Current Management of Type 2 Diabetes: Why Thiazolidinediones Should Be the Cornerstone of Therapy

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ABSTRACT

Type 2 diabetes affects millions of people in the United States, and its incidence is increasing at an alarming rate. A key underlying feature of type 2 diabetes is insulin resistance, which is associated with characteristic clinical features and increased cardiovascular risk. Currently, there are several classes of drugs that are used to manage type 2 diabetes. However, only the thiazolidinediones (TZDs) have been shown to consistently improve estimates of β-cell function. By improving insulin sensitivity and potentially preserving β-cell function, the TZDs are able to provide durable glycemic control. The TZDs also have been found to reduce inflammatory markers, improve vascular function and lipid profiles, and decrease blood pressure in patients with type 2 diabetes, which may improve long-term cardiovascular outcomes. Studies are being conducted to determine the role of TZDs in the prevention of cardiovascular complications in patients with type 2 diabetes. The effectiveness of these agents in improving multiple cardiovascular surrogate markers make the TZDs particularly appealing as a pivotal treatment option and suggests that they be considered a cornerstone of therapy in the management of type 2 diabetes.

INTRODUCTION

Diabetes mellitus is a growing healthcare problem that causes significant morbidity and mortality.[1] Diabetes affects at least 18 million adults in the United States, and this prevalence is expected to increase further as a result of the growing epidemic of obesity in this country.[2-4] Type 2 diabetes is marked by 2 underlying defects: insulin resistance, which manifests as a decrease in uptake of glucose by insulin-sensitive tissues, and the inability of the β cell to produce enough insulin in response to the insulin resistance.[5-7] As a result of this resistance to insulin, pancreatic β cells release larger amounts of insulin to maintain euglycemia. However, in susceptible individuals, the β-cell response is ultimately not optimal with β-cell dysfunction, resulting in a decrease in insulin secretion and development of hyperglycemia.[6] Because hyperglycemia can cause damage to several organ systems, diabetes is a chronic disease that results in the development of various microvascular and macrovascular complications. By maintaining tight glycemic control, patients can delay the progression and severity of long-term microvascular complications such as nephropathy, neuropathy, retinopathy,

Table 1. Oral Antihyperglycemic Agents Available in the United States*

Class	Mechanism of action	Agent
Thiazolidinediones	Insulin sensitizer/may preserve β-cell function	Rosiglitazone, pioglitazone
Sulfonylureas	Insulin secretagogue	Chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, glyburide
Other insulin secretagogues	Insulin secretagogue	Repaglinide, nateglinide
Biguanides	Decrease hepatic glucose output	Metformin
α-Glucosidase inhibitors	Delay carbohydrate absorption	Acarbose, miglitol

*Adapted with permission from *JAMA*. 2002;287:367.[12]

and possibly macrovascular complications such as cardiovascular disease.[8,9]

The treatment of diabetes has advanced greatly during the past few years with a better understanding of the disease itself and development of new medications. Unfortunately, many patients are still unable to maintain glycemic control because of inappropriate treatment and/or inability to follow an appropriate diet or pharmacologic regimen. This, combined with the progression of the disease, leads to development of multiple complications, including cardiovascular disease, which is the leading cause of death in patients with diabetes.[10]

This article will provide a review of type 2 diabetes and treatment options for managing the disease. The review will focus on the thiazolidinediones (TZDs) and will include information about their mechanism of action, therapeutic effects, and potential cardiovascular benefits.

GOALS OF THERAPY AND TREATMENT OPTIONS

The American Diabetes Association has recommended a set of glycemic goals for patients with diabetes, which include a preprandial glucose level of 90 to 130 mg/dL and a glycosylated hemoglobin (HbA_{1c}) level of 7% or less.[1] In addition, the American Association of Clinical Endocrinologists has set even stricter glycemic goals, recommending a preprandial glucose level of 110 mg/dL or less, a postprandial glucose level of 140 mg/dL or less, and an HbA_{1c} level of 6.5% or less.[11] By attaining these goals, patients may reduce their risk for developing long-term complications. To reach these goals, nonpharmacologic, and often pharmacologic, therapy is necessary.

Initial therapy for type 2 diabetes includes an appropriate diet and exercise regimen, because both improve insulin resistance and decrease blood glucose levels.[1] However, many patients also need medications to achieve and maintain the target blood glucose levels recommended above. Currently, there are 5 classes of oral antidiabetic agents with unique mechanisms of action (Table 1). The 5 classes include the TZDs, biguanides, sulfonylureas, nonsulfonylurea secretagogues, and α-glucosidase inhibitors. The TZDs improve

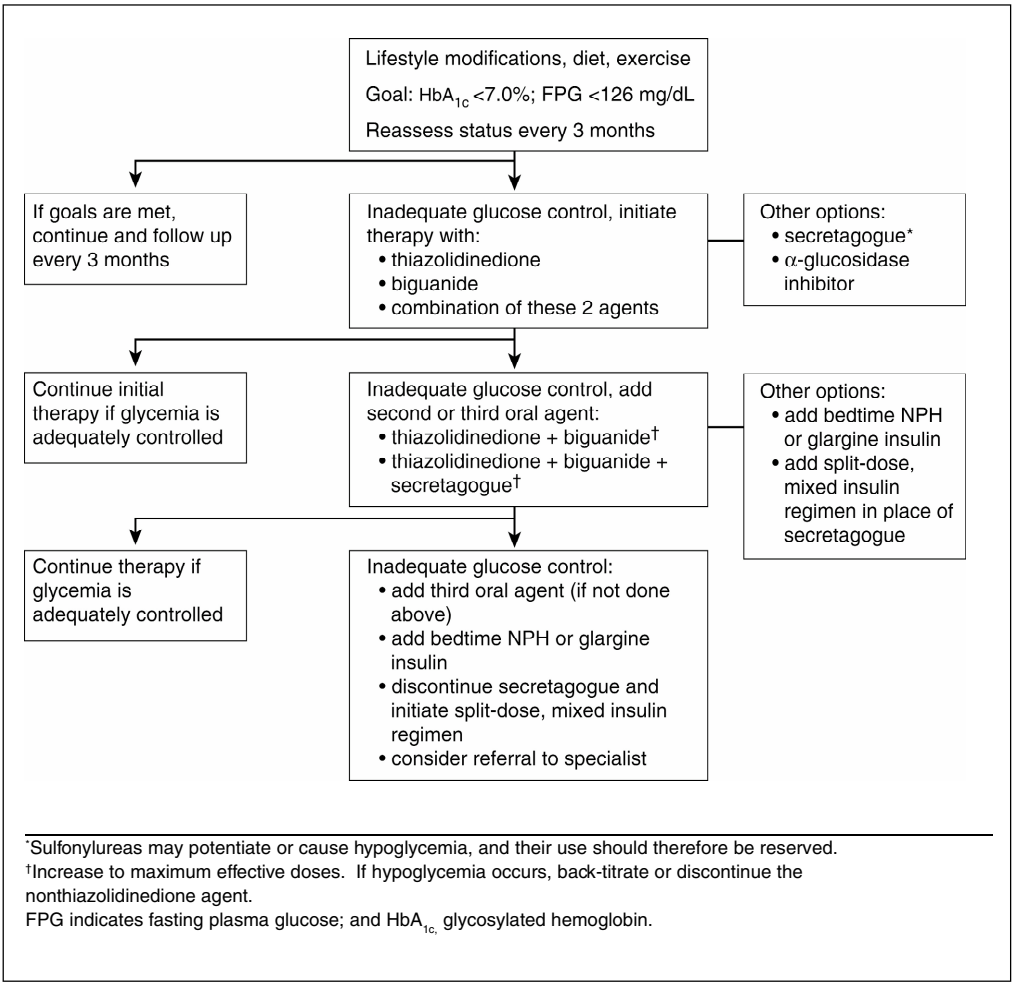

Figure 1. Proposed treatment algorithm for the management of patients with type 2 diabetes inadequately controlled with diet and exercise. (Reproduced with permission from *Endocrinologist.* 2003;13(suppl 1):S1-S21.[13])

insulin sensitivity and stimulate glucose uptake by muscle and adipose tissue. Biguanides primarily decrease glucose output by the liver. Both the sulfonylureas and nonsulfonylurea secretagogues target β cells to produce more insulin, whereas the α-glucosidase inhibitors reduce glucose absorption by the gut.[5,12] Because all of these classes can effectively reduce blood glucose levels, the optimal treatment regimen must be individualized based on the patient and severity of the disease. Additionally, treatment algorithms have been proposed and may provide an initial guide for selection of therapy in patients with type 2 diabetes (Figure 1).[13]

Recently, comparisons between glyburide and glimepiride have demonstrated that glyburide therapy impairs ischemic preconditioning, probably via nonselective closure of K-ATP channels.[14] Although further study in this area is needed, if a sulfonylurea secretagogue is selected for therapy, it may be reasonable to use a nonglyburide product, such as glimepiride. This choice

not only addresses the potential concern of ischemic preconditioning, but also allows for a lower risk of hypoglycemia with the longer-acting secretagogue.[15]

Many patients with type 2 diabetes who are on monotherapy have difficulty achieving or maintaining HbA_{1c} levels below 7%. The United Kingdom Prospective Diabetes Study (UKPDS) was a landmark study that assessed 5102 patients newly diagnosed with type 2 diabetes.[16,17] This study evaluated whether intensive pharmacologic therapy reduced the risk of diabetic complications and whether sulfonylureas, metformin, or insulin had specific advantages in managing patients with diabetes. During the first 10 years of the study, intensive treatment reduced HbA_{1c} levels more than conventional dietary treatment (7.0% vs 7.9%; $P<.0001$), and microvascular complications were reduced by 25%. However, HbA_{1c} levels eventually increased over time in both the intensive and conventional treatment groups, indicating that the disease continued to progress despite initial glycemic control with pharmacologic agents such as sulfonylureas, metformin, or insulin.

THIAZOLIDINEDIONES: MECHANISM OF ACTION AND DURABLE GLYCEMIC CONTROL

TZDs reduce hyperglycemia by improving insulin sensitivity. Rosiglitazone and pioglitazone are the only 2 drugs in this class currently available in the United States. TZDs bind to the nuclear peroxisomal proliferator-activated receptor-γ (PPAR-γ), subsequently activating genes that encode proteins involved in the metabolism of glucose and lipids.[18] This leads to an increase in glucose uptake in skeletal muscle and adipose tissue, a reduction in hepatic glucose output, and finally, an increase in free fatty acid uptake. These factors combine to lower glucose levels and can decrease HbA_{1c} levels over time.[18]

A number of studies have shown that TZDs provide long-term glycemic control in patients with diabetes. Monotherapy with rosiglitazone has been shown to decrease HbA_{1c} by 1.2% to 1.5% compared with placebo after 26 weeks of therapy.[19] An open-label study compared the effects of rosiglitazone and glyburide on glycemic control.[20] Fasting plasma glucose decreased by 50 mg/dL and 25 mg/dL after 8 and 52 weeks of therapy, respectively, with rosiglitazone; durable glycemic control was maintained for 52 weeks. Notably, twice as many patients achieved levels of HbA_{1c} below 7% when treated with rosiglitazone compared with glyburide after 52 weeks of therapy. Pioglitazone also effectively decreases both HbA_{1c} and fasting plasma glucose in patients with type 2 diabetes.[21] Pioglitazone 15 to 45 mg daily decreased HbA_{1c} levels by 1.0% and 1.6%. Fasting plasma glucose decreased as well by 74.5 mg/dL, 42.0 mg/dL, and 43.7 mg/dL in patients treated with pioglitazone 45 mg, 30 mg, and 15 mg, respectively. The TZDs are as efficacious as sulfonylureas in achieving glycemic control. One possible explanation for the lower fasting glucose may be the enhanced insulin sensitivity provided by TZD therapy.

Another advantage of TZDs is their ability to improve measures of β-cell function. The homeostasis model assessment (HOMA) has been utilized as a research tool to evaluate measures of β-cell function and insulin resistance. In a randomized study, 493 patients with type 2 diabetes received rosiglitazone 2 mg or 4 mg twice daily or placebo for 26 weeks. This study showed an increase in β-cell function of 49.5% and 60.0% and a reduction in insulin resistance of 16.0% and 24.6% when patients were treated with 4 mg and 8 mg daily of rosiglitazone, respectively[19] (Figure 2). The Troglitazone in the Prevention of

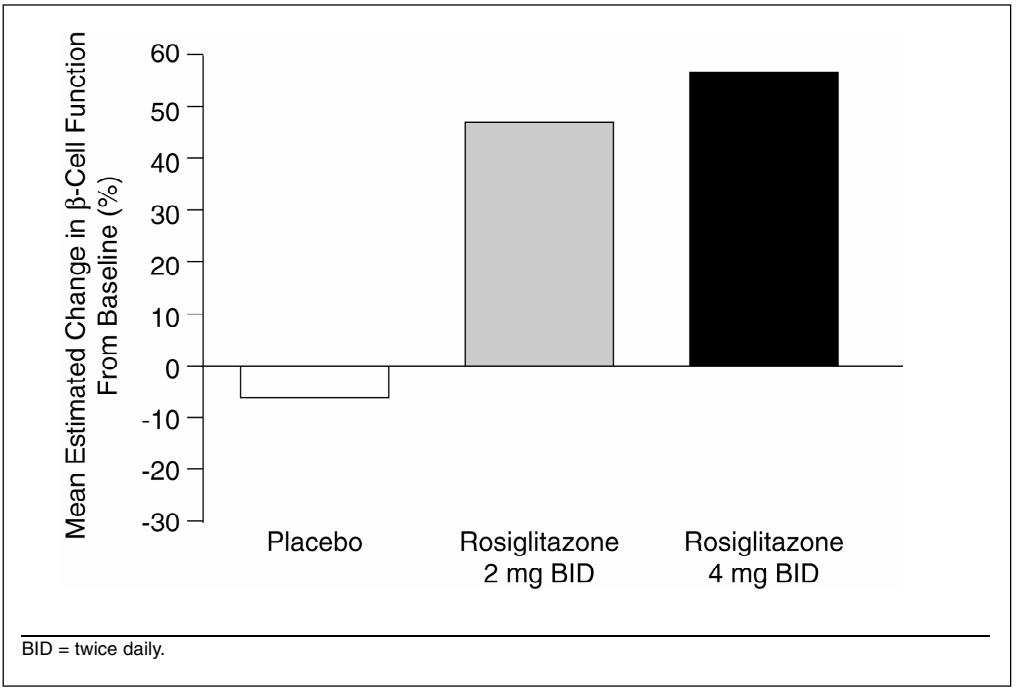

Figure 2. Estimate of β-cell function as calculated by the homeostasis model assessment (HOMA) model. Data are the percentage change compared with the baseline assessment. Rosiglitazone treatment resulted in 50% and 60% improvement at 4 and 8 mg/day, respectively. (Reproduced with permission from *J Clin Endocrinol Metab.* 2001;86:280-288.[19])

Diabetes (TRIPOD) study evaluated the prevention of type 2 diabetes in high-risk subjects.[22] Two hundred sixty-six hispanic women who had had gestational diabetes were randomized to receive either troglitazone or placebo. After a 30-month follow-up period, the troglitazone group had a 12.1% decrease in diabetes incidence compared with 5.4% in the placebo group ($P<.01$). Preservation of β-cell function associated with improved insulin sensitivity likely contributed to the decreased incidence of diabetes in the troglitazone-treated patients. After a mean follow-up of 30 months, troglitazone treatment reduced new-onset diabetes by 56%. The greatest benefit occurred in women whose insulin resistance was significantly decreased by troglitazone and who still had moderate β-cell insulin secretory capacity.

A study conducted by Ovalle and Bell[23] evaluated the effects of TZDs on β-cell function in patients with type 2 diabetes. The study group consisted of 28 patients whose meal-stimulated C-peptide levels were documented before the addition of troglitazone to a failing regimen of metformin and sulfonylurea, who were then compared with 26 patients who had their C-peptide levels documented before adding metformin to a failing sulfonylurea monotherapy regimen. C-peptide levels in the TZD group increased significantly with therapy (3.2 ng/dL ± 5 to 4.3 ng/dL ± .5; $P=.01$) and remained unchanged in the control group. This study suggested that TZDs may improve pancreatic β-cell function by yet another measurement in patients with type 2 diabetes.

These studies illustrate a consistent correlation between the reduction of insulin resistance by TZDs and improvement in measures of β-cell function.

Table 2. Risk determinants for the diagnosis of the metabolic syndrome as defined by ATP III

Risk factor	Defining level
Abdominal obesity	
(waist circumference)	
Men	>40 inch (>102 cm)
Women	>35 inch (>88 cm)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose†	≥110 mg/dL

*Reproduced with permission from *JAMA*. 2001;285:2486-2497.[25] ATP III indicates Adult Treatment Panel III; and HDL, high-density lipoprotein.

†Impaired fasting glucose has recently been revised to 100 to 125 mg/dL.[1]

This may slow the rate of β-cell apoptosis in persons genetically predisposed to type 2 diabetes. By improving insulin resistance and potentially maintaining β-cell function, the TZDs may target the underlying metabolic defects in type 2 diabetes and produce a sustained therapeutic effect on glycemic control.

THIAZOLIDINEDIONES: IMPROVED INSULIN SENSITIVITY AND CARDIOVASCULAR BENEFITS

Insulin resistance is one of the first measurable defects in diabetes. The Insulin Resistance Atherosclerosis Study (IRAS) revealed a direct link between the insulin resistance syndrome and atherosclerosis.[24] The insulin resistance syndrome, or the metabolic syndrome, consists of a group of metabolic abnormalities, including elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, hypertension, proinflammatory states, or abdominal obesity.[25] Diagnosis of the metabolic syndrome is based on the condition that 3 of the 5 criteria listed in Table 2 are present. It should be noted that the definition of impaired fasting glucose has recently been revised to 100 to 125 mg/dL[1]; therefore, the fasting glucose criterion for the metabolic syndrome (≥110 mg/dL) preceded this recent change. The presence of the metabolic syndrome is associated with a high risk of coronary artery disease,[26] and improving insulin resistance in patients with type 2 diabetes reduces the risk factors associated with the metabolic syndrome.

A study conducted in 4000 high-risk Scandinavians compared the prevalence of the metabolic syndrome with the incidence of cardiovascular morbidity and mortality.[27] This study confirmed that 80% of patients with type 2 diabetes met the criteria for the metabolic syndrome. Furthermore, mortality from cardiovascular disease was significantly higher in patients with the metabolic syndrome (12%) than in patients without (2.2%; $P<.001$). The Helsinki Policemen Study and the Paris Prospective Study also support the correlation between insulin resistance and the occurrence of coronary events.[28,29] The Helsinki Policemen Study revealed that the presence of hyperinsulinemia increased the risk for coronary heart disease.[29] The Paris Prospective Study was a long-term investigation of a large population of middle-aged men.[28] This study found that increased fasting insulin levels predicted an increase in

cardiovascular disease mortality. Cellular mediators of insulin resistance, including resistin, free fatty acids, and adiponectin, have all been favorably impacted by the TZDs.[30] Of these, the adipocytokine adiponectin has been the subject of research interest in several scientific reports.[31-34] Patients with type 2 diabetes are clearly at increased risk for coronary heart disease, and therefore, improving insulin resistance may slow or delay the development of cardiovascular disease.

Lipids

Patients with type 2 diabetes invariably manifest the characteristic triad of dyslipidemia that includes a low plasma HDL, an increase in small, dense low-density lipoprotein (LDL) particles, and high triglyceride levels.[35,36] The smaller LDL and HDL particles in patients with insulin resistance may be the result of increased hepatic lipase activity. Therefore, the atherogenicity of LDL cholesterol is enhanced, whereas the cardioprotective properties of HDL cholesterol are decreased.[37] TZD therapy not only improves insulin sensitivity, but also results in a more favorable lipid profile. Ghazzi and colleagues[38] demonstrated that troglitazone therapy decreased triglyceride levels while increasing HDL levels in patients with type 2 diabetes. Similarly, treatment with 15, 30, and 45 mg of pioglitazone significantly decreased triglycerides compared with placebo (P .05) and significantly increased HDL cholesterol (P .05).[21] Rosiglitazone therapy also decreased triglycerides in patients with a high baseline level, increased HDL cholesterol by 10% to 30%, and increased the HDL_2 atheroprotective subfraction by 12.6%.[18,19,39,40]

Despite often normal levels of LDL cholesterol, insulin resistance is characterized by a predominance of small, dense, atherogenic LDL particles that are susceptible to oxidative modification.[37] Oxidation is an important, initial step in the atherosclerotic process. Notably, treatment with TZDs increases the ratio of large, buoyant LDL to small, dense LDL, which enhances resistance to oxidation and makes the particles less atherogenic.[41,42] Three hundred thirty-two patients with type 2 diabetes were enrolled in an 8-week, open-label, run-in treatment phase of rosiglitazone 8 mg daily.[41] A shift from small, dense LDL to the larger subfraction occurred in 52% of the patients. In addition to lowering blood glucose levels, TZDs offer the further advantage of improving the lipid profile associated with insulin resistance. However, it is important to note that the effect of TZDs on lipids is certainly not sufficient to recommend replacing statin therapy for dyslipidemia.[43]

Blood Pressure

Patients with type 2 diabetes are at considerable risk for cardiovascular disease, and up to 30% have clinically significant hypertension.[44] Patients with diabetes are twice as likely to have hypertension as those without diabetes.[45] The UKPDS blood pressure substudy revealed a significant reduction in microvascular and macrovascular complications when blood pressure was controlled in patients with diabetes.[46] In addition to lowering blood glucose levels, TZDs have been shown to improve blood pressure. A study comparing troglitazone and glyburide examined the vascular effects of these medications on blood pressure at rest and during mental stress in patients with type 2 diabetes.[47] Troglitazone significantly reduced blood pressure (P<.05) at baseline and during periods of stress, whereas glyburide had no effect on blood pressure. A reduction in vascular resistance may mediate the decrease in blood pressure. Another study comparing rosiglitazone 4 mg

twice daily versus glyburide in 203 patients with type 2 diabetes also showed a significant decrease in blood pressure with the TZD.[48] Rosiglitazone decreased systolic and diastolic blood pressure by 5 to 6 mm Hg in patients with type 2 diabetes.[49,50] By improving blood pressure, TZDs may provide another mechanism to prevent long-term vascular complications in patients with type 2 diabetes.

Hemostasis and Fibrinolysis

A direct correlation exists between insulin resistance and increased levels of plasminogen activator inhibitor type-1 (PAI-1). Levels of PAI-1 are elevated in patients with type 2 diabetes.[36] Increases in PAI-1 concentrations and corresponding inhibition of fibrinolysis indicate alterations in coagulation that may be associated with increased arterial thrombosis. PAI-1 directly antagonizes the activity of tissue plasminogen activator (tPA), which blocks the conversion of plasminogen to plasmin and slows the breakdown of fibrinogen. When fibrinogen levels increase, clot lysis is inhibited.[51] In addition, increased levels of PAI-1 in the arterial wall may play a role in the pathogenesis of thrombosis and myocardial infarction. Bruno and associates[52] demonstrated that patients with type 2 diabetes had a higher prevalence of hyperfibrinogenemia, and fibrinogen level was independently associated with HbA_{1c} levels.

TZDs have been shown to decrease levels of PAI-1, which could lead to beneficial effects on cardiac outcomes. A 26-week, double-blind study evaluated glyburide alone compared with glyburide in combination with rosiglitazone in 114 patients with type 2 diabetes.[39] The patients receiving glyburide and rosiglitazone had a 21.8% decrease in PAI-1 antigen and a 33.8% decrease in PAI-1 activity; hemostatic markers increased in the glyburide group. A decrease in PAI-1 levels also has been observed with troglitazone therapy.[53] These findings suggest that TZDs may play a critical role in reducing endothelial damage by improving fibrinolytic activity and hemostatic function, which could potentially lead to a decreased risk for cardiovascular events.

Inflammation and Vascular Effects

Insulin modulates vasodilatory properties of the vasculature. However, the presence of insulin resistance in individuals with type 2 diabetes diminishes this response.[54] C-reactive protein (CRP) and interleukin-6 (IL-6) are nontraditional, independent markers of inflammation. Elevated CRP levels are associated with increased cardiovascular risks and correlate with insulin sensitivity.[55,56] Treatment with TZDs has been shown to reduce certain proinflammatory markers. Mohanty and colleagues[57] reported a decrease in CRP of 30% when 11 obese patients without diabetes were treated with rosiglitazone 4 mg daily for 6 weeks. Another randomized, double-blind study evaluating 357 patients with type 2 diabetes assessed the efficacy of rosiglitazone on CRP, IL-6, and matrix metalloproteinase-9 (MMP-9).[58] A significant decrease in CRP levels (26.8%; $P<.05$) and MMP-9 levels (12.4%; $P<.05$) from baseline was observed in the rosiglitazone treatment group; however, IL-6 levels were similar in the rosiglitazone and placebo groups. Studies with troglitazone also show a similar reduction in inflammatory markers.[59] The decrease in CRP with statins also is associated with a decrease in cardiac events.[60] Although cardiac outcome studies with TZD therapy are still awaited, the improvement in insulin sensitivity and decrease in inflammatory and hemostatic markers suggest that these agents hold the promise of cardiovascular benefit in patients with diabetes.

Insulin resistance impairs the

vasodilatory effects of insulin on the vasculature.[61] Studies have shown that the insulin-sensitizing effects of TZDs improve endothelium-dependent vascular response.[57,62] Increased levels of asymmetric dimethylarginine (ADMA) have been associated with endothelial dysfunction and increase cardiovascular risk, and recent studies have shown that rosiglitazone significantly decreases ADMA levels.[63] In an accompanying editorial, it was recommended that physicians involved in the care of patients with cardiovascular disease read the Stuhlinger article at least twice because of the importance of the relationship between insulin resistance and plasma ADMA levels.[64] Endothelial dysfunction increases glomerular permeability, leading to an increase in urinary albumin excretions. Notably, treatment with rosiglitazone decreased microalbuminuria by 54% in patients with diabetes.[65] Similar improvements in albumin excretion have been observed with pioglitazone and troglitazone.[66,67] The potential benefits of insulin-sensitizing agents on endothelial dysfunction and vasodilation make TZDs particularly valuable for patients with type 2 diabetes.

Outcome Trials

Current data hold the promise that early therapy with TZDs may be beneficial for the prevention of macrovascular complications. Several outcome trials are being conducted to address the effect of TZDs on cardiovascular outcomes, specifically, prevention of macrovascular complications. A Diabetes Outcome Progression Trial (ADOPT) is an international, multicenter study of the comparative efficacy of rosiglitazone, glyburide, or metformin in patients recently diagnosed with type 2 diabetes.[68] Patients will be titrated to the maximum daily dose of 1 of the 3 medications and treated for 4 years. This trial will provide important data comparing the efficacy of these agents, including time to failure and whether these medications improve β-cell function and markers of cardiovascular disease. Action to Control Cardiovascular Risk in Diabetes (ACCORD) is another trial investigating the best method of delaying macrovascular complications by stringent control of glycemia (HbA_{1c} <6%), cholesterol, and blood pressure.[69] The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial and Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial are currently evaluating the role of TZDs with regard to improving glycemic control and cardiovascular risk factors. The DREAM trial will study primary prevention of type 2 diabetes in 4000 high-risk patients, whereas the RECORD trial will evaluate the effect of glycemic control on prevention of cardiovascular end points in type 2 diabetes. The results of these studies and other ongoing studies are eagerly anticipated and should help healthcare providers determine the most effective therapy for preventing long-term complications in patients with type 2 diabetes.

CORNERSTONE OF THERAPY

The use of conventional medications such as sulfonylureas or insulin to lower HbA_{1c} levels may lead to hypoglycemia. Additionally, the UKPDS showed that these agents do not maintain durable glycemic control when used alone. The potential to achieve target HbA_{1c} levels without producing hypoglycemia makes TZDs appealing for use in clinical practice.[19,70] TZDs offer a variety of benefits that support early use in the management of type 2 diabetes. They effectively lower glucose levels, improve insulin sensitivity, preserve β-cell function, and may exert beneficial cardiovas-

cular effects. The UKPDS showed that the lower the HbA_{1c} level, the lower the risk for long-term complications.[16,17] Therefore, attaining and maintaining HbA_{1c} treatment goals is critical in the management of type 2 diabetes.

Currently, lifestyle modifications such as diet and exercise should be initiated early and maintained throughout the course of therapy in patients with diabetes. If HbA_{1c} levels remain above 7%, pharmacologic therapy may be initiated (Figure 1). Monotherapy with rosiglitazone has been shown to decrease HbA_{1c} levels without causing hypoglycemia.[19] A multicenter, double-blind trial studied once- and twice-daily dosing with rosiglitazone.[70] HbA_{1c} levels significantly decreased between 0.8% and 1.5% depending on the dose (P<.0001). Overall, once-daily dosing controlled glycemia in drug-naive patients, however, 4 mg twice daily may be necessary for more advanced diabetes.

Many patients eventually require combination therapy to reach the HbA_{1c} target glucose level of 7.0% or lower.[1] If HbA_{1c} levels remain above 7% for patients on monotherapy, combination treatment may be considered. Because TZDs and biguanides lower glucose levels by complementary mechanisms, combining these drugs increases their potential benefits. Inzucchi and colleagues[71] evaluated the efficacy and metabolic effects of metformin and troglitazone in 29 patients with type 2 diabetes.[71] Patients received either metformin or troglitazone for 3 months and then both drugs simultaneously thereafter. During monotherapy, both drugs showed comparable decreases in glucose concentrations; however, combining the drugs lowered fasting and postprandial glucose by an additional 18% and 21%, respectively.

In another study, combination therapy with metformin and rosiglitazone was studied in 300 patients whose diabetes was inadequately controlled with metformin alone (2.5 g/day).[53] The study showed significant dose-dependent improvement in HbA_{1c}, fasting glucose, and β-cell function in the metformin-rosiglitazone groups. Mean levels of HbA_{1c} decreased by 1.0% and 1.2% in the 4-mg and 8-mg rosiglitazone groups, respectively (P<.001). Of the patients who received 8 mg/day of rosiglitazone in combination with metformin, 28.1% achieved an HbA_{1c} level of 7% or less (P<.001). The effect on long-term glycemic control is also consistent with the improvement in insulin sensitivity and β-cell function. The combination of a TZD with metformin decreases hyperglycemia with a low risk for hypoglycemia, improves insulin sensitivity, preserves β-cell function, and may improve cardiovascular outcomes. Thus, TZDs, either alone or in combination, should be considered early in the course of therapy for patients with type 2 diabetes.

CONCLUSION

Type 2 diabetes is a growing epidemic in the United States and is a disease associated with significant long-term complications. An important underlying cause of macrovascular complications is insulin resistance, characterized by a cluster of metabolic abnormalities known as the metabolic syndrome. The TZDs improve insulin sensitivity and measures of β-cell function. Thereby, these agents not only improve glycemic control, but, moreover, have a sustained durable effect over time. In addition, various studies have shown that TZDs improve lipid profiles and vascular function, potentially reducing the risk of cardiovascular events. Other potential cardiovascular benefits associated with TZD therapy include reduction in blood pressure, improvement in hemostatic parameters, and reduction in inflamma-

tory markers. Currently, several ongoing trials are being conducted to address the role of the TZDs in the prevention and management of type 2 diabetes and associated cardiovascular complications. Because the TZDs provide durable glycemic control with favorable effects on measures of β-cell function and consistent benefit on numerous cardiovascular risk factors, these agents should be initiated early in the course of therapy and should be considered a cornerstone of therapy for patients with type 2 diabetes.

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