory action of insulin may be decreased—an abnormality that might be attributable to impairment in the ability of the endothelium to produce nitric oxide or enhanced inactivation of nitric oxide (69, 70). In addition, endothelium-dependent vasodilatation mediated by insulin appears to be related to insulin-mediated glucose disposal (69, 71).

The ability of blood vessels to dilate in response to stimuli, including ischemia, is called vascular reactivity or flow-mediated dilatation. Brachial artery vasoactivity is a noninvasive method of assessing arterial endothelial function in vivo (72). Since endothelial injury is an early event in atherogenesis, it has been suggested that abnormal flow-mediated dilatation precedes development of structural changes in the vessel wall (72). Furthermore, in young adults, impaired flow-mediated dilatation is associated with the same risk factors known to predispose to atherosclerosis and its complications; such factors include tobacco use, hypercholesterolemia, and diabetes mellitus (72). Avena and colleagues (41) demonstrated normalization of impaired brachial artery vasoactivity in troglitazone-treated persons with peripheral vascular disease. In contrast, in a study of obese persons with insulin resistance, Tack and associates (63) demonstrated that troglitazone administration improved insulin sensitivity but had no effect on endothelium-dependent or endothelium-independent vascular responses.

Endothelium-dependent response to acetylcholine in the coronary arteries has been studied in a small number of diabetic patients with vasospastic angina (73). The vasodilatory response improved substantially and anginal episodes decreased after therapy with troglitazone (400 mg/d for $>$4 months) but not diet or glibenclamide. In vitro data suggest that other thiazolidinediones may have the same effect.

Taken together, these studies suggest that troglitazone improved endothelial function. Prospective clinical trials are needed to determine whether this improvement will be seen with the other thiazolidinediones and whether it slows the development of atherosclerosis.

Effects on the Vascular Wall and Atherosclerotic Plaque

Recent reports have established the presence of PPAR-γ in human endothelial cells (74), vascular smooth-muscle cells (44), monocytes and macrophages (39), and human arterial lesions (39, 75), all of which play important pathogenetic roles in atherosclerosis.

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This finding suggests that PPAR-γ agonists, such as the thiazolidinediones, may directly affect the molecular mechanisms involved in atherosclerosis.

Vascular smooth-muscle cell proliferation and migration are responses to arterial injury and are important in restenosis and atherosclerosis. In vitro studies have demonstrated that troglitazone, rosiglitazone, pioglitazone, and prostaglandin J2 (the endogenous ligand of PPAR-γ) inhibit vascular smooth-muscle cell proliferation and migration (44–46, 76). Furthermore, neointimal thickening after balloon injury to the aorta is attenuated by treatment with troglitazone (45). Long-term studies on cardiovascular events have not been done, but short-term studies have demonstrated an effect of troglitazone on the arterial wall in people with type 2 diabetes.

Carotid intima–media complex thickness, which is associated with insulin resistance, can be measured noninvasively by using B-mode ultrasonography (34, 72). This measurement may serve as a surrogate marker for atherosclerotic events because patients with increased intima–media complex thickness have a higher rate of cardiovascular events over time (77). Treatment with troglitazone significantly decreased intima–media complex thickness as early as 3 months after the administration; this decrease was maintained over 6 months, but no further decrease occurred. No relation was observed between decrease in intima–media complex thickness and changes in the glycosylated hemoglobin or postprandial triglycerides, suggesting that this decrease is mediated through other mechanisms. These effects of the thiazolidinediones may be direct cellular effects on the atherosclerotic process that are not linked to their effects on insulin resistance.

Recent work has provided important insight into the nature of atherosclerosis and the molecular changes that may contribute to acute cardiac events (78). Disruption of the fibrous cap, or plaque rupture, exposes the highly thrombogenic lipid core present in most arterial atherosclerotic lesions to the coagulation factors present in the circulation, thereby precipitating most acute myocardial events (79). Matrix metalloproteinases, a family of highly regulated enzymes that can degrade collagens and other matrix proteins, are thought to contribute to this process. Monocyte-derived macrophages and vascular smooth-muscle cells are sources of these matrix metalloproteinases.

Troglitazone has been shown to inhibit the expression and functional activity of matrix metalloproteinase-9 in human monocyte-derived macrophages (39) and human vascular smooth-muscle cells (44). Activation of PPAR-γ may also have an anti-inflammatory effect in monocytes and macrophages (80). All of these molecular observations must be integrated into the rapidly emerging and expanding picture of PPARs and their various agonists in vascular cells (40).

Fibrinolysis, Coagulation, and Platelet Aggregation

Elevated plasma levels of plasminogen activator inhibitor type 1 (PAI-1) is associated with cardiovascular disease (14). Levels of PAI-1, the primary inhibitor of endogenous-type fibrinolysis, are elevated in persons with diabetes and in obese nondiabetic persons with insulin resistance. Many data support the importance of an elevated PAI-1 level in the pathogenesis of cardiovascular disease, thrombosis, and myocardial infarction. Impaired fibrinolytic function in diabetes correlates with the severity of vascular disease in diabetes (80) and is a risk factor for myocardial infarction in both diabetic and nondiabetic persons. An increased PAI-1 level is now recognized as an integral part of the insulin resistance syndrome and correlates significantly with plasma insulin and triglyceride levels. Insulin infusion during and after infarction, which is known to improve outcomes, has been shown to decrease plasma PAI-1 levels (81). Immunohistochemical analysis of coronary lesions from patients with coronary artery disease have demonstrated an imbalance of the local fibrinolytic system with increased coronary artery tissue levels of PAI-1 in patients with type 2 diabetes (82). Impaired fibrinolysis has also been noted in other insulin-resistant states, such as the polycystic ovary syndrome (25). In patients with type 2 diabetes and those with diabetes and the polycystic ovary syndrome, troglitazone treatment significantly decreased plasma levels of PAI-1 (25, 26).

In vitro studies of troglitazone have demonstrated not only a direct effect on the vessel wall, leading to decreased synthesis of PAI-1, but also an indirect effect on hepatic synthesis secondary to attenuation of hyperinsulinemia (27). Metformin therapy also decreases PAI-1 levels, which supports the notion that this change is mediated by a decrease in insulin resistance (83). In vitro data suggest that pioglitazone may also have a similar effect on PAI-1. Therefore, reduction of PAI-1 levels

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may be a class effect of insulin sensitizers. Although increase in PAI-1 level is associated with increased risk for myocardial infarction, no study has demonstrated diminution of this risk by reduction of the plasma PAI-1 level. Clinical trials are needed to demonstrate such a benefit. Until then, the American Diabetes Association recommendations for aspirin use should be followed.

Effects on the Pancreas

Although the thiazolidinediones do not stimulate insulin secretion, recent studies suggest that they affect pancreatic β-cell function. This action may be important because restoration of pancreatic function may play a role in maintaining long-term glycemic control (84), which has been elusive in management of type 2 diabetes with other oral agents.

β-Cell proinsulin processing is impaired in type 2 diabetes, resulting in an elevated ratio of proinsulin to insulin that is partially corrected by troglitazone therapy (85). The pulsatile nature of the insulin secretory pattern is also impaired and tied to diabetes and is restored by such treatment (25). It is not clear what causes these effects. They may be mediated indirectly by a decrease in insulin resistance, thus "offloading" the pancreas; by reduction in free fatty acids, which may improve pancreatic function; or by a direct effect on β-cells. Animal studies suggest that thiazolidinediones may improve β-cell function by decreasing the fat content of the pancreatic islet (86). Treatment of Zucker fatty rats with rosiglitazone produced substantial protection against the adaptive changes to pancreatic islet structure caused by sustained hyperinsulinemia (30). In a large clinical trial using a mathematical model to assess β-cell function, the combination of rosiglitazone and metformin showed significant improvement in β-cell function compared with metformin alone (6).

Albuminuria

Albuminuria and microalbuminuria are manifestations of early nephropathy and important predictors of cardiovascular disease. Although the exact mechanism of increased cardiovascular risk in microalbuminuria is unknown, it appears that several other cardiovascular risk factors decrease in the presence of microalbuminuria and correlate with the degree of microalbuminuria (87, 88).

Troglitazone and rosiglitazone have been shown to protect against nephropathy in animals (30, 31). In a 12-week study, Imano and colleagues (32) found that treatment with troglitazone but not metformin decreased microalbuminuria but not blood pressure in patients with incipient diabetic nephropathy. Rosiglitazone has also been shown to decrease albuminuria, whereas glyburide does not (33). The clinical implications of these findings are unclear. Longer-term studies are necessary to confirm these findings and to determine whether these drugs have a role in the treatment of diabetic nephropathy, perhaps as an adjunct to treatment with angiotensin-converting enzyme inhibitors.

Body Weight

Data from clinical trials suggest that the thiazolidinediones may increase body weight, particularly when used in combination with sulfonylureas (4, 5). Some, but not all, of this weight gain may be related to improvement in glycemic control and decreased urinary caloric loss. Some weight gain may be secondary to fluid retention, as evidenced clinically by edema (4, 5, 89). Stimulation of adipogenesis through PPAR-γ is another potential mechanism for weight gain.

The clinical significance of increased body weight with the thiazolidinediones is unclear. Weight gain usually increases insulin resistance, which in turn increases glucose levels. However, thiazolidinediones clearly decrease insulin resistance and glucose despite weight gain. Thus, other mechanisms must be involved in the relation between weight and insulin resistance. For instance, increased intra-abdominal fat is associated with increased insulin resistance. The distribution of the increased body fat produced by the thiazolidinediones may therefore be important. Kelley and associates (29) demonstrated that troglitazone therapy in persons with type 2 diabetes decreases intra-abdominal fat mass but does not affect total body fat or weight. This effect may have clinically significant implications given the association between abdominal fat and various metabolic disorders, including hyperlipidemia, hypertension, and type 2 diabetes.

The Polycystic Ovary Syndrome

Recent data suggest that insulin resistance and hyperinsulinemia are important in the pathogenesis of the polycystic ovary syndrome (25). Treatment with drugs that reduce insulin levels, such as metformin and troglitazone, has been shown to correct many of the meta-

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Table 2. **Experimental Nonhypoglycemic Effects of the Thiazolidinediones**

System	Effect	Reference
Pancreas (β cells)	Decrease in islet fat	86
	Increase in β-cell function	84, 85
Cancer cells*	Decrease in growth and differentiation of colon cancer cells	92
	Decrease in growth and increase in necrosis of prostate cancer cells	93
	Decrease in growth and increase in apoptosis of breast cancer cells	94
Bone	Decrease in marrow adipogenesis	95
	Increase in osteoblastogenesis	95
Polycystic ovary syndrome	Decrease in insulin resistance	25
	Decrease in ovarian steroidogenesis	25
Werner syndrome	Increase in insulin sensitivity	96
Adipose tissue	Decrease in omental adipocyte differentiation	97, 98
	Increase in subcutaneous adipocyte differentiation	97, 98
	Increase in lipid accumulation and differentiation in preadipocytes	98
Ovarian tissue	Decrease in progesterone production in granulosa cells	99

* Effects demonstrated in human cancer cells.

bolic abnormalities associated with the polycystic ovary syndrome (25, 90). Such correction results in resumption of ovulation, decreased insulin resistance, and improved β-cell function (91); it also produces improvement in cardiovascular risk factors, such as dyslipidemia and impaired fibrinolysis. Thiazolidinediones may therefore be useful as primary or adjunctive treatment in women with the polycystic ovary syndrome. However, neither rosiglitazone nor pioglitazone has been tested in this regard.

Miscellaneous Effects

Because PPAR-γ receptors are ubiquitous in human tissues (7, 39, 44, 74, 75), the thiazolidinediones may have many other actions. The effects demonstrated by the thiazolidinediones on various systems, including bone, adipose tissue, and ovaries, are shown in **Table 2**. These drugs may also play a role in modulating tumor growth (92–95). The clinical implications of these data are unclear at present.

Adverse Events

Treatment with troglitazone is associated with abnormalities in liver function test results in approximately 2% of patients. Occasional severe liver failure led to its withdrawal from clinical use (100–102). In contrast, in clinical trials, rosiglitazone and pioglitazone have not been associated with an excessive rate of abnormalities on liver function tests. Nevertheless, severe liver injury was reported in two patients treated with rosiglitazone (103, 104). The exact mechanism of this reaction is poorly understood. Further investigation is needed to determine whether PPAR-γ activation in the liver produced these effects. Elucidation of the mechanism may enable the design of drugs that do not produce hepatic toxicity. Until the pathogenesis of this idiosyncratic liver injury is better understood, U.S. Food and Drug Administration guidelines for liver function monitoring in patients receiving rosiglitazone and pioglitazone should be followed. These include avoiding use of thiazolidinediones in patients with abnormal liver function test results and monitoring liver function test results bimonthly in patients receiving rosiglitazone and pioglitazone.

Another side effect of the thiazolidinediones is a decrease in hematocrit attributable to an increase in plasma volume, weight gain, and edema.

Conclusions and Implications for Clinical Practice

The thiazolidinediones have a novel mechanism of action that may affect not just hyperglycemia but also several other disease processes. Evidence in the literature supports the ability of the thiazolidinediones to target various aspects of the insulin resistance syndrome, and therapy with these drugs may therefore reduce the risk for cardiovascular disease. The potential beneficial nonhypoglycemic effects of the thiazolidinediones include decreases in plasma insulin and triglyceride levels, an increase in HDL cholesterol level, decreased lipid oxidation, favorable redistribution of body fat, a decrease in vascular resistance, and improvement in endothelial function. Potentially deleterious effects include elevation of LDL cholesterol level, edema, and weight gain. It is currently unclear whether these effects are class effects or whether individual drugs have specific advantages. Long-term clinical trials are needed to determine whether this class of drugs will reduce the burden of cardiovascular disease in patients with type 2 diabetes. The ability of the thiazolidinediones to bind with the ubiquitous nuclear receptor PPAR-γ provides fertile ground for further research into other potential clinical applications.

Although our enthusiasm for the thiazolidinediones

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is tempered somewhat by their occasional and sometimes serious side effects, we are optimistic that direct treatment of insulin resistance through reduction of PPAR-γ receptor and free fatty acid levels is promising. We look forward to exploration of these hypotheses in clinical trials that have cardiovascular event prevention as the end point.

From Tulane University Medical Center, New Orleans, Louisiana.

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Requests for Single Reprints: Vivian A. Fonseca, MD, Department of Medicine, Section of Endocrinology, Tulane University Medical Center SL53, 1430 Tulane Avenue, New Orleans, LA 70112-2699; e-mail, vfonseca@tulane.edu.

Current Author Addresses: Drs. Parulkar, Pendergrass, Granda-Ayala, and Fonseca: Department of Medicine, Section of Endocrinology, Tulane University Medical Center SL53, 1430 Tulane Avenue, New Orleans, LA 70112-2699.
Dr. Lee: 2727 West Holcombe Boulevard, Houston, TX 77025.

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