Consulting on the Patient With Type 2 Diabetes: Matching Medication to Disease Mechanism

A Continuing Education Activity

HIGHLIGHTS

- Pathophysiology

- Goals of Treatment

- Assessing Risks and Benefits to Develop Effective Treatment Plans

- Conclusions

SELF-STUDY CONTINUING EDUCATION ACTIVITY
Consulting on the Patient With Type 2 Diabetes: Matching Medication to Disease Mechanism

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Learning Objectives
At the conclusion of this activity, participants should be able to:

1. Understand that type 2 diabetes is a dual-defect disease characterized by insulin resistance and ß-cell dysfunction.
2. Implement pharmacologic interventions as an adjunct to diet and exercise for patients with type 2 diabetes.
3. Identify treatment strategies, based on major outcome studies, that may delay or prevent the development of type 2 diabetes.

Target Audience
This program was developed to meet the educational needs of pharmacists who are interested in raising the level of care for their patients with type 2 diabetes.

Accreditation
The University of Kentucky College of Pharmacy is approved by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is approved for 1 contact hour (0.1 CEU) of continuing pharmacy education credit in states that recognize ACPE providers. Statements of credit will indicate hours and CEUs based on participation and will be issued online.

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ABSTRACT

Type 2 diabetes places a significant burden on the health care system today and its incidence is expected to increase at an alarming rate over the next 20 years. Type 2 diabetes is associated with increasing insulin resistance and ß-cell dysfunction, and with macro- and microvascular complications (including cardiovascular disease, retinopathy, peripheral neuropathy, and end-stage renal disease). The primary rationale for intensive management of type 2 diabetes is to reduce or prevent microvascular and cardiovascular events; therefore, treatment goals encompass glycemic, blood pressure, and lipid targets. Thiazolidinediones (TZDs) improve insulin sensitivity and preserve ß-cell function, and clinical evidence supports the early use of these agents in preventing the progression of diabetes in high-risk patients. The durability of glycemic control with monotherapy varies among orally available antidiabetic agents, and, inevitably, patients with type 2 diabetes will require a combination of antidiabetic agents to reach glycemic goals. Fixed-dose combination therapy is associated with increased adherence to the treatment regimen and improved outcomes. Intensive management of patients with type 2 diabetes has been shown to decrease the rate of complications and reduce health care costs.

Introduction

Diabetes mellitus represents a major public health crisis. In 2005, the prevalence of diabetes in the United States was 20.8 million people (7 percent of the total population), including 6.2 million people with undiagnosed diabetes (CDC 2005). Twenty years ago, there were 6.4 million adults with diabetes (Bloomgarden 2006). Since then, the incidence of diabetes in the United States has increased at an alarming rate (Bloomgarden 2006). In 2003, the number of adults diagnosed with diabetes more than doubled, to 13.8 million. In addition, 5 million people had undiagnosed diabetes, and 41 million people were diagnosed with prediabetes.

The cost of diabetes in 2003 was approximately $92 billion (Bloomgarden 2006). This figure is conservative, however, given that the American Diabetes Association (ADA) estimated that in 2002, direct and indirect costs associated with diabetes were $132 billion (Hogan 2003). If additional costs are included, such as pain, suffering, and caregiver burden, then the actual costs associated with diabetes in the United States are more than double what spending would be if diabetes was not present.

If current trends continue, it is estimated that 30.3 million Americans will have diabetes in 2030, representing a 71 percent increase since 2000 (Wild 2004). Not only is diabetes the most expensive disease in this country today, it is associated with significant morbidity and mortality. Diabetes was the sixth leading cause of death in the United States in 2002, a figure that is likely conservative, as up to 60 percent of decedents with diabetes did not have diabetes listed anywhere on their death certificate (CDC 2005). Overall, the risk of death among people with diabetes is about twice that of people of similar age without diabetes (CDC 2005). The Centers for Disease Control and Prevention has estimated that diabetes will result in the deaths of 622,000 people in the United States by the year 2025, making diabetes the country's leading cause of death (CDC 2005). This figure represents more deaths than the top six causes of death in 2002 combined.

Generally, research spending for any disease should be approximately 5 percent of the total annual cost associated with the disease. Using Bloomgarden's conservative $92 billion estimate as a benchmark, annual research spending on diabetes should be near $4.6 billion. However, in 2002, the investment in research by the National Institutes of Health, the main body responsible for funding U.S. research, was less than $800 million (Bloomgarden 2006).

Pathophysiology

The development of diabetes is dependent on defects in both insulin action and insulin secretion, leading to hyperglycemia and metabolic derangements that eventually compromise every organ in the body (DeFronzo 1992). The delicate balance of glucose homeostasis is dependent on the gastrointestinal (GI) handling of carbohydrates, tissue glucose uptake, hepatic glucose production, and the ability of certain tissues, particularly fat and muscle, to use glucose. The pancreatic β-cells in

the islets of Langerhans need to secrete insulin in a glucose-dependent manner to properly metabolize glucose. Therefore, the multifactorial processes leading to normoglycemia include absorption of carbohydrates from the gut, metabolism of glucose in the liver, utilization of glucose by muscle and fat, and the production and secretion of adequate amounts of insulin.

The development of overt type 2 diabetes and its associated complications occurs along a continuum of metabolic disease. This deleterious pathophysiologic process may begin as early as 10 to 15 years prior to the clinical diagnosis of type 2 diabetes. Once type 2 diabetes is diagnosed, it is common for patients to present with complications that have already developed in association with insulin resistance, such as hypertension and dyslipidemia. Contributing to the early stages of diabetes are genetic susceptibility and environmental factors, such as nutrition, obesity, and physical inactivity. Pancreatic β-cells are initially able to maintain normal glucose tolerance by compensatory hypersecretion of insulin, but as insulin resistance increases, β-cell function fails to keep up, and eventually declines. As a result, hyperglycemia develops and overt diabetes occurs. Although it takes years to progress from impaired glucose tolerance (IGT) to diabetes and, thus, to the serious complications of diabetes, the metabolic process is continuous, making it important to expend efforts as early as possible toward preventing diabetes.

Goals of treatment

Once a diagnosis of diabetes is made, it is important to initiate treatment immediately in an effort to achieve and maintain glycemic levels as close to the normoglycemic range as possible (Nathan 2006). The ADA and the European Association for the Study of Diabetes published an algorithm for the initiation and adjustment of therapy, which includes lifestyle modifications to be reinforced at every patient visit and the use of antihyperglycemic agents. The algorithm recommends the use of specific agents predicated on their efficacy, extraglycemic effects, safety, synergies, and expense (Nathan 2006). Lifestyle modifications in combination with metformin are recommended as the initial treatment strategy following the diagnosis of diabetes. If glycemic goals are not achieved, additional therapy is recommended with a thiazolidinedione (TZD), insulin, or a sulfonylurea. Pramlintide, exenatide, α-glucosidase inhibitors, and the glitinides were not included in the treatment algorithm because of limitations in efficacy and clinical data and their relative expense (Nathan 2006). Of great importance is that the consensus statement recommends that clinicians not wait long before adding another agent for those patients who are not meeting a glycated hemoglobin (A_{1C}) goal of less than 7 percent. No limits are set on the number of agents required to meet glycemic goals.

Rather, it is suggested that medications be added as rapidly as possible when target glycemic goals are not achieved or sustained (Nathan 2006).

Treatment goals from various organizations for patients with type 2 diabetes are shown in Table 1 (page 4). The ADA recommends a target A_{1C} of less than 7 percent, but a level as close to normal (less than 6 percent) as possible without significant hypoglycemia may be recommended for individual patients (ACE 2002). The A_{1C} goal of the American College of Endocrinology (ACE) is 6.5 percent or less and is, therefore, in general agreement with the ADA (ACE 2002). Pre- and postprandial plasma glucose target levels also have been identified. The preprandial plasma goal ranges from 90 to 130 mg/dL. The ADA's postprandial goal is less stringent at less than 180 mg/dL, and the ACE's is more stringent at less than 140 mg/dL (ADA 2007, ACE 2002). These associations are in agreement regarding blood pressure, lipid, and triglyceride goals (ADA 2007, Chobanian 2003, NCEP 2001). Because diabetes is a continuous disease process, it is clinically important for all of these goals to be met as quickly as possible for patients with type 2 diabetes.

Selection of agents to meet goals of therapy

In the majority of patients with type 2 diabetes, more than one medication will be needed to meet glycemic goals (Nathan 2006). Early data by DeFronzo and colleagues (1995) support the importance of adding antidiabetic agents instead of merely making drug substitutions. The value of combining glyburide with metformin, rather than switching from glyburide to metformin, was demonstrated by significant reductions in A_{1C} after 29 weeks of combination therapy compared with results seen with either agent used as monotherapy. Since then, numerous studies have continued to show the benefits of combination therapy compared with switching monotherapies in patients who do not meet glycemic targets. The exception to this rule is an initial agent that is efficacious but cannot be tolerated; in this case, a different monotherapy may be tried.

Prevention of cardiovascular disease (CVD) is the hard clinical endpoint that clinicians strive to achieve in the management of patients with type 2 diabetes. Recently, several large long-term, randomized, controlled landmark studies have been conducted evaluating the TZD class of agents in reducing the risk of CVD, preventing type 2 diabetes, and slowing disease progression.[*] In the PROactive Study, pioglitazone (a TZD) was shown to reduce the secondary composite endpoint of all-cause mortality, nonfatal myocardial infarction (MI), or stroke in a population of patients with type 2 diabetes at high

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[*]Bloomgarden 2006, Hogan 2003, Wild 2004, DeFronzo 1992, Nathan 2006, ADA 2007, ACE 2002, Chobanian 2003, NCEP Expert Panel 2001, DeFronzo 1995, and Dormandy 2005.

TABLE 1
Treatment goals for patients with type 2 diabetes

	ADA 2007	ACE 2002	JNC 7 2003	ATP 3 2001
A_{1C} (%)	<7.0*	≤6.5	—	—
Preprandial glucose (mg/dL)[†]	90–130	<110	—	—
Postprandial glucose (mg/dL)[†]	<180	<140	—	—
Blood pressure (mm Hg)	<130/80	—	<130/80	—
LDL-C (mg/dL)	<100	—	—-	<100
Triglycerides (mg/dL)	<150	—	—-	—
HDL-C (mg/dL)	Men >40			
	Women >50	—	—	—

*2006 ADA guidelines suggest that a more stringent A_{1C} goal of <6% can be considered in certain patients.

[†]Based on measurements of plasma glucose.

A_{1C}=glycated hemoglobin, ACE=American College of Endocrinology, ADA=American Diabetes Association, ATP 3=Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, HDL-C=high-density lipoprotein cholesterol, JNC 7=Seventh Report of the Joint National Commission on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, LDL-C=low-density lipoprotein cholesterol.

SOURCES: ADA 2007, ACR 2002, CHOBANIAN 2003, NCEP 2001.

logic therapy aimed at several modifiable risk factors with strict treatment goals (Gaede 2003). Over a mean follow-up period of 7.8 years, most patients in the intensive-therapy arm required multiple medications to meet the goals of lowered levels of fasting plasma glucose (FPG), triglycerides, cholesterol, and blood pressure (Gaede 2003). The targeted, intensified intervention regimen was associated with a nearly 50 percent risk reduction of CV events compared with conventional therapy (Gaede 2003).

In the UKPDS 75 study, patients with type 2 diabetes who achieved a strict A_{1C} goal lower than 6 percent and a systolic blood pressure (SBP) goal of below 130 mm Hg had a lower incidence of death associated with diabetes, MI, stroke, and microvascular endpoints compared with patients who were less intensively treated (Stratton 2006). A nearly 21 percent reduction in overall complications was observed for every 1 percent reduction in A_{1C}. For every 10-mm Hg reduction in SBP, there was a nearly 11 percent overall risk reduction (Stratton 2006). Data from these studies support the importance of multifactorial treatment with tight control of glycemia, blood pressure, and lipids in patients with type 2 diabetes to reduce microvascular and macrovascular complications.

risk of macrovascular events (Dormandy 2005). In a study of disease progression, patients at high risk of developing diabetes (IGT, impaired fasting glucose [IFG], or both) who received treatment with rosiglitazone had a 60 percent risk reduction in the progression to diabetes compared with patients treated with placebo (DREAM 2006). Additionally, based on the secondary outcome, the majority of patients treated with rosiglitazone reverted to normoglycemia. In a third study, treatment-naïve patients with type 2 diabetes treated with rosiglitazone were 32 percent and 63 percent less likely to fail monotherapy on the basis of confirmed hyperglycemia compared with patients treated with metformin and glyburide, respectively (Kahn 2006). This study provided a much-needed update to the landmark United Kingdom Prospective Diabetic Study (UKPDS), which preceded the availability of TZDs. These data provide a good rationale for the use of a TZD, both as monotherapy and in combination with other agents for effective treatment of type 2 diabetes.

Use of multiple oral agents

Due to the complexities of diabetes, clinicians need to consider the use of multiple oral agents in an intensive treatment program to best manage their patients. Results from the STENO-2 and UKPDS 75 studies support this approach (Gaede 2003, Stratton 2006). In STENO-2, patients with type 2 diabetes and microalbuminuria were randomly assigned to treatment with intensive or conventional therapy (Gaede 2003). The intensive therapy policy used a multifactorial intervention with a step-wise approach to behavior modification and pharmaco-

Oral therapy

There are five classes of oral agents from which to choose when designing an aggressive treatment strategy for patients with type 2 diabetes. It is likely that a combination of agents will eventually have to be used. A comprehensive review of these agents is beyond the scope of this article; however, they are briefly described below.

One class of antidiabetic medications is the insulin secretagogues. These include the sulfonylureas, such as chlorpropamide and glyburide, and the meglitinides, such as nateglinide and repaglinide (Cheng 2005). The secretagogues are glucose-independent and are most commonly recommended for patients with residual pancreatic β-cell function and minimal insulin resistance, such as newly diagnosed, nonobese patients with type 2 diabetes. Meglitinides have a faster onset of action and a shorter half-life than the sulfonylureas and are, therefore, useful for controlling mealtime or postprandial glucose levels. The main adverse event associated with these agents is hypoglycemia.

Another class of medications comprises the α-glucosidase inhibitors (such as acarbose and miglitol) (Cheng 2005). These agents inhibit the breakdown of carbohydrates and are recommended in patients who have relatively normal fasting glucose levels, but who experience problems controlling carbohydrate intake and thus develop elevated postprandial glucose levels (Cheng 2005). These agents are often administered with the largest meal of the day. The main adverse event associated with these agents is GI upset and flatulence.

Metformin is the only clinically useful member of the biguanide class, and is associated with neutral weight effects or weight loss. Therefore, it is a useful treatment option for a patient with type 2 diabetes at any time during the course of his or her illness, as long as no contraindications are present (Cheng 2005). The mechanisms by which metformin lowers glycemia are not fully understood, but its antihyperglycemic effects are exerted by decreasing hepatic glucose output, and to a lesser degree, by increasing glucose uptake in skeletal muscle (Cheng 2005). Newly diagnosed patients as well as those who have trouble losing weight are good candidates for metformin. Metformin is frequently used as a component of combination therapy. GI upset, diarrhea, and liver dysfunction are the main adverse events associated with metformin.

The TZDs, represented by rosiglitazone and pioglitazone, enhance insulin action through complex mechanisms linked to activation of the transcription factor PPAR-gamma (Saltiel 1996). Because these agents target insulin resistance, they should be considered at any point during the development and progression of type 2 diabetes. The TZDs are an appropriate choice for combination therapy, and evidence suggests these drugs possess beneficial effects beyond glycemic control. Weight gain and edema are the most common adverse events associated with TZDs.

Two new and functionally related classes of oral antidiabetic agents are glucagon-like peptide-1 (GLP-1) agonists (such as exenatide) and the dipeptidyl peptidase-IV (DPP-4) inhibitors (such as sitagliptin). The GLP-1 agonists have an incretion-like effect in facilitating insulin release at mealtimes in a glucose-dependent manner. They also enhance gastric emptying, suppress glucagon secretion, and produce weight loss. The DPP-4 inhibitors produce a GLP-1–like effect by decreasing the metabolism of this hormone; therefore, they also increase insulin release in a glucose-dependent manner and decrease glucagon levels (Merck 2007). DPP-4 inhibitors may be used as monotherapy or as combination therapy with metformin or TZDs (Merck 2007). The DPP-4 inhibitors have exhibited a favorable safety and adverse-event profile. However, additional studies are needed to define their long-term efficacy and safety, and to determine their relative merits compared with other available therapeutic options.

Combination therapy

As when choosing the most appropriate agent for monotherapy, the selection of antidiabetic drugs for combination therapy should be based on benefits beyond glucose reduction. Derived from complementary mechanisms of action, the combination of metformin and a TZD offers potential advantages that extend beyond glycemic control. Metformin is able to improve the lipid profile and also is associated with significant CV benefits (Cheng 2005, UKPDS 1998). Thiazolidinediones have shown favorable effects on CV risk factors, and recently have been shown to also reduce CV events (Dormandy 2005, DREAM 2006). Coupled with enhancing insulin sensitivity, TZDs may help preserve pancreatic β-cell function (Cheng 2005). If metformin monotherapy fails, combination therapy with a TZD, which is associated with significantly better glycemic control, extends the viability of oral therapy, and delays the need for in-

FIGURE 1

Reductions in A_{1C} and FPG with fixed-dose combination of rosiglitazone/metformin
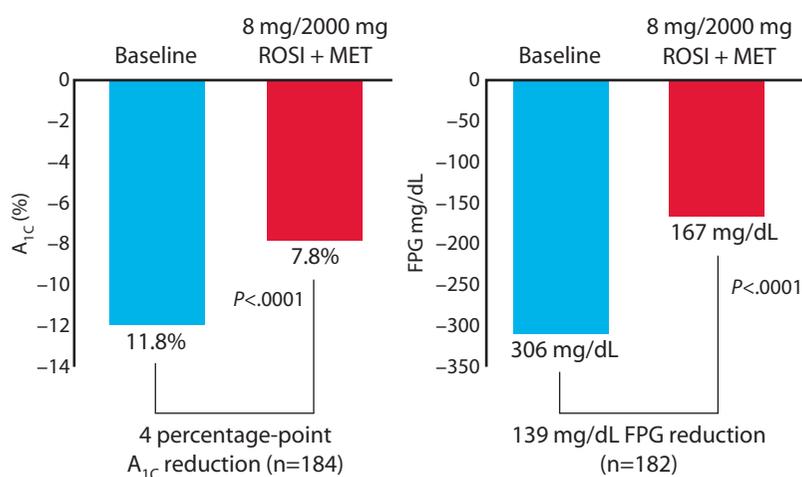
A_{1C}=glycated hemoglobin, FPG=fasting plasma glucose, MET=metformin, ROSI=rosiglitazone.
SOURCE: ROSENSTOCK 2006

TABLE 2

Thiazolidinedione + sulfonylurea versus sulfonylurea monotherapy: health care utilization event rates

| | Mean (SD) rate of occurrence* | | |
Event	GLP (n=110)	ROSI + GLP (n=115)	*P* value
Hospitalization	0.76 (1.82)	0.37 (1.07)	.0263
Emergency department visits	1.47 (3.91)	0.59 (1.32)	.0006
Unscheduled physician office visit	7.94 (11.28)	5.95 (1.32)	.2144
Self-reported bed days	3.03 (20.80)	0.85 (4.80)	.0002
Self-reported restricted activity days	22.82 (71.76)	16.48 (49.11)	.3522

*Event rates are per 1,000 patient days and are cumulative to the study's end.
GLP=glipizide, ROSI=rosiglitazone.
Reproduced with permission from the *American Journal of Managed Care*.
SOURCE: HERMAN 2005

sulin by up to 8 years, should be implemented (Shearer 2004). In addition, metformin coupled with a TZD has been shown to reduce or delay complications and improve survival compared with metformin combined with a sulfonylurea (Shearer 2004).

Clinical trial evidence supports the use of combination therapy when striving to reach strict glycemic goals. In the EMPIRE study, a double-blind, randomized, parallel-group study, a similar percentage of patients with type 2 diabetes treated with maximal doses of metformin (2 g/day) or rosiglitazone (8 mg/day) plus metformin (1 g/day) were able to attain A_{1C} levels of less than 7 percent as recommended by the ADA (Weissman 2005). However, when the target was the more stringent A_{1C} goal of 6.5 percent or less set by the ACE, only 28 percent of monotherapy recipients met the goal compared with 41 percent of combination-therapy patients.

The combination of pioglitazone and sitagliptin was evaluated in a randomized, double-blind, placebo-controlled study (Merck 2007). Fewer than a quarter (23 percent) of patients on pioglitazone monotherapy were able to reach A_{1C} levels below 7 percent (Merck 2007). However, combination therapy was associated with A_{1C} levels below 7 percent in 45 percent of patients.

Fixed-dose combinations

Prescribing multiple oral agents creates a large "pill burden" on patients; clearly, this is a drawback of multidrug combinations. Fixed-dose combination (FDC) products offer patients the benefit of having fewer medications to deal with, as well as an increased likelihood of therapy adherence (Vanderpoel 2004). It is anticipated that improved compliance through the use of FDC products will result in improved clinical outcomes, fewer visits to the emergency room, and better overall medical care utilization.

Clinical evidence

The effectiveness of FDC therapy in patients with type 2 diabetes has been demonstrated in clinical trials. Rosenstock (2006) evaluated an FDC of rosiglitazone and metformin in drug-naïve patients with type 2 diabetes and very poor glycemic control (baseline A_{1C} levels were greater than 11 percent and FPG levels were more than 270 mg/dL). The FDC therapy of rosiglitazone and metformin was started at 4 mg/1,000 mg and increased by 2 mg/500 mg-increments up to 8 mg/2,000 mg as needed and tolerated (Rosenstock 2006). Response to treatment was rapid. Four weeks after initiating therapy with the 4 mg/1,000 mg fixed-dose product, a clinically significant reduction in FPG was observed (Rosenstock 2006). At week 24, patients achieved clinically and statistically significant reductions in A_{1C} and FPG compared with baseline (Figure 1, page 5).

The FDC of a TZD (rosiglitazone) and a sulfonylurea (glimepiride) also has been compared with monotherapy with either agent in treatment-naïve patients with type 2 diabetes, mean baseline A_{1C} of 9 percent or more, and mean baseline FPG of 207 mg/dL or higher (Palmer 2006). Patients in the 28-week study were randomly assigned to daily treatment with glimepiride (1 mg titrated up to 4 mg), rosiglitazone (4 mg titrated up to 8 mg), or an FDC — either 4 mg/1 mg titrated up to 4 mg/4 mg or 4 mg/1 mg titrated up to 8 mg/4 mg. Reductions in A_{1C} and FPG were observed quickly in both FDC regimens, with statistically significant reductions compared with those of either monotherapy group. After 28 weeks of therapy, patients on the FDC therapy regimens achieved clinically and statistically significant reductions in A_{1C} (2.4 percent and 2.5 percent reductions in the 4 mg/4 mg and 8 mg/4 mg groups, respectively) compared with patients treated with glimepiride monotherapy (1.7 percent reduction; *P*<.0001) and those treated with

rosiglitazone monotherapy (1.8 percent reduction; *P*<.001). More than 70 percent of patients on FDC therapy achieved the ADA target of A_{1C} less than 7 percent compared with fewer than 50 percent in either monotherapy treatment group. Similarly, more than half of the FDC-treated patients reached A_{1C} levels of 6.5 percent or less, compared with less than a third of monotherapy-treated patients (Palmer 2006).

These data demonstrate that early intensive and aggressive therapy, even with lower doses of an FDC composed of a TZD with metformin or a sulfonylurea, is associated with a significant reduction in A_{1C}.

Cost-benefit of glycemic control

Treatment decisions should be made on the basis of clinical evidence coupled with a cost-benefit analysis. Tight glycemic control is beneficial for both the patient and the entire health care system, as it is associated with significant cost benefits. Patients who are critically ill or who are undergoing any type of cardiac or surgical procedure tend to have better clinical outcomes if their blood glucose is well controlled (ACE/ADA 2006). Controlling hyperglycemia in hospitalized patients with diabetes (both newly diagnosed and previously diagnosed) has been shown to be cost-effective (ACE/ADA 2006). The effectiveness of an aggressive diabetes consultation team, particularly for inpatients, also has been demonstrated (ACE/ADA 2006). The length of hospital stay was shortened by 56 percent by the use of such a team, and was associated with a cost reduction of $2,353 per patient.

Additionally, the Asheville Project reviewed the effects of a community-based pharmacy providing pharmaceutical care services for patients with diabetes (Cranor 2003). The patients were given the chance to meet with pharmacists who were trained and certified diabetes educators. Patients were educated regarding medications, diabetes risks and complications, lifestyle modifications, home glucose meter use, and information about adherence to treatment regimens (Cranor 2003). Pharmacists also made recommendations to providers on how to adjust or alter therapies. While participating in the program, the majority of patients experienced reductions in A_{1C} (Cranor 2003). This model for pharmaceutical care service was associated with decreases in direct medical costs of $1,200 to $1,872 per patient per visit compared with baseline costs, and patient productivity in-

FIGURE 2

DREAM: Proportion of at-risk patients who developed diabetes or returned to normoglycemia*
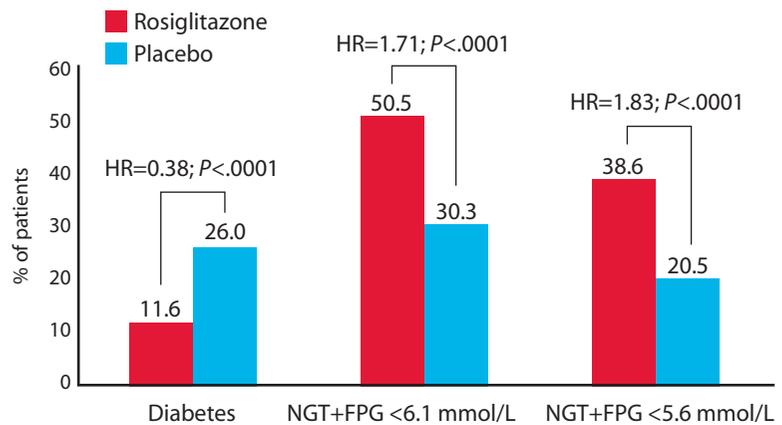
FPG=fasting plasma glucose, HR=hazard ratio, NGT=normal glucose tolerance.
*Normoglycemia was defined as a 2-hour plasma glucose concentration <7.8 mmol/L and FPG concentration <6.1 mmol/L (or <5.6 mmol/L for more stringent definition).
SOURCE: DREAM 2006

creased by $18,000 (Cranor 2003). These data suggest that diabetes education is critical in the cost-effective management of patients with type 2 diabetes.

In another study, costs associated with diabetes disease management were analyzed in a retrospective examination of patients who participated in an HMO-sponsored disease management program (Sidorov 2002). More than 3,000 patients who participated were compared with a similar number of patients not in such a program (Sidorov 2002). Program patients achieved A_{1C} goals and had fewer emergency department visits and hospitalizations, leading to statistically significant lower mean paid claims per member per month. In addition, utilization of the disease management program was associated with significant increases with A_{1C} evaluations and lipid testing, as well as in screening for eye and renal complications.

Health care utilization costs over a 2-year period were analyzed in a randomized, double-blind, parallel-group study evaluating the use of glipizide monotherapy versus the early addition of rosiglitazone to glipizide therapy (Herman 2005). Combination therapy was associated with significantly fewer hospitalizations, self-reported bed days, and emergency department visits (Table 2, page 6). In addition, patients' use of a TZD and a sulfonylurea resulted in significantly shorter hospitals stays compared with those patients who received monotherapy with a sulfonylurea. Lower utilization of health care resources in the combination arm was reflected by significant economic benefits with a total cost savings per patient per month of $164. These benefits in reduced costs with combination therapy were evident de-

spite the difference in cost of therapy of $11 and $99 per patient per month for glipizide monotherapy and combination therapy, respectively.

Optimization of glycemic management is medically effective, as evidenced by lives saved and reduced mortality, and also is cost-effective to the health care system (ACE/ADA 2006).

Assessing risks and benefits to develop effective treatment plans

UKPDS data, generated using agents available more than a decade ago (insulin, metformin, chlorpropamide, and glyburide), found that none of these agents could help patients to maintain long-term glycemic control when used as monotherapy (UKPDS 1998, UKPDS 1995). The observed progressive increase in hyperglycemia was associated with a progressive decrease in β-cell function in both overweight and nonoverweight patients regardless of the antidiabetic agent used (UKPDS 1995). These data support the importance of early aggressive management of type 2 diabetes to improve clinical outcomes. As the UKPDS preceded the availability of the TZDs, its results are in need of update.

Summary of new data

Conducted in 2006, DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) was the first study to show that in patients who were at high risk for developing type 2 diabetes, rosiglitazone reduced the risk of disease development or death from any cause by 60 percent (DREAM 2006). In fact, the data showed that for every 7 people with impaired fasting glucose or IGT who received rosiglitazone for 3 years, 1 person was prevented from developing diabetes. Regression to normoglycemia was significantly higher in rosiglitazone-treated patients compared with placebo-treated patients (Figure 2, page 7), a finding that was sustained when a stringent definition of normal FPG was used (DREAM 2006).

The authors offered several explanations for the beneficial effects observed with rosiglitazone, one of which was that the agent reduced insulin resistance in hyperglycemic individuals (DREAM 2006). Supporting explanations included the ability of rosiglitazone to reduce the physiologic demand for basal as well as prandial insulin secretion, thereby increasing insulin sensitivity resulting in β-cell cytoprotection (DREAM 2006). Although rosiglitazone had no effect on the secondary CV composite outcome, it was associated with significant reductions in blood pressure compared with effects of placebo, suggesting that it has other CV benefits (DREAM 2006).

ADOPT (A Diabetes Outcome Progression Trial) was conducted to gain further information about the effects of antidiabetic agents with differing mechanisms of action on diabetes progression (Kahn 2006). Patients were followed for 4 years. Results showed that the risk of monotherapy failure was reduced by 32 percent with rosiglitazone compared with metformin (*P*<.001) (Kahn 2006). Patients treated with rosiglitazone also were 63 percent less likely to fail monotherapy compared with patients treated with glyburide (*P*<.001), a finding that was more pronounced in patients 50 years of age or older, women, or patients with a body mass index ≥ 30 kg/m^2 (Bloomgarden 2006, Kahn 2006). When a lower threshold for monotherapy failure was used (FPG level >140 mg/dL), rosiglitazone was associated with 36 percent and 62 percent reductions compared with metformin and glyburide, respectively (*P*<.002) (Kahn 2006).

Progressive loss of glycemic control was delayed for a longer time with rosiglitazone than with either metformin or glyburide (Figure 3, page 9) (Kahn 2006). Complementary to the greater durability of glycemic control with rosiglitazone was the observation that it slowed the loss rate of β-cell function and improved insulin sensitivity to a greater extent than metformin or glyburide (Kahn 2006). Treatment with rosiglitazone was associated with weight gain, increased levels of low-density lipoprotein cholesterol (and greater use of statins), edema, hematocrit reduction, and fractures in women (Kahn 2006). Although fractures were observed in all treatment groups, rosiglitazone was associated with more fractures of the upper and lower limbs (Kahn 2006). GI side effects were more common with metformin therapy, and glyburide was associated with weight gain and hypoglycemia (Kahn 2006).

Data from DREAM and ADOPT provide clinical and research evidence for early targeted treatment in patients at high risk for developing type 2 diabetes and in those who are newly diagnosed. Based on the results of DREAM and ADOPT, it has been hypothesized that rosiglitazone increases insulin sensitivity while preserving β-cell function. This theory is supported by the ability of patients to maintain glycemic control with rosiglitazone monotherapy for long periods. Inevitably, patients will require combination therapy to maintain glycemic control, and data from ADOPT provides the rationale that a TZD should be included in such combination therapy.

Clinical management issues with TZDs

Modest weight gain is a common side effect when using TZDs to treat patients with type 2 diabetes. The reasons are many (including the development of edema), but one possible cause also may be an increase in subcutaneous fat while decreasing visceral fat and hepatic fat (Figure 4). In both the DREAM and ADOPT studies, patients treated with rosiglitazone experienced what might be described as a "redistribution" of fat (DREAM 2006,

FIGURE 3
Durability of glycemic control*
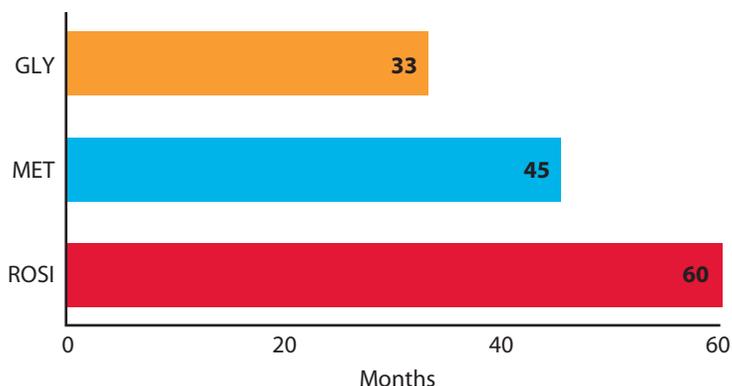
GLY=glyburide, MET=metformin, ROSI=rosiglitazone.
*Glycemic control was defined as a mean glycated hemoglobin level of <7%.
SOURCE: KAHN 2006

with rosiglitazone and glyburide; however, the concurrent increase in hip circumference with rosiglitazone produced no change in the waist-to-hip ratio (Kahn 2006). This redistribution of body fat and associated increase in adiponectin provide a rationale for the improvement in insulin sensitivity observed, despite a mean weight gain of 4.8 kg (Kahn 2006).

The edema associated with TZD use is not fully understood but the mechanisms are likely a class effect due to expansion of plasma volume (Nesto 2004). Supported by the finding that diuretics such as spironolactone may be effective in minimizing fluid retention associated with TZDs, it has been postulated that TZD-associated edema is mediated via PPAR-γ stimulation of the renin angiotensin system (Karalliedde 2005). Edema associated with TZD use is generally similar for rosiglitazone and pioglitazone when used as monotherapy or when combined with other antidiabetic agents; the incidence of edema increases when either TZD is combined with insulin (Nesto 2004). Thiazolidinediones are not recommended for use in patients with advanced heart failure (New York Heart Association class III or IV) (Nesto 2004). In clinical trials of TZDs, congestive heart failure (CHF) was not frequently encountered (Nesto 2004). The incidence of
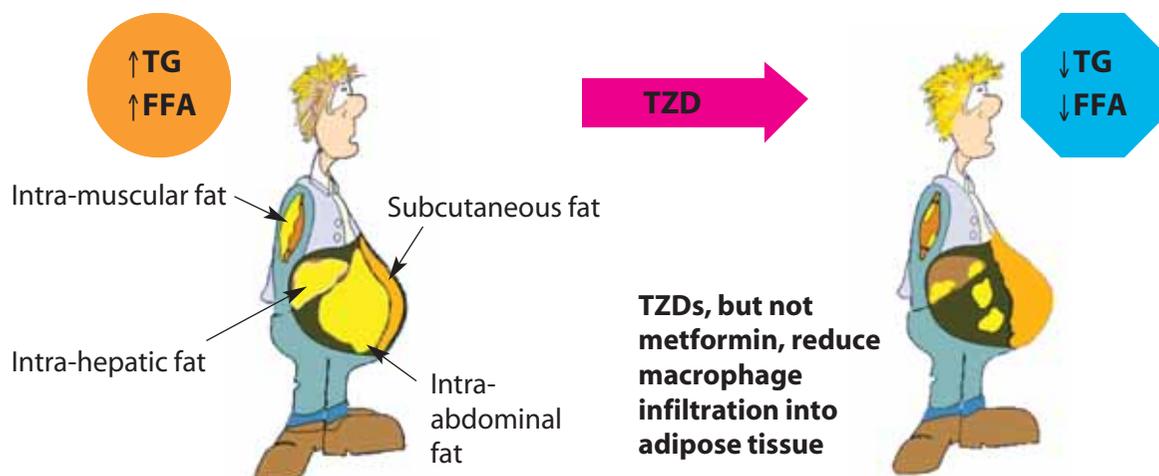
Kahn 2006). Despite a mean weight increase of 2.2 kg in the rosiglitazone group in DREAM, body composition measurements indicated that hip circumference increased compared with waist circumference, suggesting the possibility that fat accumulated preferentially in the femorogluteal subcutaneous compartments (DREAM 2006, Kahn 2006). This body composition change was accompanied by increased plasma levels of adiponectin (an insulin-sensitizing hormone) and reduced levels of inflammatory cytokines. In ADOPT, waist circumference increased from baseline in patients treated

FIGURE 4
Effect of TZDs on fat topography

FFA=free fatty acid, TG=triglyceride, TZD=thiazolidinediones.
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CHF with TZD monotherapy was less than 1 percent and increased to 2 to 3 percent with concomitant insulin. Patients treated with TZDs should be observed for signs and symptoms of heart failure, and therapy should be reevaluated if deterioration in cardiac status occurs.

Conclusions

Diabetes is a dual-defect disease of insulin resistance and β-cell deterioration and is the endpoint of a continuum of metabolic dysfunction. Diabetes presents a huge economic burden, and if not prevented or better controlled, the epidemic will continue to increase, as will the associated health care costs. Various professional organizations have set treatment goals for the management of patients with type 2 diabetes. The ADA recommends that A_{1C} levels be below 7 percent and, if possible without hypoglycemic complications, lowered to a more rigorous target of less than 6 percent. Owing to the multifactorial nature of diabetes and the importance of reducing CV complications, other treatment goals include control of blood pressure and abnormal lipid profiles. Evidence supports the use of antidiabetic therapy early in the course of the disease to improve glycemic control and prevent or delay disease progression. The TZDs have recently demonstrated the ability to improve CV outcomes and progression from prediabetes to overt type 2 diabetes, making them appropriate agents for early aggressive treatment of diabetes, alone or in combination with other effective agents. Aggressive therapy should include agents with differing mechanisms of action, such as TZDs, metformin, insulin and sulfonylureas, and possibly GLP-1 agonists or DPP-4 inhibitors. Intensive management of patients with type 2 diabetes has been shown to reduce health care utilization and costs, and decrease the morbidity and mortality associated with the disease.

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