Effects of Thiazolidinediones for Early Treatment of Type 2 Diabetes Mellitus

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Abstract

The thiazolidinediones (TZDs) are a new class of oral antidiabetic agents used in the treatment of type 2 diabetes mellitus. TZDs are selective and potent agonists of peroxisome proliferator-activated receptor-gamma, which is expressed in target tissues for insulin action and in a variety of cells that play an important role in atherosclerosis. TZDs primarily improve glycemic control by reducing insulin resistance in target tissues. Evidence also suggests that the TZDs may have a direct, beneficial effect on β-cell function. In patients with impaired glucose tolerance (prediabetics), treatment with a TZD improves insulin secretory responses and proinsulin concentrations. These β-cell–specific effects may result in prolongation of β-cell function and the enduring glycemic control necessary to prevent microvascular complications. Durable glycemic control has not been clearly demonstrated with other antihyperglycemic agents.

The TZDs may prevent or delay the macrovascular complications associated with type 2 diabetes. TZDs improve the characteristic dyslipidemia of type 2 diabetes, promote decreases in blood pressure, and enhance fibrinolysis. In addition, they exert direct effects on the vasculature, including the ability to decrease the intimal medial thickness and inhibit transendothelial migration of monocytes. These demonstrated antiatherogenic effects may reduce the cardiovascular complications commonly associated with type 2 diabetes. TZDs also reduce microalbuminuria to a greater extent than other agents. Use of a TZD early in the course of therapy may reduce the risk of development of many of the long-term microvascular and macrovascular complications associated with type 2 diabetes.

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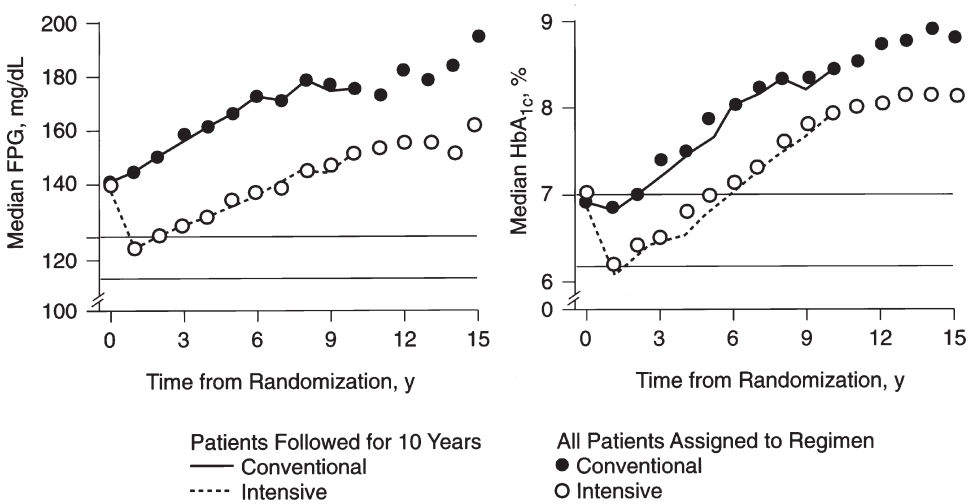
Type 2 diabetes is caused by a combination of insulin resistance and an intrinsic β-cell defect. Insulin resistance is the inability of target tissues, such as muscle, fat, and liver, to respond to normal circulating concentrations of insulin. Insulin resistance results in compensatory hyperinsulinemia and, in time, glucose tolerance becomes impaired as flaws in insulin secretion prevent β cells from meeting the demand for insulin.[1] The decline in β-cell function is believed to begin years before clinically apparent hyperglycemia occurs,[2] and data from animal studies suggest that development of hyperglycemia is associated with increased β-cell death.[3] In addition, in patients with type 2 diabetes, neither the decline in β-cell function nor hyperglycemia appears to be lastingly remedied by treatment with sulfonylurea drugs, metformin, or insulin.[4-6] Thus, in addition to these traditional agents, there is clearly a need for drug therapy that prevents the progressive decline in β-cell function and thereby increases the likelihood of enduring glycemic control.

One of the most desirable results of the specific β-cell effects of thiazolidinediones (TZDs) appears to be improved β-cell longevity with resultant lasting glycemic control, which has been elusive with other agents to date. The United Kingdom Prospective Diabetes Study (UKPDS) included more than 5000 patients with newly diagnosed type 2 diabetes who were assigned to either conventional diet therapy or intensive therapy with a sulfonylurea, metformin, or insulin and followed for an average of 10 years.[5,6] Although the study demonstrated that intensive therapy decreases the risk of microvascular complications, none of the therapies succeeded in maintaining the

Figure 1. Cross-sectional and 10-year Cohort Data for Fasting Plasma Glucose (FPG) and Hemoglobin A_{1c} (HbA_{1c}) in Patients on Intensive or Conventional Treatment



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initial improvement in glycemic control beyond 1.5 years, despite escalating doses (**Figure 1**).[5] Most likely, this apparently inevitable secondary failure is caused by progression of the intrinsic abnormality in the β cells, which was not corrected by the interventions used in the study. This phenomenon of secondary failure justifiably might be considered the most important complication of type 2 diabetes. However, there is reason to believe that the phenomenon may not be inexorable. Preliminary evidence suggests that TZDs in a combination regimen may induce recovery of pancreatic β cells and can provide sustained improvement in glycemic control for up to 3 years.[7,8]

Microvascular complications associated with uncontrolled hyperglycemia, such as retinopathy, nephropathy, and neuropathy, can be reduced with intensive glucose-lowering therapy.[5,6] Although most of the morbidity and mortality in patients with type 2 diabetes is caused by cardiovascular complications, reducing the risk of macrovascular complications in patients with type 2 diabetes apparently depends on more than glycemic control. Insulin resistance is believed to contribute greatly to the extraordinary burden of atherosclerosis that characterizes type 2 diabetes. Medications that reduce insulin resistance might, therefore, be expected to reduce the risk of atherosclerosis as well as other cardiovascular complications.

Ideally, the drug chosen initially to treat type 2 diabetes will improve the intrinsic β-cell defect and thus promote durable glycemic control. Additionally, the ideal agent will reverse insulin resistance and thereby contribute to prevention of cardiovascular disease. TZDs appear to be capable of achieving both of these goals. Furthermore, by contributing to the prevention of the long-term microvascular and macrovascular complications of type 2 diabetes, TZDs may reduce long-term costs associated with this disease and its complications.

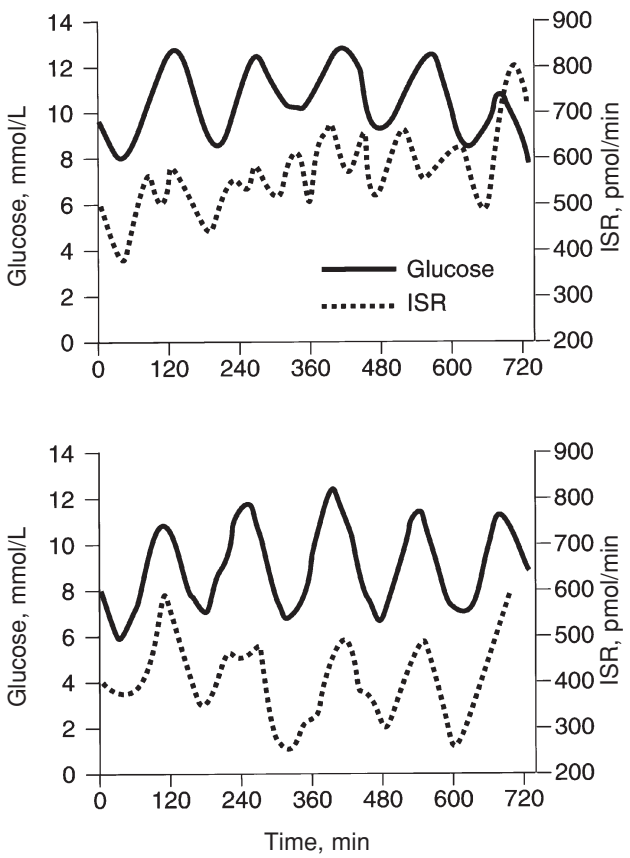
···UNIQUE MECHANISM OF ACTION OF TZDs···

The TZDs are selective and potent agonists of peroxisome proliferator-activated receptor-gamma (PPAR-γ), a nuclear receptor that is expressed in target tissues for insulin action, including adipose tissue, skeletal muscle, and the liver.[9] The presence of PPAR-γ also has

been documented in a variety of cells that play an important role in atherosclerosis, such as endothelial cells, vascular smooth muscle cells, monocytes, and macrophages.[10]

TZDs primarily improve glycemic control by reducing insulin resistance in target tissues.[9,11] Improvement of insulin sensitivity in adipose and muscle tissues is substantially greater with TZDs than with other oral antidiabetic agents. The biguanides lower blood glucose primarily by improving insulin sensitivity in the liver and thereby decreasing hepatic glucose output,[12,13] whereas sulfonylureas (and other insulin secretagogues) stimulate insulin release from the pancreatic β cell.[14] TZD-induced insulin sensitivity leads to reduced demand for insulin secretion by the β cells, which may result in prolongation of β-cell viability. However, evidence suggests that the TZDs also may have a direct ameliorative effect on β-cell dysfunction, something not demonstrated by earlier oral antidiabetic agents. Characteristically, the β cells of patients with type 2 diabetes and of individuals with impaired glucose tolerance have lost the ability to synchronize bursts of insulin secretion with rapid increases in blood glucose concentration.[15] This dyssynchronous insulin secretion, reflecting β-cell dysfunction, is normalized by TZDs. In a randomized, double-blind study, obese subjects with impaired glucose tolerance were assessed at baseline and after 12 weeks of either troglitazone 400 mg daily or placebo.[16] In the troglitazone-treated patients, insulin secretory responses to oscillations in plasma glucose were improved by 49% compared with baseline (P=.04), as shown in **Figure 2**.[16] No significant change was seen in the placebo group. These results suggest that TZDs improve β-cell response to glucose.

Figure 2. Glucose and Insulin Secretion Rate (ISR) Profiles During Oscillatory Glucose Infusion

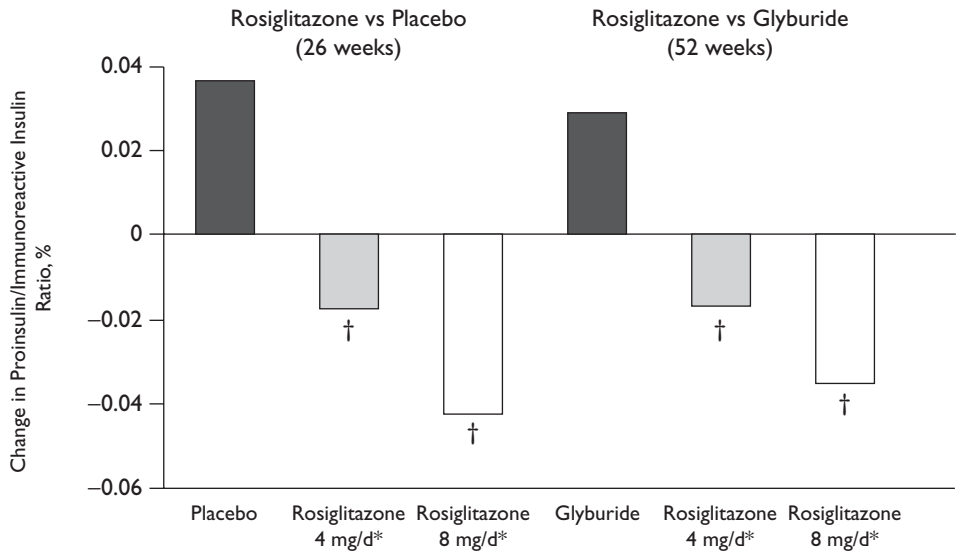


Example of improved entrainment before (top) and after (bottom) troglitazone. Glucose profiles are shown in solid lines and ISR profiles are shown in dotted lines.
Source: Reproduced with permission from *J Clin Invest.* 1997;100: 530-537.

The β cells of patients with type 2 diabetes are further dysfunctional in their processing of insulin, secreting increased amounts of proinsulin compared with normal subjects.[17] Increases in proinsulin may result from an increased demand for insulin in patients with β-cell dysfunction, leading to release of contents from insulin-containing granules before processing is complete. Treatment with TZDs has been shown to significantly reduce the proinsulin/insulin ratio when compared with placebo or glyburide (**Figure 3**).[18-20] These data provide further evidence that TZDs improve β-cell function.

In patients with type 2 diabetes as well as in those with insulin resistance, free fatty acids are deposited not only in adipocytes, but also inappropriately in the muscle, liver, pancreas, and β cells.[21,22] As free fatty acids accumulate in the pancreatic β cells, stimulation of nitric oxide synthase and increases in nitric oxide lead to increased β-cell apoptosis.[22] Animal stud-

Figure 3. The Thiazolidinedione, Rosiglitazone, Improves the Proinsulin/Insulin Ratio and Improves β-Cell Function in Patients With Type 2 Diabetes



Source: Reproduced with permission from *Diabetes Obes Metab.* 2001;3(suppl 1):S34-S43.
*Given in divided doses.
†Significant differences from placebo or glyburide.

ies indicate that TZDs decrease circulating free fatty acids and islet-cell fat in parallel with β-cell rejuvenation.[23,24]

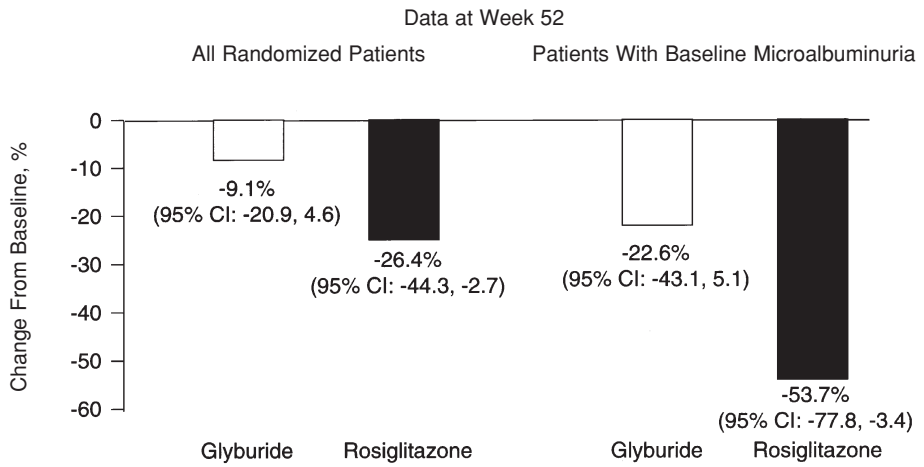
···TZDs AND MICROVASCULAR COMPLICATIONS···

To date, no completely persuasive evidence indicates that TZDs are superior to their predecessor drugs in preventing microvascular complications, although some research indicates that TZDs may be superior in patients who have renal glomerulopathy. The TZDs are able to reduce microalbuminuria within the first year of therapy and to an extent exceeding that of other oral agents. In a 52-week comparative study, rosiglitazone-treated patients with microalbuminuria at baseline had a mean decrease of 54% in urinary albumin excretion compared with baseline, whereas patients treated with glyburide had a mean decrease of 23% (**Figure 4**).[25] Similarly, urinary albumin excretion was significantly reduced ($P<.01$) in patients with type 2 diabetes and microalbuminuria treated with pioglitazone, whereas patients treated with a sulfonylurea showed little change in urinary albumin excretion.[26] Troglitazone significantly reduced urinary albumin excretion in patients with type 2 diabetes and microalbuminuria beginning 4 weeks after initiation of therapy; the effect was maintained throughout the 12-week study.[27] Notably, urinary albumin excretion was unchanged in patients treated with metformin in this study. Because similar decreases in glucose concentrations were noted in both the TZD and non-TZD groups in these studies, the beneficial effect of TZDs on microalbuminuria is most likely attributable to factors other than glycemic control. Plausible candidate mechanisms are a direct vascular effect on glomerular endothelial function or a favorable influence on intraglomerular pressure.

···TZDs AND MACROVASCULAR COMPLICATIONS···

Treatment with a TZD in the early stages of type 2 diabetes has been suggested to help prevent macrovascular

Figure 4. Effect of Treatment for 52 Weeks With Rosiglitazone or Glyburide on Urinary Albumin Excretion in Patients With Type 2 Diabetes With and Without Microalbuminuria at Baseline



CI indicates confidence interval.
Source: Reference 25.

complications. Evidence that the insulin-resistant state can be atherogenic depends on observations such as those of Despres et al, who found that compensatory hyperinsulinemia was associated with an increased likelihood of a coronary ischemic event.[28] This study suggests that the increased ischemic risk imposed by insulin resistance may be mediated at least in part by factors that accompany insulin resistance and that are associated with increased atherosclerotic risk, most notably, dyslipidemia, hypertension, and hypercoagulability.

Dyslipidemia

Patients with type 2 diabetes generally show evidence of a characteristic dyslipidemia with elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, and an increase in small, dense low-density lipoprotein (LDL) cholesterol, as well as a level of LDL cholesterol that is often undesirably high. Favorable lipid-modifying effects have been reported for troglitazone[11,29-31] and pioglitazone.[32] Notably, recent reports have indicated that treatment with rosiglitazone affects LDL particle size favorably.[33] Although an 8% increase in LDL cholesterol occurred during the first 8 weeks of treatment with rosiglitazone, patients with small, dense LDL cholesterol particles had significant improvement in LDL density.[33] The proportion of light, buoyant, presumably less-atherogenic LDL particles increased, and a significant improvement in LDL density occurred in 71% of patients. This phenomenon, along with a significant increase in levels of HDL cholesterol (HDL_2 levels were preferentially increased), suggest that rosiglitazone, like troglitazone and pioglitazone, may have antiatherogenic lipid-modifying effects. Additional studies are needed to substantiate the significance of these promising findings.

Blood Pressure

In addition to favorable lipid-modifying effects, TZDs promote lower blood pressure.[30,34,35] In an open-label, randomized study, patients received glyburide or rosiglitazone, and ambulatory blood pressure was assessed over a 24-hour period at baseline and after 52 weeks of treatment.[34] In the rosiglitazone group, diastolic blood pressure decreased significantly from baseline (–2.3 mm Hg, P=.0016); however,

no significant change was noted in diastolic blood pressure in the glyburide group. Systolic blood pressure increased significantly from baseline in the glyburide group, but was slightly decreased in the rosiglitazone group.[34] In a comparative trial of troglitazone and glyburide, diastolic blood pressure was significantly decreased in the troglitazone group (–6.5 mm Hg at 48 weeks), whereas in the glyburide group, no significant changes in blood pressure were detected.[30] In a multicenter, parallel-group study, the effects of pioglitazone and acarbose on blood pressure were assessed.[35] Patients with type 2 diabetes treated with pioglitazone had a modest, yet significant, decrease in systolic blood pressure after 26 weeks of treatment (median change from baseline of –5 mm Hg, $P<.05$). No significant changes in blood pressure were observed in the acarbose-treated patients. The decreases in blood pressure generated by TZDs may reduce macrovascular complications in patients with type 2 diabetes.

Fibrinolysis

Plasminogen activator inhibitor type 1 (PAI-1) inhibits endogenous intravascular fibrinolysis,[36] and increased PAI-1 concentrations are associated with increased risk of cardiovascular disease. Typically, individuals with type 2 diabetes have elevated concentrations of PAI-1.[10] TZDs have been shown to reduce circulating levels of prothrombotic PAI-1. In women with polycystic ovary syndrome, which is associated with insulin resistance and defects in fibrinolysis, troglitazone markedly reduced PAI-1 concentrations.[37] Recently, the addition of rosiglitazone to sulfonylurea therapy had a much greater effect on PAI-1 antigen (the absolute amount of PAI-1) and PAI-1 activity than use of sulfonylurea alone.[38] In a double-blind, parallel-group study, patients with type 2 diabetes were randomized to treatment with glibenclamide or glibenclamide plus rosiglitazone for 26 weeks. PAI-1 antigen and PAI-1 activity were both reduced by the addition of rosiglitazone to glibenclamide (**Table 1**). Decreases in PAI-1 observed following treatment with TZDs potentially contribute to a decreased risk of cardiovascular events because of improved fibrinolytic activity and, consequently, lower risk of thrombosis.

Inflammation

Patients with type 2 diabetes have increased inflammation as indicated by increased generation of reactive oxygen species by mononuclear cells.[39] Patients with diabetes also have elevated levels of interleukin-6, tumor necrosis factor-α, and C-reactive protein.[40,41] Various studies have shown that C-reactive protein is elevated during inflammation and independently predicts the development of cardiovascular events, particularly myocardial infarction.[42] Elevation of C-reactive protein also has been associated with the development of type 2 diabetes.[43] Treatment with rosiglitazone has been shown to reduce serum C-reactive protein levels in patients with type 2 diabetes, evidence of an anti-inflammatory effect.[44] Further studies may continue to support the potential anti-inflammatory properties of the TZDs.

Direct Vascular Effects

In addition to these persuasive anti-inflammatory, antiatherogenic, and antithrombogenic influences, other factors, such as direct stimulation of metabolic pathways in the endothelium, likely contribute to the potential for macrovascular protection offered by TZDs. Addressing

Table 1. Effect of Combination Therapy With Rosiglitazone and Glibenclamide on PAI-1 Antigen and PAI-1 Activity in Patients With Type 2 Diabetes: Percentage Change From Baseline at Week 26

Treatment	PAI-1 antigen (ng/mL)	PAI-1 activity (u/mL)
Glibenclamide (N=49)	12.8 (–4.5, 33.1)	10.9 (–11.3, 38.6)
Glibenclamide + rosiglitazone (N=46)	–7.2 (-23.0, 11.9)	–20.7 (–36.2, –1.5)

PAI-1 indicates plasminogen activator inhibitor-1.
Source: Adapted from *Diabetologia*. 2000;43(suppl 1):A267 with permission from Springer-Verlag © 2000.

Table 2. Effects of Thiazolidinediones on Cardiovascular Risk Factors

- Reduce insulin resistance and compensatory hyperinsulinemia
- Control hyperglycemia
- Lower blood pressure
- Reduce thrombogenic factors (PAI-1)
- Modify lipid profile
  —Increase HDL cholesterol level
  —Decrease triglyceride level
  —Replace small, dense LDL particles with large, buoyant particles
- Inhibit transendothelial migration of monocytes; suppress metalloproteinase activity
- Decrease intimal medial thickness

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor 1.

this point are several recent reports on the antiatherogenic effect of TZDs. Increased thickness of the carotid artery intima media is associated with an increased risk of cardiovascular disease.[45] In 1998, Japanese investigators published their observation that troglitazone, but not a sulfonylurea, significantly reduced carotid intimal-medial thickness ratio, an effect not attributable to differences in glycemic control or lipid levels.[46] In this study, patients were treated with troglitazone, a sulfonylurea, or diet alone for 6 months. Carotid artery intima-media thickness was measured using high-resolution B-mode ultrasonography. After 3 months of treatment with troglitazone, the decrease in intima-media thickness reached statistical significance (change of –0.080 mm versus control change of 0.027; $P<.001$). The decrease in thickness was maintained over 6 months, indicating that the effect of troglitazone on intima-media thickness was both prompt and nontransient. A similar effect has been reported with pioglitazone.[47]

Troglitazone treatment for 6 months also significantly reduced intimal hyperplasia in patients with type 2 diabetes following stenting of coronary arteries compared with diet alone.[48] In another study of patients with type 2 diabetes, treatment with troglitazone was associated with reduced restenosis following coronary stent implantation.[49] Preclinical studies have demonstrated that rosiglitazone reduced the incidence of myocardial infarction after ischemic injury.[50] Taken together, these data suggest that TZDs have a potent inhibitory effect on progression of atherosclerotic lesions and may exert direct cardioprotective benefits in patients with type 2 diabetes.

Troglitazone was recently reported to reverse exertional angina pectoris in patients with type 2 diabetes.[51] Exercise time was significantly extended in patients treated with troglitazone for 4 months, but not in control subjects. Troglitazone also reduced episodes of angina in patients with coronary vasospastic angina pectoris and diabetes.[52] Patients were assessed after 4 months of treatment with troglitazone. The number of angina episodes per month was significantly reduced, from 15 to 3 ($P=.030$) after treatment, and duration of angina was reduced from 76 to 10 minutes per month ($P=.027$). These results indicate that TZDs may improve endothelial function.

Using a hypercholesterolemic animal model, researchers have demonstrated that troglitazone inhibits the development of atherosclerosis in mice fed either a high-fat or high-fructose diet.[53] Analysis of the lesions suggests that troglitazone decreased monocyte recruitment. Similarly, in hypercholesterolemic male mice fed a high-fat, high-cholesterol diet, treatment with rosiglitazone inhibited the development of atherosclerosis.[54] TZDs appear to inhibit transendothelial migration of monocytes, which are destined to become lipid-laden macrophages (and, hence, foam cells), and curtail production and activity of plaque-destabilizing metalloproteinase, which contributes to potentially antiatherogenic, coronary-protective effects.

One additional experimental observation provides support for the idea that TZDs have an antiatherogenic effect that is artery based and independent of favorable effects on extra-arterial risk factors. Aortas from dyslipidemic mice treated with rosiglitazone after being exposed to

angiotensin II, which accelerates atherosclerosis, developed significantly less atherosclerosis than the aortas of a parallel control group from which rosiglitazone was withheld.[55] Mice treated with rosiglitazone had a 60.4% decrease in lesion area compared with controls ($P<.01$). Therefore, TZD protection occurred, despite endothelial toxicity induced by dyslipidemia and angiotension II.

In summary, TZDs exert powerful extra-arterial and intra-arterial antiatherogenic effects (**Table 2**), which have special potential value to patients with type 2 diabetes who are at increased risk for cardiovascular disease. A number of clinical outcome trials, such as the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, are currently under way to evaluate the potential of the TZDs in preventing the development and progression of cardiovascular disease in patients with type 2 diabetes.

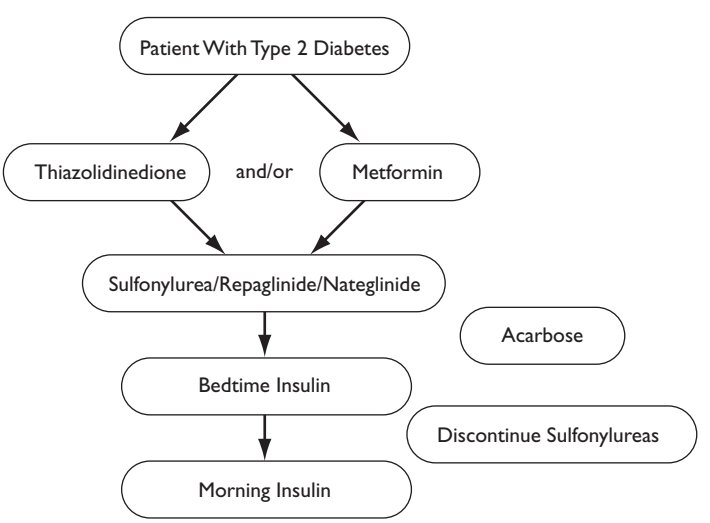
···TZDs IN COMBINATION WITH OTHER GLUCOSE-LOWERING AGENTS···

Many patients with type 2 diabetes have difficulty maintaining glycemic control while on monotherapy with the available oral antidiabetic agents. As mentioned previously, data from the UKPDS demonstrate that neither metformin nor sulfonylureas maintained the initial improvement in glycemic control beyond 1.5 years, even with increased doses.[5,6] To avoid significant hyperglycemia, patients often need medication added to their regimen. Any delay in initiating combination therapy while the patient's blood glucose level is not controlled increases the risk for microvascular complications. Because the mechanism of action of the TZDs is different from the mechanisms of other agents, the combination of a TZD with a biguanide, a sulfonylurea, or both can be beneficial for many patients with type 2 diabetes. In addition, the TZDs may be able to provide long-term glycemic control by preserving β–cell function and improving insulin sensitivity.[7,8]

The combination of a TZD and a biguanide offers several benefits (**Figure 5**). One major advantage with this combination is that neither agent causes clinically significant hypoglycemia, a disadvantage with the sulfonylureas. In addition, because these agents have complementary mechanisms of action, TZDs and biguanides produce an additive effect on blood glucose control.[9,13] The combination of a TZD and a biguanide significantly reduces fasting plasma glucose concentrations and glycosylated hemoglobin (HbA_{1c}) levels compared with metformin alone.[56,57]

For some patients, the combination of a TZD with a sulfonylurea and with or without a biguanide is a reasonable choice (Figure 5). In a randomized, double-blind, placebo-controlled trial, patients receiving rosiglitazone plus a sulfonylurea had significantly lower fasting plasma glucose and HbA_{1c} levels than patients on sulfonylurea monotherapy.[58] Similar results were achieved with the combination of pioglitazone and a sulfonylurea.[59] Furthermore, for patients treated with a sulfonylurea and a biguanide who have not achieved adequate glycemic control, the addition of a TZD has been beneficial.[60] By initiating combination therapy early in the course

Figure 5. Proposed Treatment Algorithm for Early Therapy of Patients With Type 2 Diabetes and Other Characteristics of Insulin Resistance



of the disease, it is hoped that many of the vascular complications associated with type 2 diabetes will be delayed or avoided. For patients with characteristics of insulin resistance, initiating therapy with a TZD early in the course of the disease may be optimal because insulin resistance and the atherogenic pattern of cardiovascular risk factors often precede the onset of clinical diabetes in many individuals, and combination therapy early in the course of disease may be warranted.[61]

···CONCLUSION···

Accumulating evidence demonstrates that because of their versatility, TZDs appear to be promising agents for achieving glycemic control in patients with type 2 diabetes. The remedial effects of TZDs on β-cell performance prompt the hope that their use soon after diagnosis will enhance prevention of microvascular complications by sustaining glycemic control over the long term. Furthermore, their antiatherogenic effects, multifactorially mediated, offer the potential to contribute to prevention of macrovascular disease.

The therapeutic advantage of TZDs is not in their effectiveness in controlling hyperglycemia, because most of the oral agents have similar glycemic effects; their advantage is in how they reduce glycemia. By improving insulin sensitivity and other metabolic abnormalities, such as β-cell dysfunction, associated with type 2 diabetes, TZDs may offer β-cell protection, as well as protection of microvasculature and macrovasculature. Initiating TZD therapy early for patients with characteristics of insulin resistance may be optimal because insulin resistance and the atherogenic pattern of cardiovascular risk factors often precede the onset of clinical diabetes in many individuals. For some patients, combination therapy may be warranted. Large-scale studies are anticipated to confirm the unique value of the TZDs in the treatment of type 2 diabetes; even now, accumalating evidence supports TZDs as a reasonable treatment option early in the course of diabetes.

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