The Role of the Thiazolidinediones in the Practical Management of Patients With Type 2 Diabetes and Cardiovascular Risk Factors

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The American Diabetes Association's objective for treating patients with type 2 diabetes mellitus is to normalize glycemia and glycosylated hemoglobin concentrations while controlling blood pressure, cholesterol, and other cardiovascular risk factors. This article focuses on the role of thiazolidinediones (TZDs) in the management of patients with type 2 diabetes with comorbid cardiovascular disease. Insulin resistance is one of the earliest and main defects in type 2 diabetes and is strongly linked to comorbid cardiovascular conditions. The TZDs rosiglitazone and pioglitazone work mainly by reducing insulin resistance and may have the potential to alter the natural history of type 2 diabetes and reduce the cardiovascular mortality and morbidity associated with this condition.
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Diabetes is a metabolic disease characterized by elevated blood glucose levels and micro- and macrovascular complications that reduce quality of life and substantially increase morbidity and mortality. The pathophysiologic basis for vascular disease is related to the presence of hyperglycemia in both type 1 and type 2 diabetes. Results of the Diabetes Control and Complications

Trial (DCCT) have clearly demonstrated the benefits of normalizing glycosylated hemoglobin (HbA_{1c}) in patients with type 1 diabetes mellitus.[1] Indeed, the DCCT proved conclusively that intensive diabetes management with near-normal glycemia delays the onset and significantly retards the progression of microvascular complications. The results were so compelling that the study was terminated early, and a new standard of care was established for patients with this form of diabetes.

In patients with type 2 diabetes, the benefits of intensive glucose control have been clearly demonstrated by the results of the United Kingdom Prospective Diabetes Study (UKPDS).[2] As in type 1 diabetes, the pathophysiologic basis for vascular disease is related to the duration and severity of uncontrolled hyperglycemia. Type 2 diabetes mellitus, however, is also associated with insulin resistance, hyperinsulinemia, and several other metabolic abnormalities, including obesity, hypertension, and dyslipidemia (collectively called the insulin resistance syndrome or the metabolic syndrome), which contribute to the development of accelerated vascular disease.[3] Although type 2 diabetics suffer from their microvascular complications, they ultimately die of atherosclerotic cardiovascular disease (CVD).

The American Diabetes Association now recommends that the glycemic objective for patients with type 2 diabetes should be similar to that for type 1 diabetes: to normalize glycemia and HbA_{1c} concentrations. In addition, aggressive therapy to control blood pressure, cholesterol, and other cardiovascular risk factors is warranted. This article focuses on the role of the thiazolidinediones (TZDs) in the practical management of patients with type 2 diabetes with comorbid CVD.

Pathophysiology of Type 2 Diabetes

Of the estimated 16 million Americans diagnosed with type 2 diabetes, more than 80% are obese and the remainder are lean.[4] The genesis of hyperglycemia in type 2 diabetes involves a triad of abnormalities: excessive hepatic glucose production, impaired pancreatic insulin secretion, and peripheral resistance to insulin action occurring principally in liver and muscle tissue.[5,6] The severity of these abnormalities and their contribution to the degree of hyperglycemia can vary considerably, causing heterogeneity in the metabolic expression of the diabetic state. In lean type 2 diabetics, impaired insulin secretion is the predominant defect and insulin resistance tends to be less severe than in obese type 2 diabetics.[7] On the other hand, insulin resistance and hyperinsulinemia are the classical abnormalities of obese patients with type 2 diabetes.[7] In this form of diabetes, insulin secretion is often excessive compared with that of the nondiabetic situation but is still insufficient to overcome the insulin resistance that is present. Because insulin resistance is one of the earliest and main defects in type 2 diabetes and is strongly linked to the associated comorbid CVD conditions, it is important to consider the use of TZDs, often referred to as "insulin sensitizers," as an important therapeutic pharmacologic agent in the clinical management of type 2 diabetes.

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TZDs: Pioglitazone and Rosiglitazone

The TZDs work mainly by reducing insulin resistance and appear to be ideally suited for treatment of the cardiovascular dysmetabolic syndrome. These agents are chemically and functionally unrelated to the other classes of oral antidiabetic agents. A thiazolidine -2,4-dione structure is common to all agents of this class, but they differ in their side chains, which alter their pharmacologic and side effect profiles. Two compounds in this class are presently approved for use in the United States. Rosiglitazone was approved in May 1999 and pioglitazone was granted approval in July 1999. The first agent in this class, troglitazone, was marketed in the U.S. from March 1997 until it was withdrawn in March 2000, when the U.S. Food and Drug Administration determined that the risk of idiosyncratic hepatotoxicity associated with troglitazone therapy outweighed its potential benefits. In clinical use so far, rosiglitazone and pioglitazone appear to be devoid of idiosyncratic, fulminate hepatotoxicity. Rosiglitazone and pioglitazone are approved for use as monotherapy and also in combination with insulin, metformin, or a sulfonylurea (SFU).

The mechanism of action indicates that the TZDs are highly selective and potent agonists for the peroxisome proliferator activated receptors (PPARs). The PPARs are a family of nuclear receptors comprised of three subtypes designated PPAR α, PPAR γ, and PPAR δ.[9] PPAR receptors are found in key target tis-

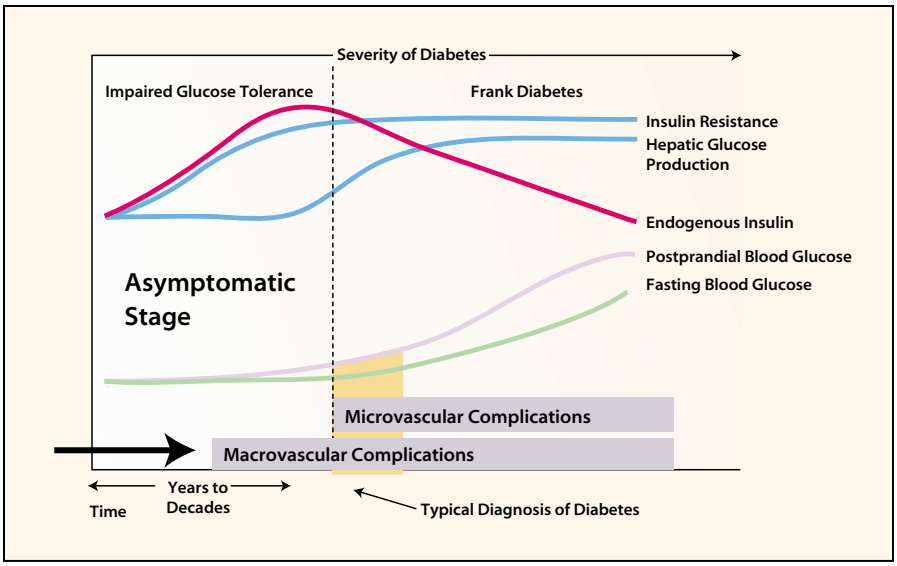

Figure 1. *The natural history of type 2 diabetes. Adapted with permission from Ramlo-Halsted and Edelman.*[11]

sues for insulin action, such as adipose tissue, skeletal muscle, and liver, and there is strong evidence to indicate that these receptors may be important regulators of adipocyte differentiation, lipid homeostasis, and insulin action.[9] Although the TZDs differ in structure, their clinical effects appear to be fairly homogenous, especially in terms of glucose control and reducing traditional and nontraditional cardiovascular risk factors, such as hypercoagulation, cardiac inflammation, endothelial dysfunction, and vasculopathy. Clinical studies on all of these cardiovascular risk factors have not been fully completed in all three TZDs; however, the data published so far have been extensive, very positive, and consistent.[10]

The Natural History of Type 2 Diabetes and the Potential Role of TZD Therapy

The natural history of type 2 diabetes directly reflects the interrelationships among the three defects of type 2 diabetes: insulin resistance, hepatic glucose production, and ß cell deficiency (Figure 1).[11] The primary and earliest pathogenic lesion is insulin resistance, with the ß cell able to compensate for a variable length of time by secreting supraphysiologic amounts of insulin. Insulin resistance, compensatory hyperinsulinemia, and mild postprandial hyperglycemia characterize impaired glucose tolerance (IGT). It is at this early stage in the natural history that insulin sensitizers may have their greatest impact on the disease. Over time in the untreated state, the ß cell begins to fail, and as relative insulin deficiency occurs, fasting hyperglycemia and full-blown type 2 diabetes develop. In addition, as insulin levels fall, the inhibitory effect of insulin on hepatic glucose production decreases and significant fasting hyperglycemia develops. Further progression of the disease is marked by an absolute insulin deficiency. It is this later stage in the natural history that characterized the subjects who were randomized into the UKPDS. It has been estimated that these "newly diagnosed" subjects had only 50% of their ß cell function at the time of randomization. No wonder all of the therapeutic interventions failed, and because of this study, type 2 diabetes has been classified as a "progressive disease"[12] (Figure 2).

The TZDs are ideally suited to possibly alter the natural history of type 2 diabetes. Early short-term studies with troglitazone in patients with IGT demonstrated impressive improvements in glycemic control into the nondiabetic range compared with placebo.[12] These and other studies were used when considering what interventions were to be used in the Diabetes Prevention Program (DPP).

The DPP is a National Institutes of Health–funded long-term study that was designed to determine whether diabetes could be prevented or delayed in people who have risk factors for developing type 2 diabetes (IGT).[12] The participants were put into one of four treatment groups. The first group was the intensive lifestyle group, who were encouraged to exercise at least 150 minutes a week and lost 10–15 pounds over the 3-year duration of the study. The other three groups were put on either metformin, troglitazone, or placebo, with only minimal lifestyle changes.

Compared with the placebo group, the subjects randomized to the intensive lifestyle group reduced

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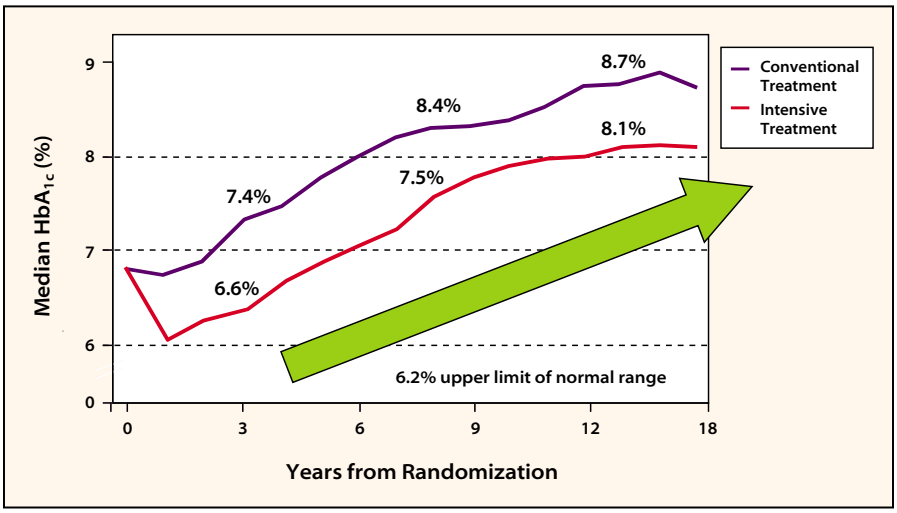

Figure 2. *Glycosylated hemoglobin (HbA_{1C}) in the UK Prospective Diabetes Study. Adapted from UK Prospective Diabetes Study Group.*[2]

their chances of developing type 2 diabetes by an impressive 58%. The individuals who were given metformin with minimal lifestyle changes showed a reduction in the development of diabetes by 31% over the 3-year study, compared with the placebo group. There was also a very significant ~75% reduction in the conversion to type 2 diabetes in the troglitazone group after 1 year, although the agent was withdrawn from the study and the U.S. market because of liver toxicity. The TRIPOD (Troglitazone in the Prevention of Diabetes) study also showed impressive results in preventing diabetes, as discussed by Dr. Goldstein earlier in this supplement.

Screening patients for IGT is probably the best method for identifying high-risk individuals because postprandial hyperglycemia occurs typically before the onset of fasting hyperglycemia in the natural history of type 2 diabetes. However, diagnosis of IGT relies on an oral glucose tolerance test, a diagnostic test that is used rarely in comparison to fasting plasma glucose (FPG) in general clinical practice because of the FPG test's convenience and greater reproducibility. These practice patterns underscore the importance of the relatively new impaired fasting glucose (IFG) criteria (ie, glucose 110–126 mg/dL) in the clinical setting to recognize people with glucose intolerance at an earlier stage in the natural history of the disease. The presence of both IFG and IGT indicates an increased risk for other syndromes associated with insulin resistance, such as hypertension and dyslipidemia, which also require aggressive diagnostic and therapeutic plans.[12]

Understanding the natural history of type 2 diabetes aids the clinician in identifying those patients most at risk for developing diabetes and in developing an effective treatment plan for those who already have the disease. Each of the available classes of oral antidiabetic agents has a different mechanism of action and is therefore potentially most effective at different stages in the continuum from IGT and IFG to diabetes. Given that insulin resistance is the major pathogenic factor in the "pre-diabetic" state of IGT and continues to persist into diabetes, insulin sensitizers such as the TZDs may be extremely useful as first-line agents in the early treatment of diabetes and in its prevention.

The potential benefits of intervening before the onset of diabetes and aggressively treating once the disease becomes manifest are tremendous. Identifying and treating the individual with IGT will most likely reduce the incidence of macrovascular disease and type 2 diabetes.

Durable Effects on Glycemic Control with the TZDs: Altering the Natural History

It is well known from clinical trials, including the UKPDS, that glucose control deteriorates with time in subjects treated with the traditional oral hypoglycemic agents (Figure 2). Clinical experience of practicing physicians corroborates the clinical trials' results in showing that successful therapy with SFUs is short lived and usually of less than 3–4 years' duration. Long-term open-label extension studies with the TZDs have demonstrated impressive durable glycemic control and lack of secondary failure commonly seen with other oral agents.

In an early open-label extension study, subjects who had diabetes for an average of 8 years who were failing maximum SFU therapy (HbA_{1c}

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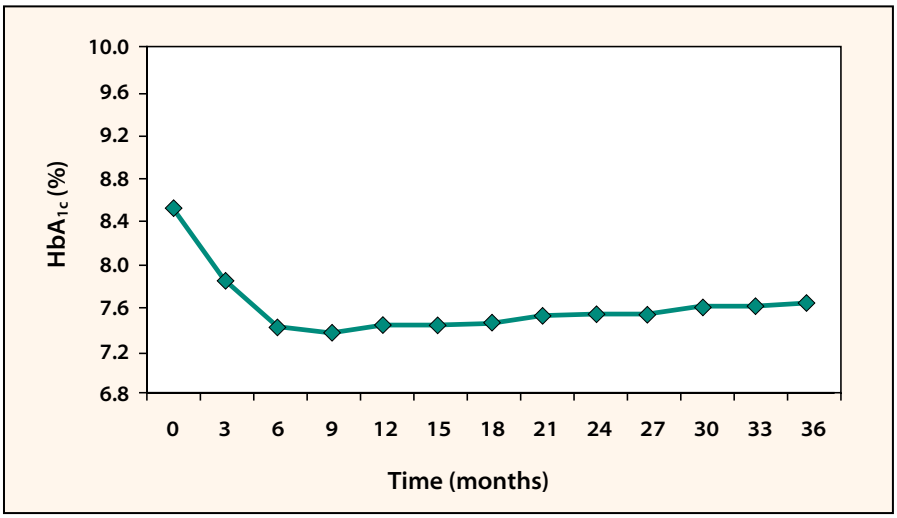

Figure 3. *Long-term rosiglitazone monotherapy (glycosylated hemoglobin [HbA_{1C}]), open-label extension. Patients received rosiglitazone 8 mg once daily or 4 mg twice daily for at least 36 months. Study/open-label extension: 011,024/084, 105. Data on file, GlaxoSmithKline.*

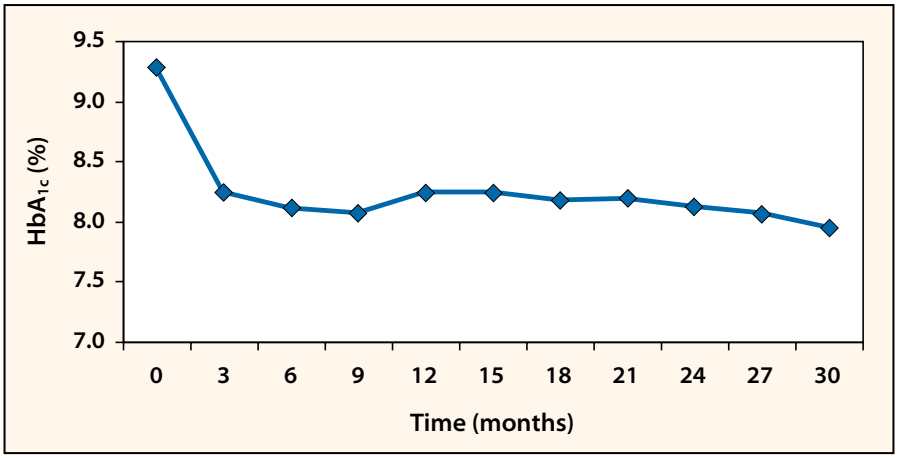

Figure 4. *Long-term rosiglitazone plus sulfonylurea (SFU), open-label extension. Patients received rosiglitazone 2 mg twice daily plus glyburide for at least 30 months. HbA_{1C}, glycosylated hemoglobin. Study/open-label extension: 079/112. Data on file, GlaxoSmithKline.*

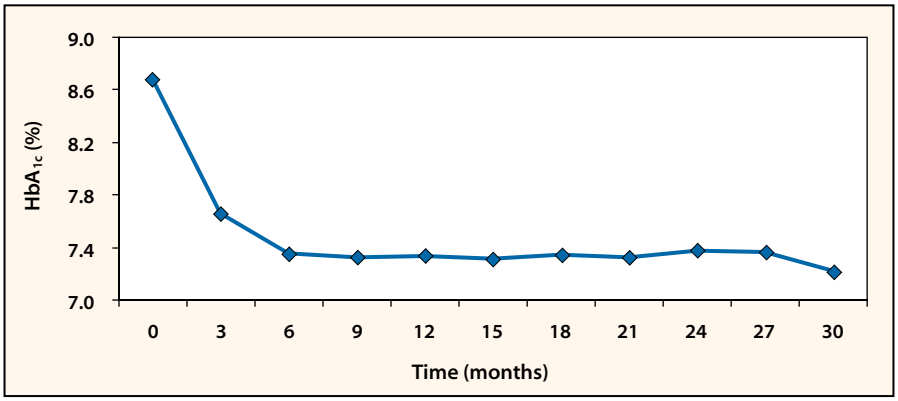

Figure 5. *Effects of rosiglitazone and metformin on glycemic control, open-label extension. Patients received rosiglitazone 4 mg twice daily plus metformin 2.5 g once daily for at least 30 months. HbA_{1C}, glycosylated hemoglobin. Study/open-label extension: 093/113. Data on file, GlaxoSmithKline.*

~9.4% at the time of randomization) maintained glycemic control (HbA_{1C} ~7.4%) for more than 2 years with the addition of troglitazone.[13] Similar studies are being conducted with both rosiglitazone and pioglitazone. Figures 3, 4, and 5 demonstrate the durable glycemic effects of rosiglitazone when used alone (Figure 3) and in combination with SFUs (Figure 4) and metformin (Figure 5). The lack of secondary failure has also been seen with pioglitazone (Figure 6).[14–17] These studies looking at durable glycemic control are open-label extension studies and have been open to criticism concerning selection bias because the subjects volunteered to enter the open-label phase.

Until recently, there was only one small, randomized, double-blind trial demonstrating a significantly reduced secondary failure rate of troglitazone monotherapy compared with an SFU over a 2-year treatment period.[18] A recently completed, larger, 2-year randomized, double-blind clinical trial compared the durability of rosiglitazone added to one-half maximum glipizide therapy versus uptitrated SFU therapy alone in preventing deterioration of glycemic control.[19] This study clearly demonstrates that, when rosiglitazone is added to the therapy of patients failing one-half maximum SFU, the secondary failure rate—defined as fasting blood sugar >180 mg/dL on two occasions—is very low (two failures) and significantly less than the rate in patients randomized to maximum SFU therapy alone (27 failures). By reducing insulin resistance with TZDs and reducing the stress put on the pancreas, it is intuitive that there would be a reduced rate of secondary failure with these agents. These data substantiate the open-label studies and demonstrate that the natural history of type 2 diabetes can be altered and that type

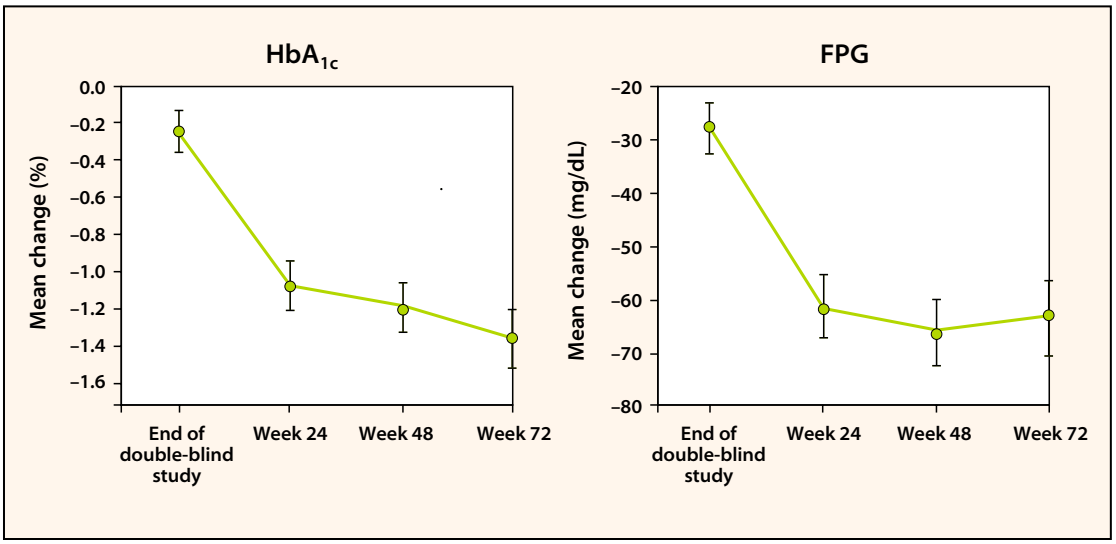

Figure 6. *Effects of pioglitazone and metformin on glycemic control, open-label extension. HbA_{1C}, glycosylated hemoglobin; FPG, fasting plasma glucose. Reproduced with permission from Einhorn et al.*[17]

2 diabetes may not have to be a "progressive disease."

Practical Use of TZDs in Clinical Practice

Pre-diabetes

Although not officially indicated, TZDs may have their greatest impact on the prevention of type 2 diabetes in subjects at risk for this condition. By preventing hyperglycemia and improving the cardiovascular risk factors that are often present in the pre-diabetic state, a significant amount of human suffering can be avoided and the drain on the health care dollar diminished. Only after several large multicenter clinical studies are completed will TZDs possibly be indicated for the prevention of type 2 diabetes and cardiovascular disease. Until then, they are used off-label by a minority of caregivers in this high-risk group, usually because they are driven by an educated, proactive patient.

Monotherapy

Monotherapy with the TZDs results in significant improvement in FPG by 60–80 mg/dL and HbA_{1C} by 1.4%–2.6% as compared with placebo.[10] Currently, the TZD class of oral agents is typically not used as first-line therapy but rather as a third-line addition to treatment of patients failing maximum doses of SFU and metformin. The latter scenario is due to many reasons, including restricted access by some managed care organizations. The maximum benefits of TZDs on glucose control are not seen when used as third-line therapy because these patients are hyperglycemic, are insulinopenic, and may have some degree of glucose toxicity as well. The improvements in cardiovascular risk factors are still in effect, although caregivers and patients may not appreciate these benefits because they are invisible compared with daily glucose measurements. The beneficial effects of TZDs on glucose control are seen when TZDs are used early in the natural history, when there is an adequate amount of endogenous insulin in the circulation. Insulin, either endogenous or exogenous, must be present for TZDs to have the maximal effect. An asymptomatic patient who is relatively newly diagnosed, with average glucose values < 200 mg/dL, may be an excellent candidate for TZD as initial monotherapy.[12]

Combination of TZDs and Other Oral Agents

The addition of TZDs to metformin is a very advantageous combination because there is little or no risk of hypoglycemia, the weight gain seen with TZDs is minimized by metformin, and both of these agents have demonstrated cardiovascular risk reduction. In a double-blind, placebo-controlled trial, more than 300 subjects were randomized to either 2500 mg/day of metformin plus either placebo, or 4 or 8 mg/d of rosiglitazone. After 6 months, FPG levels were 40 mg/dL lower with a reduction in HbA_{1c} of 1.0% in the 4 mg rosiglitazone/metformin group and 53 mg/dL lower with a reduction in HbA_{1c} of 1.2% in the 8 mg rosiglitazone/metformin group. In addition, ß cell function as measured by the HOMA improved significantly.[19,20]

Pioglitazone is also effective in combination with metformin. In a large 16-week study, compared with placebo, pioglitazone at 30 mg/d significantly reduced FPG by 38 mg/dL and reduced HbA_{1C} by 0.8%.[21]

It is important to mention that the improvements in cardiovascular risk factors, such as fibrinogen and C-

reactive protein, may not be realized in these clinical trials because they emphasize only glycemic control.

TZDs and insulin secretagogues, such as SFUs, are also an excellent combination, although there is a risk of hypoglycemia as well as the potential for weight gain. In a double-blind study, pioglitazone 30 mg/d was added to an SFU, resulting in a reduction in FPG of 58 mg/dL and a reduction in HbA_{1C} of 1.3%.[22] Similar reductions have also been seen in studies combining rosiglitazone and SFUs.[22]

The combination of TZDs and the fast-acting non-SFU insulin secretagogues is also clinically attractive because drugs such as nateglinide and repaglinide do not chronically stimulate the pancreas and may confer a reduced rate of hypoglycemia. α-glucosidase inhibitors, such as acarbose and miglitol, can also be used in combination with TZDs, although large clinical trials using these medications are lacking.

Combination of Insulin and TZDs

The TZDs are potent insulin sensitizers, thus are well suited for use in insulin-requiring patients with type 2 diabetes. In several studies, troglitazone was documented to not only improve glycemic control, but also to reduce exogenous insulin requirements in obese patients with type 2 diabetes.[23] It is important to realize that the main reason for using a TZD with insulin is to improve glycemic control, not to reduce insulin requirements. Reducing insulin requirements is a secondary benefit. Both rosiglitazone and pioglitazone agents have been shown to improve glycemia when combined with insulin. In one 16-week study, Rubin and co-workers[24] demonstrated that adding pioglitazone 15 mg and 30 mg daily to the therapy of patients receiving a median dose of 60.5 U insulin resulted in mean FPG reductions of 36 mg/dL and 49 mg/dL and HbA_{1C} reductions of 0.7% and 1.0%, respectively, compared with placebo. The insulin-sparing properties of rosiglitazone were shown in a 6-month study conducted by Raskin and colleagues.[25] They demonstrated that the addition of rosiglitazone 2 mg twice daily and 4 mg twice daily improved glycosylated hemoglobin by 0.6% and 1.2%, respectively, as compared with placebo in 312 patients with type 2 diabetes uncontrolled on ~70 U insulin daily (baseline HbA_{1C}, 9%). Moreover, insulin requirements were also reduced by ~5 U and 10 U in the two rosiglitazone treatment groups in keeping with the insulin-sensitizing effects of the TZDs.

When initiating TZD treatment in type 2 diabetic subjects who are on insulin and have suboptimal glucose control, the current insulin dosage should be continued and the lowest dosage of the TZD should be added once daily with a meal. If FPG levels are consistently > 140 mg/dL, the TZD dosage should be increased after 2–4 weeks, up to the maximum daily dosage, until FPG levels are consistently within the target range. Only when blood glucose is under control may the total daily dosage of insulin be lowered by 10%–25%.

Side Effects Limiting Success with TZDs

The main concern with troglitazone was liver toxicity, which is why it was withdrawn from the market. At this point, after extensive use of TZDs around the world in millions of people, liver toxicity does not seem to be an important clinical problem. Baseline liver function tests should be measured, and if abnormal, an investigation should be initiated into the primary cause. Hepatitis or fatty liver often may be the culprit. Therapy with TZDs should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 times the upper limit of normal).[10] In patients with normal baseline liver enzymes, following initiation of therapy with rosiglitazone or pioglitazone, it is recommended that liver enzymes be monitored every 2 months for the first 12 months and periodically thereafter. Patients with mildly elevated liver enzymes (alanine aminotransferase [ALT] levels 1.0 to 2.5 times the upper limit of normal) at baseline or during therapy with rosiglitazone or pioglitazone should be evaluated to determine the cause of the liver enzyme elevation. Initiation, or continuation, of therapy with a TZD in patients with mild liver enzyme elevations should proceed with caution and include appropriate close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time, ALT levels increase to more than three times the upper limit of normal in patients on therapy with rosiglitazone or pioglitazone, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain greater than three times the upper limit of normal, TZD therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, and/or dark urine, liver enzymes should be checked.[10] The decision whether to continue the patient on therapy with rosiglitazone or pioglitazone should be guided by clinical judgment pending laboratory evaluation. If jaundice is observed, drug therapy should be discontinued.

Fluid retention, ankle edema,

weight gain, and precipitation of congestive heart failure (CHF) in patients with underlying heart disease represent the major concern of most caregivers. When looking at the incidence of these side effects, it is very important to analyze double-blind, placebo-controlled trial data and not rely on anecdotal information.

Because of increases in plasma volume, both TZDs should be used cautiously in patients with peripheral edema or early CHF. TZDs have caused pre–load-induced cardiac hypertrophy in preclinical studies. In three echocardiographic clinical studies (a 52-week study using rosiglitazone 4 mg PO twice daily, a 26-week study using rosiglitazone 8 mg PO once daily, and a 26-week trial with pioglitazone) in patients with type 2 diabetes, no deleterious alterations in cardiac structure or function were observed.[26,27] These studies were designed to detect a change in left ventricular mass of 10% or more. Patients with severe CHF, defined as New York Heart Association (NYHA) functional class III and IV, were not studied. As a result, patients with NYHA class III or IV heart failure should not receive a TZD unless the expected benefit is judged to outweigh the potential risk.[22,27]

Conclusion

TZDs improve the main and earliest defect in type 2 diabetes, namely, insulin resistance. The benefits go far beyond glucose control as they improve many of the traditional and nontraditional cardiovascular risk factors seen in type 2 diabetes. TZDs may have their greatest impact on the prevention of type 2 diabetes in subjects at risk for this condition. By preventing hyperglycemia and improving cardiovascular risk factors that are often present in the pre-diabetic state, a significant amount of human suffering can be avoided and the drain on the health care dollar diminished. It will only be after several large multicenter clinical studies are completed that TZDs may be indicated for the prevention of type 2 diabetes and cardiovascular disease.

TZD therapy has been shown to be beneficial in all stages of the natural history of diabetes. In the early stages, TZDs work well as monotherapy with the caveat that the patient has sufficient amounts of endogenously produced insulin and there is not a significant amount of glucose toxicity. In the middle stages of the natural history, TZDs are very effective when used in combination with metformin, SFUs, and other oral agents. The response to these various combinations depends on the degree of glucose control, duration of diabetes, and other concomitant conditions. Lastly, in the later stages of type 2 diabetes, when endogenous insulin secretion is

Main Points

- Because insulin resistance is one of the earliest and main defects in type 2 diabetes and is strongly linked to the associated comorbid cardiovascular conditions, it is important to consider the use of thiazolidinediones (TZDs), often referred to as "insulin sensitizers," as an important therapeutic pharmacologic agent in the clinical management of type 2 diabetes.
- The TZDs work mainly by reducing insulin resistance and appear to be ideally suited for treatment of the cardiovascular dysmetabolic syndrome.
- Given that insulin resistance is the major pathogenic factor in the "pre-diabetic" state of impaired glucose tolerance and continues to persist into diabetes, insulin sensitizers such as the TZDs may be extremely useful as first-line agents in the early treatment of diabetes and in its prevention.
- Long-term open-label extension studies with the TZDs have demonstrated impressive durable glycemic control and lack of secondary failure commonly seen with other oral agents.
- The addition of TZDs to metformin is a very advantageous combination because there is little or no risk of hypoglycemia, the weight gain seen with TZDs is minimized by metformin, and both of these agents have demonstrated cardiovascular risk reduction.
- The TZDs are potent insulin sensitizers, thus are well suited for use in insulin-resistant patients with type 2 diabetes. Reducing insulin requirements is a secondary benefit. It is important to realize that the main reason for using a TZD with insulin is to improve glycemic control, not to reduce insulin requirements.
- Therapy with TZDs should not be initiated in patients with increased baseline liver enzyme levels. In patients with normal baseline liver enzymes, following initiation of therapy with rosiglitazone or pioglitazone, it is recommended that liver enzymes be monitored every 2 months for the first 12 months and periodically thereafter.

very low and exogenous insulin is required, TZDs work well to control hyperglycemia in addition to reducing cardiovascular risk factors.

Insulin resistance is not only one of the main defects of type 2 diabetes, it is also intimately related to the cardiovascular comorbid conditions of type 2 diabetes. It makes strong clinical sense that by improving insulin resistance, there will also be a diminished demand on ß cell, and there is the potential for altering the natural history of type 2 diabetes. ■

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