

# Management of Type 2 Diabetes: Focus on the Thiazolidinediones

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In 1988, Reaven<sup>1</sup> introduced a concept that linked the hormone insulin and resistance to its biological activity with a cluster of cardiovascular risk factors that included visceral obesity, complex lipid abnormalities, hypertension, and impaired glucose tolerance. This cluster of risk factors is now known as the metabolic syndrome or the insulin resistance syndrome. More recently, it has become apparent that insulin resistance, the metabolic syndrome, cardiovascular disease, and the development of type 2 diabetes are related.<sup>2</sup> Patients with the metabolic syndrome have an increased risk of developing type 2 diabetes, most likely by possessing a genetic predisposition to the disease in an environment of insulin resistance and hyperinsulinemia. Pancreatic beta cells, unable to withstand the biological stresses associated with insulin resistance, begin to die through apoptosis, or programmed cell death. Unabated apoptosis gradually leads to diminished beta cell numbers, eventual beta cell failure, and clinical diabetes.

In patients with type 2 diabetes, endothelial dysfunction associated with hyperglycemia<sup>3,4</sup> in combination with increases in blood pressure and dyslipidemia results in atherosclerotic macrovascular complications. By the time most patients are diagnosed with clinical diabetes, many have advanced macrovascular complications, including coronary heart disease, atherosclerosis, and systolic dysfunction. Often, type 2 diabetes is the end stage of a process that has been present for years prior to its detection (**Figure 1**). Elevated fasting plasma glucose (FPG) concentrations are in fact often late findings in the course of this disease. Increases in postprandial glucose concentrations precede increases in FPG levels by years, but are seldom identified in clinical practice.

The prevalence of type 2 diabetes mellitus in the United States has increased by 33% over the past decade.<sup>5</sup> More than 18 million Americans now have diabetes,<sup>6</sup> and the number is expected to double in the next 25 years. In 2002, the estimated national cost of diabetes was approximately \$132 billion,<sup>7</sup> and this number is expected to increase to \$156 billion in 2010 and to \$192 billion by 2020. Eliminating or reducing the health care problems caused by diabetes through

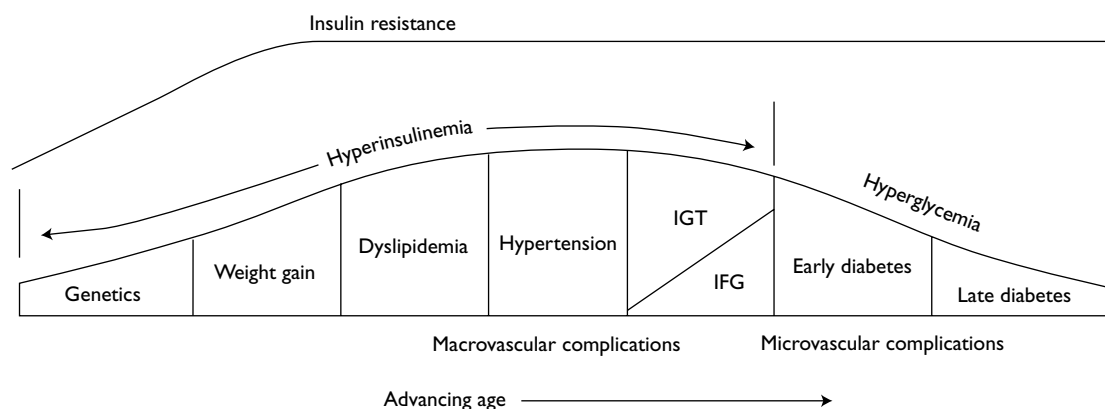
## TAKE HOME POINTS

- Insulin resistance is a common pathophysiologic element in the metabolic syndrome and type 2 diabetes.
- Data suggest that, in addition to improving plasma glucose levels, thiazolidinediones (TZDs) improve both insulin sensitivity and beta-cell function, 2 key elements in the pathophysiology of type 2 diabetes.
- Although TZDs are not used as first-line agents, some data suggest that TZDs may be more beneficial when used earlier in the treatment of type 2 diabetes when there are more beta cells to preserve and there is a better chance of improving insulin sensitivity.
- TZDs are usually initiated at low doses, and the onset of action is 8 to 12 weeks.
- Adverse effects associated with TZDs include weight gain and edema. Monitoring of liver enzymes is recommended.

factors such as preventative care, early diagnosis, and early, intensive disease management will likely reduce health care expenditures while improving the quality of life for people with diabetes.

The United Kingdom Prospective Diabetes Study (UKPDS) provided valuable information about the treatment of type 2 diabetes.<sup>8</sup> In spite of early and aggressive treatment in that study, therapy with sulfonylureas, metformin, or insulin failed to preserve beta-cell function over time. All treatment arms failed to control glycosylated hemoglobin (HbA<sub>1c</sub>) levels, indicating a continued loss of beta cells and beta-cell function. For many clinicians, the paradigm of “treatment failure” in diabetes seems to be instinctive—use one medication until it fails and then continue the process

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**Figure 1.** The insulin resistance syndrome and course of type 2 diabetes mellitus. IFG = impaired fasting glucose; IGT = impaired glucose tolerance.

until all therapies have failed. However, there are data to suggest that the thiazolidinedione (TZD) class of antidiabetic agents may preserve beta cells and provide positive metabolic effects in patients with type 2 diabetes.<sup>9</sup> This article presents a brief case that demonstrates the signs and symptoms of a patient at risk for type 2 diabetes and reviews the efficacy, safety, and tolerability of the TZDs.

### CASE PRESENTATION

A 38-year-old man presents to his primary care physician requesting a refill of his allergy medication that he takes year-round for his perennial allergic rhinitis. On physical examination, the patient's height is 5 ft 9 in and his weight is 225 lb, resulting in a body mass index of 32. Vital signs are stable, but his blood pressure is 140/90 mm Hg. The patient's waist measures 40 in. The patient relates that he recently participated in a hospital health fair where he was told that his triglycerides were elevated. He has brought a copy of the results that show a triglyceride level of 220 mg/dL, a low-density lipoprotein cholesterol level of 109 mg/dL, and a high-density lipoprotein cholesterol level of 38 mg/dL. After volunteering this information, the patient's demeanor changes, and he appears much more serious as he recalls that his father was told that he had high cholesterol just before suffering a fatal myocardial infarction at age 50 years. His mother was diagnosed with type 2 diabetes mellitus at age 69 but was told that she could control her disease by diet alone.

Based on the physical examination and family history of cardiovascular disease and type 2 diabetes, the physician orders an FPG test. The results indicate an FPG of 110 mg/dL, which is above normal but lower than the threshold for diagnosis of diabetes (ie,  $\geq 126$  mg/dL).

However, because of a high suspicion for diabetes, a standard 2-hour glucose tolerance test with a 75-g glucose load is administered; this reveals a glucose level of 204 mg/dL. This study is repeated 2 weeks later with similar results, indicating a diagnosis of type 2 diabetes, based on American Diabetes Association (ADA)<sup>10</sup> criteria. An HbA<sub>1c</sub> test reveals a level lower than 6.0%.

### TYPE 2 DIABETES MELLITUS

This patient is one of the millions of Americans with the metabolic syndrome and early type 2 diabetes. He meets all 5 criteria for the diagnosis of the metabolic syndrome: abdominal obesity, elevated blood pressure, hypertriglyceridemia, low high-density lipoprotein cholesterol, and impaired fasting glucose (**Table**).<sup>11</sup> The diagnosis of type 2 diabetes is based on the criteria established by the ADA for an oral glucose tolerance test and not the FPG criteria.<sup>10</sup> Criteria for the diagnosis of diabetes are: symptoms of diabetes plus casual plasma glucose concentration  $\geq 200$  mg/dL; or fasting plasma glucose  $\geq 126$  mg/dL; or 2-hour plasma glucose  $\geq 200$  mg/dL during oral glucose tolerance test using 75-g glucose load.<sup>10</sup> The patient's FPG level was in the range that indicates impaired fasting glucose, not diabetes. However, 2 hours after a standard glucose challenge, his blood glucose concentration exceeded 200 mg/dL, consistent with a diagnosis of type 2 diabetes. Management of this patient requires an understanding of the metabolic syndrome and early type 2 diabetes and their relationship to cardiovascular disease.

### Pathophysiologic Factors

In patients with a genetic predisposition to type 2 diabetes, weight gain is often a visible sign that suggests abnormalities of energy storage and utilization. Weight

gain and increasing plasma free fatty acid levels appear to be critical in activating insulin resistance in skeletal muscle, adipocytes, and the liver. Pancreatic beta cells, which are resistant to the metabolic effects of insulin at normal concentrations, respond to this altered metabolic state by increasing insulin concentrations. Continued stress on beta cells leads to beta-cell failure in patients with limited beta-cell reserve. Hyperinsulinemia translates into abnormal free fatty acid production. In the metabolic syndrome, these abnormalities in free fatty acid generation and energy utilization and storage contribute to endothelial damage and vascular inflammation. In addition, abnormal deposition of free fatty acids in beta cells is part of the pathophysiologic progression to type 2 diabetes.<sup>12,13</sup>

### ROLE OF TZDS IN TREATMENT OF EARLY TYPE 2 DIABETES

The case patient is exhibiting defects of insulin resistance, the constellation of risk factors seen in the metabolic syndrome, and early type 2 diabetes. Haffner and colleagues demonstrated that patients with insulin resistance alone<sup>14</sup> or with insulin resistance and type 2 diabetes<sup>15</sup> have more atherogenic risk factor profiles than insulin-sensitive type 2 diabetes patients.

The ADA recommends that lifestyle interventions be included in the treatment of all patients with type 2 diabetes. Diet and exercise are effective tools to improve blood glucose control, reduce cardiovascular risk factors, and promote weight loss.<sup>10,16</sup> Data from the Diabetes Prevention Program showed that intensive lifestyle intervention reduced the onset of diabetes by 58% in persons at high risk for developing type 2 diabetes.<sup>16</sup> For most patients, however, compliance with diet and exercise programs is difficult. Thus, many patients with type 2 diabetes need to be treated with an antidiabetic agent in addition to lifestyle interventions to achieve glycemic control and lower the risk for complications.

Choosing drug therapy for the case patient will require knowledge of drug mechanism of action and the potential for therapy to cause hypoglycemia. Currently, 5 classes of oral antidiabetic agents are available: sulfonylureas, nonsulfonylurea secretagogues, biguanides,  $\alpha$ -glucosidase inhibitors, and TZDs. Although these agents target various pathophysiologic processes associated with type 2 diabetes, all effectively reduce plasma glucose levels.<sup>17–19</sup> The sulfonylureas are the oldest and most commonly used class of oral hypoglycemic agents and work by stimulating the pancreas to produce more insulin; similar effects are produced by the nonsulfonylurea secretagogues. Biguanides decrease plasma glucose levels by reducing glucose output by the

**Table.** Risk Determinants for the Diagnosis of the Metabolic (or Insulin Resistance) Syndrome

Risk Factor	Defining Level
Abdominal obesity (waist circumference)	
Men	> 40 in (> 102 cm)
Women	> 35 in (> 88 cm)
Triglycerides	≥ 150 mg/dL
High-density lipoprotein cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130/ ≥ 85 mm Hg
Fasting glucose	≥ 110 mg/dL

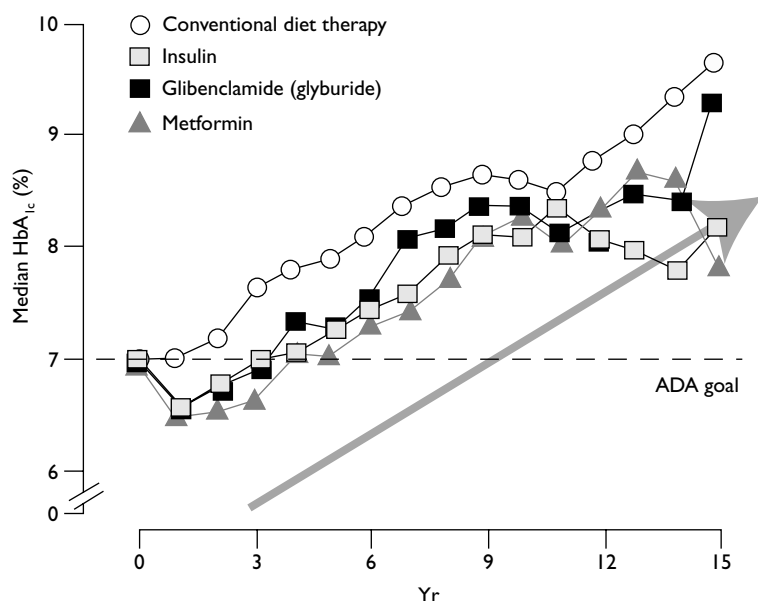
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liver. The  $\alpha$ -glucosidase inhibitors reduce glucose absorption in the small intestines; however, many patients are unable to tolerate the associated gastrointestinal side effects. The mechanism of action of the TZDs is unique in that these agents improve both insulin sensitivity and beta-cell function, 2 key elements in the pathophysiology of type 2 diabetes.<sup>20,21</sup>

Unlike sulfonylureas and metformin, the TZDs are not commonly used as first-line therapy and are often reserved until just prior to initiating insulin. However, sulfonylureas and metformin have been shown to fail over time (**Figure 2**),<sup>8</sup> requiring either a change in therapy or addition of other medications. There are data to suggest that TZDs are more beneficial when used earlier in the treatment of type 2 diabetes when there are more beta cells to preserve and there is a better chance of improving insulin sensitivity,<sup>9,17,22,23</sup> which may lead to more durable glycemic control over the long term. Based on these factors, metformin, a TZD, or a combination of both agents may be considered as appropriate first-choice therapy for the case patient and similar patients. A recently proposed treatment algorithm for the management of type 2 diabetes suggested that first-line oral therapy may include metformin, a TZD, or a combination of both agents.<sup>24</sup>

### CLINICAL EFFECTS OF TZDS

TZDs are ligands for the peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) and affect gene transcription and protein synthesis in the cell nucleus.<sup>25</sup> TZDs work by combining with the PPAR- $\gamma$  receptor in the nucleus to turn on the switch for adipogenesis, lipid metabolism, and the development of GLUT-4, a protein essential in normal glucose transport that is deficient in many patients with type 2 diabetes. By inducing GLUT-4,



**Figure 2.** Median HbA<sub>1c</sub> values for patients with type 2 diabetes mellitus treated with conventional diet therapy, insulin, glyburide, or metformin and followed up for 12 years in the United Kingdom Prospective Diabetes Study. ADA = American Diabetes Association; HbA<sub>1c</sub> = glycosylated hemoglobin. (Adapted from Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes [UKPDS 34] [published erratum appears in *Lancet* 1998;352:1557]. UK Prospective Diabetes Study [UKPDS] Group. *Lancet* 1998;352:858. Copyright 1998, with permission from Elsevier)

TZDs reduce plasma glucose concentrations, mitigating insulin resistance. Hence, these drugs affect insulin resistance and glucose transport at a basic pathophysiologic level. The TZDs decrease fat accumulation in both skeletal and cardiac muscle and lower free fatty acid levels.<sup>26</sup> Further, TZDs appear to provide cardiovascular benefits, including reduction of blood pressure, alteration of fat distribution, and improvements in lipid profiles, endothelial function, and inflammatory markers.<sup>27-29</sup>

TZDs effectively control plasma glucose levels and can be used alone or in combination with other antidiabetic agents.<sup>30-32</sup> Additionally, the TZDs may provide a more sustained, durable response compared with other oral antidiabetic agents. In a 2-year, randomized, double-blind study, 227 patients older than 60 years with type 2 diabetes being treated with submaximal doses of a sulfonylurea were randomized to treatment with either placebo plus glipizide or to rosiglitazone plus glipizide.<sup>33</sup> Physicians following these patients were encouraged to titrate individual dosages based on ADA-recommended targets to a maximum of 40 mg/d of glipizide or 8 mg/d of rosiglitazone. Investigators found that early addition of rosiglitazone to sulfonylurea therapy improved insulin sensitivity and beta-cell function compared with sulfonylurea therapy alone (Figure 3) and resulted in reduced disease progression with superior glycemic control that was sustained over 2 years. In the rosiglitazone plus glipizide group, 50% of patients achieved an HbA<sub>1c</sub> less than 7% compared with only 22% of patients taking glipizide monotherapy.

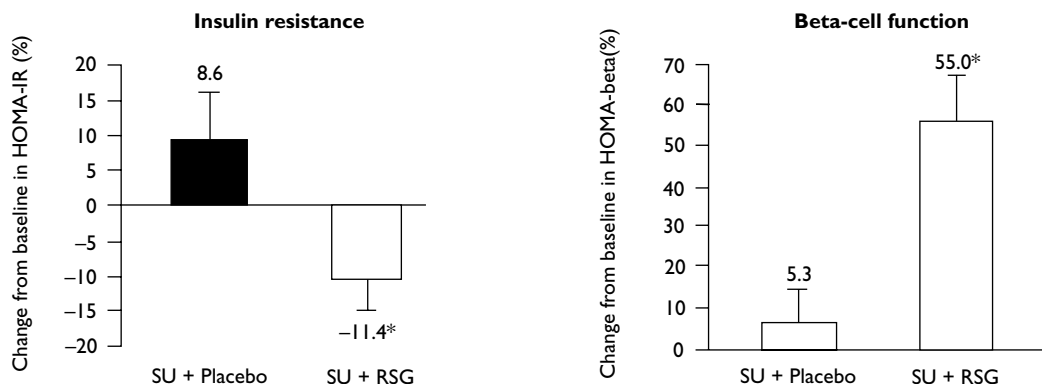
Although the TZDs are not approved by the US

Food and Drug Administration for the treatment of metabolic syndrome or prediabetes, recent studies have suggested that the TZDs may delay or prevent the onset of clinical diabetes in patients at high risk for type 2 diabetes.<sup>34,35</sup> In the Troglitazone in the Prevention of Diabetes (TRIPOD) study,<sup>34</sup> women who had had gestational diabetes were randomized to treatment with troglitazone or placebo after delivery. After an average follow-up of 30 months, the onset of diabetes was reduced by 56% in troglitazone-treated patients. In a double-blind, placebo-controlled trial, treatment of nondiabetic patients with persistently impaired glucose tolerance with rosiglitazone had similar effects.<sup>35</sup> After 12 weeks of treatment with rosiglitazone, 4 of 9 patients had normal glucose tolerance. These studies suggest that TZDs can improve insulin sensitivity and may delay or prevent the development of type 2 diabetes, although additional studies are needed to substantiate these effects.

Treatment with TZDs should be individualized, and many patients respond when TZDs are initiated at low doses (rosiglitazone, 4 mg; pioglitazone, 15 mg). The usual onset of action is 8 to 12 weeks. The dosage may be increased for patients who do not respond adequately over this time period. By allowing sufficient time to elapse between dose adjustments, maximal pharmacologic effects can occur while minimizing side effects.

#### SAFETY AND TOLERABILITY OF TZDS

The TZDs are generally safe and well tolerated with a low incidence of adverse effects. Consistent with their mechanism of action, TZDs are rarely associated with



**Figure 3.** Rosiglitazone (RSG) added to sulfonylurea therapy (SU) significantly decreased insulin resistance (IR) and improved beta-cell function (estimated by homeostatic model assessment [HOMA]) compared with sulfonylurea therapy alone. \* $P < 0.0001$  versus SU + PBO; intent to treat without last observation carried forward, subjects with baseline and week 104 values. (Adapted with permission from Rosenstock J, Porter LE, Heise MA, et al. Type 2 diabetes in the elderly: reaching durable glycemic goals with combination sulfonylurea and rosiglitazone [abstract]. Rosiglitazone 135 Study Group. Presented at the 18th International Diabetes Federation Congress; 2003 Aug 24–29; Paris, France. Available at [www.easd.org/customfiles/easd/18IDF/abstracts/2258-2341.pdf](http://www.easd.org/customfiles/easd/18IDF/abstracts/2258-2341.pdf). Accessed 20 May 2005.)

hypoglycemia. However, several safety issues are relevant when considering the use of these agents.

### Hepatic Effects

Troglitazone, the first TZD available in the United States, was removed from the market because of an idiosyncratic hepatotoxicity. The newer TZDs, pioglitazone and rosiglitazone, do not appear to cause hepatotoxicity, and data have shown that hepatotoxicity is not a class effect with these agents.<sup>36</sup> Although monitoring of liver enzymes is recommended when beginning therapy and periodically thereafter, hepatotoxicity with the available TZDs is unlikely.

### Weight Gain

Weight gain has been reported in patients treated with TZDs. Modest weight gain may be associated with improved glycemic control in patients with type 2 diabetes because it occurs with all antidiabetic agents except metformin,<sup>8</sup> which tends to be associated with weight loss or no change in weight. In the UKPDS,<sup>8</sup> traditional agents (sulfonylureas and insulin) were associated with weight gain (approximately 3–7 lb) over time. TZDs are associated with a similar amount of weight gain. In clinical trials, mean weight gain was less than 5 lb for patients taking 4 mg/d and less than 7 lb for those taking 8 mg/d<sup>37</sup> after 52 weeks of rosiglitazone monotherapy; similar effects have been observed with pioglitazone.<sup>38</sup> Greater weight gain is possible in patients being treated with a TZD and insulin in combination.

### Edema and Congestive Heart Failure

Patients with type 2 diabetes are at increased risk for cardiovascular disease, and many have preexisting heart disease. Therefore, attention has been given to the fact that edema can occur in patients treated with a TZD. People with type 2 diabetes often have other risk factors for congestive heart failure (CHF), such as coronary artery disease and hypertension, and diabetes is a strong, independent risk factor for CHF.<sup>39</sup> The ADA and the American Heart Association recently provided a consensus statement on TZD use, edema, and CHF to provide clinicians with recommendations for patients who experience an unexpected weight gain or edema while taking a TZD.<sup>40,41</sup> The working group evaluated the use of TZDs in patients with preexisting heart disease and in those who developed edema while taking a TZD both in clinical and epidemiologic studies. They found that the incidence of CHF in TZD-treated patients is less than 1%; combination therapy with insulin increases the incidence to 1% to 3%. Patients taking insulin who are on higher doses of a TZD and have other risk factors for CHF appear to have the highest incidence of CHF. Readers should refer to the consensus paper, available in both *Circulation* and *Diabetes Care*, for a more detailed review of the recommendations.<sup>40,41</sup> These guidelines provide information about the use of TZDs in patients with and without symptomatic heart disease, monitoring patients on TZD therapy, and evaluation of edema. It is important to remember that, although TZDs can be used cautiously in patients with

class I or II New York Heart Association heart failure categories, they are not recommended for use in patients with class III or IV CHF.

## CONCLUSION

With epidemiologic data indicating that more than 18 million Americans have type 2 diabetes, it is clear that medications that provide durable glycemic control are needed. The TZDs address the very essence of type 2 diabetes by altering insulin sensitivity and decreasing beta-cell failure, yet these agents have historically been reserved for treatment of patients only after other drugs have failed. Clearly, use of TZDs earlier in the treatment of type 2 diabetes would better serve patients as they have a greater number of beta cells to preserve and fewer disease complications. Additionally, the TZDs appear to exert cardiovascular benefits, including reduction of blood pressure, alteration of fat distribution, and improvements in lipid profiles, endothelial function, and inflammatory markers, and may prevent or delay the onset of some of the morbidity associated with type 2 diabetes. As more aggressive treatment of type 2 diabetes is being advocated by the ADA and the American Association of Clinical Endocrinologists,<sup>10,42</sup> earlier use of TZDs may be an appropriate part of this new approach to treatment. **HP**

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