

New Directions for Type 2 Diabetes Mellitus Management

Lawrence Blonde, MD

Diabetes is a common disorder associated with a multitude of short-term and long-term complications, including diabetic retinopathy, nephropathy, and neuropathy. This disorder is also associated with a marked increased risk for macrovascular disorders, especially cardiovascular disease.¹ The prevalence of diabetes has increased steadily, with current estimates of 16 million individuals in the United States affected by type 2 diabetes.² In the United States, the annual total healthcare costs associated with diabetes are estimated to be \$98 billion.² Increasing evidence suggests that appropriate and timely management of patients with type 2 diabetes should improve both short- and long-term outcomes, enhance quality of life, and decrease overall healthcare expenditures.

The contents of this supplement to *The American Journal of Managed Care* are derived from a roundtable meeting, "New Directions for Type 2 Diabetes Mellitus Management," held in September 2001. The faculty assembled for the roundtable were challenged to reappraise the current management of patients with type 2 diabetes. This supplement strives to provide clinicians and administrators with an overview of the economic impact of both short- and long-term consequences associated with type 2 diabetes; the association between type 2 diabetes, insulin resistance, and cardiovascular disease; current treatment approaches for managing type 2 diabetes; beneficial effects of the thiazolidinediones (TZDs); and recommendations for more appropriate use of TZDs in patients with type 2 diabetes.

The first article in this supplement, written by Terrance Killilea, PharmD, is titled "Long-term Consequences of Type 2 Diabetes Mellitus: Economic Impact on Society and Managed Care." Patients with type 2 diabetes use more medications than age-matched controls and have a higher incidence of hospitalizations, with longer duration and higher rates of complications.^{3,4} In one study of patients with diabetes evaluated during the first 8 years after diagnosis, medical costs for these patients were significantly higher than for patients who did not have diabetes when other variables were matched between the 2 groups.⁵ The cost benefits of treatment were reviewed by Dr Killilea, including a study showing decreased admissions for cardiovascular disease after adequate control of diabetes.⁶ Dr Killilea also discusses the short-term economic and quality-of-life improvements from a landmark study conducted by Testa and Simonson, which showed that improved glycemic control could be associated with both improved quality of life and enhanced productivity.⁷

The article by Gregory E. Tennyson, MD, titled "Understanding Type 2 Diabetes Mellitus and Associated Cardiovascular Disease: Linked by Insulin Resistance" stresses that considerable morbidity in type 2 diabetes may be linked causally to insulin resistance or its associated conditions. Insulin resistance is a central component of the pathophysiology of type 2 diabetes and is believed to be a major contributor to many macrovascular complications associated with type 2 diabetes.^{8,9} Insulin resistance precedes the development of type 2 diabetes in most individu-

als and continues to be present during the entire course of the disease.⁹ Treatments that reduce insulin resistance may help improve cardiovascular risk factors and ultimately minimize complications. For example, treatment with rosiglitazone, which improves insulin sensitivity, has been shown to reduce proinflammatory markers, including interleukin-6, C-reactive protein (CRP), and leukocyte count.¹⁰ Treatments that reduce the levels of these markers are hypothesized to be associated with long-term cardiovascular benefit, and investigations to test this hypothesis are being conducted. Rosiglitazone also has been shown to increase brachial artery reactivity, a measure of endothelial function, in obese subjects who do not have diabetes, and decreases reactive oxygen species generation, p47^{phox}, CRP, and monocyte chemoattractant protein-1.¹¹ Similar anti-inflammatory effects have been observed with troglitazone.¹² These anti-inflammatory effects may have long-term implications for prevention of atherosclerosis.

Dr Tennyson also notes that the incidence of insulin resistance is rapidly rising in the United States and is likely to lead to significant increases in type 2 diabetes and in cardiovascular morbidity and mortality.¹³ Decreasing insulin resistance with lifestyle measures or with agents that increase insulin sensitivity is believed to favorably alter the progression from insulin resistance and the metabolic syndrome to the development of type 2 diabetes and cardiovascular disease. Data from the Diabetes Prevention Program Research Group and the Troglitazone in the Prevention of Diabetes (TRIPOD) study support this view.^{14,15} Additional long-term prospective studies evaluating the ability of the TZDs and other agents to delay or prevent the development of type 2 diabetes are presently under way.

In his review, titled "Current Treatment Approaches to Type 2 Diabetes Mellitus: Successes and Shortcomings," Francis M. Collins, MD, emphasizes the importance of achieving glycemic control (American Diabetes Association goal of a glycosylated hemoglobin <7% or American Association

of Clinical Endocrinologists goal of an HbA_{1c} <6.5%), blood pressure of less than 130/80 mm Hg, and appropriate control of dyslipidemia, with a low-density lipoprotein cholesterol (LDL-C) level less than 100 mg/dL. His article provides a succinct review of the various classes of oral antidiabetic agents and focuses on the importance of prompt initiation of combination therapy when monotherapy is unlikely to achieve or fails to achieve desired glycemic goals. He addresses some limitations of present antidiabetic therapies, particularly the paucity of evidence that many antidiabetic agents substantially improve cardiovascular risk.

The article, "Effects of Thiazolidinediones for Early Treatment of Type 2 Diabetes Mellitus," written by David J. Kudzma, MD, reviews several intriguing studies suggesting that TZDs may enhance or improve β -cell function, leading to durable improvements in glycemic control.¹⁶ This is an important attribute because declining β -cell function is associated with progressive loss of glycemic control in subjects with type 2 diabetes.

The use of TZDs in patients with type 2 diabetes also may be associated with improvement in risk factors for macrovascular disease. The TZDs have been shown to decrease free fatty acids and triglyceride levels. Treatment with these agents also may be associated with an increase in the proportion of larger, more buoyant LDL-C particles and an increase in high-density lipoprotein cholesterol (HDL-C) levels.¹⁷⁻¹⁹ In addition, a small improvement in blood pressure has been noted with use of these agents.^{20,21} Plasminogen activator inhibitor 1 levels, which are elevated in many subjects with type 2 diabetes, have been demonstrated to decrease after TZD therapy.²² TZDs also have been associated with a decrease in the intimal medial thickness of the vasculature.²³⁻²⁴ Dr Kudzma noted the ability of TZDs, in preliminary studies, to decrease albuminuria.²⁵ Dr Kudzma suggested that these data support the use of TZDs earlier in the management of type 2 diabetes. Ongoing prospective trials, if positive, will provide

important additional evidence to support this approach.

The final article in this supplement, "Thiazolidinediones in the Treatment of Managed Care Patients With Type 2 Diabetes," by Ram Pathak, MD, Azar Afaq, MD, and Lawrence Blonde, MD, provides a review of the effects of TZDs and clinical recommendations for optimizing their use. Emerging evidence indicates that TZDs improve hyperglycemia, insulin sensitivity, and HDL-C levels. In addition, evidence indicates that treatment with drugs from this class is associated with larger, more buoyant LDL-C particles and improvement in several other cardiovascular risk markers or factors in patients with type 2 diabetes. Because many patients with type 2 diabetes fail to achieve glycemic goals with traditional therapy, earlier and more aggressive therapy that uses appropriate choices from all of the antidiabetic agents, including the TZDs, may provide a successful strategy to benefit patients. Furthermore, if TZD-induced improvements in cardiovascular risk factors translate into reduced vascular events, then earlier use of these agents may improve both short- and long-term outcomes and reduce overall healthcare costs.

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