ABSTRACT

The risk of death among persons with diabetes is twice that of the nondiabetic population. In one study, the average loss of life-years among males and female persons with diabetes exceeded 7 years. Diabetes is not only associated with complications such as retinopathy, nephropathy, and neuropathy, but also a marked increase in the risk of coronary heart disease and other atherosclerotic disorders. Almost fifty percent of individuals who have both diabetes and a history of myocardial infarction (MI) will have another MI within 7 years. Ideally, treatment of diabetes should be aimed at preventing complications by using both pharmacologic and nonpharmacologic means. Three case studies elucidate the importance of continual monitoring, reevaluation of treatment, adherence to treatment and dietary regimens, patient education, and providing insulin therapy to achieve adequate glycemic control. In all cases, combination therapy was required.


CONTROLLING POSTPRANDIAL GLUCOSE

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The United States is experiencing an epidemic of diabetes, particularly type 2 diabetes. The prevalence of diabetes rose from 4.9% to 6.5% in the last decade, an increase of 33%. Recent data from the Centers for Disease Control and Prevention indicate that 17 million Americans now have diabetes, one third of whom (5.9 million) have not yet been diagnosed.

Even though diabetes is frequently not included on death certificates of diabetic patients, it remains the sixth leading cause of death in this country. There are 450,000 deaths annually among people with diabetes, and 19% of all US deaths occur among diabetic individuals. The overall mortality rate for people with diabetes is at least 2 times greater than that of the nondiabetic population, and the relative risk is especially great for young adults and women. The loss of life-years associated with diabetes is significant. Morgan and colleagues examined a registry of deaths for those with and without diabetes. Among 1694 deaths, males with diabetes lost an average of 7.0 life-years from the time of diagnosis and females with diabetes lost an average of 7.5 life-years. Although the registry most likely underrepresented persons with diabetes, it clearly demonstrated the significant loss of life-years associated with the disease (Figure 1).

In addition to the complications of diabetic retinopathy, nephropathy, and neuropathy, diabetes is associated with a marked increase in the risk of coronary heart disease and other atherosclerotic disorders. In a study from Haffner et al, people with diabetes who had no history of a myocardial infarction (MI) had the same high risk of having a future MI as nondiabetic individuals who had already experienced a previous MI. Among patients who had both diabetes...
and a prior MI, nearly 50% of them had another MI within the next 7 years.

Treating diabetes and attempting to prevent complications require a delicate balancing act and developing a plan that incorporates nonpharmacologic and pharmacologic approaches to control blood glucose levels. Avoiding complications requires continual monitoring and reevaluation of treatment to ensure that glucose levels are maintained within the accepted guidelines, as demonstrated in the following case study.

**Case Study 1**

A 50-year-old Hispanic woman presented for a reevaluation. She had 3 children, one weighed 8 lbs 2 oz at birth. With each pregnancy, she experienced gradual, but continual, weight gain. She had a family history of diabetes and hypertension, was sedentary, and smoked 5 to 10 cigarettes per day. She complained of fatigue, difficulty losing weight, nocturia once or twice per night, recurrent bladder infections, intermittent blurred vision, and occasional numbness of the feet.

Physical examination revealed a height of 5'4" and a weight of 175 lb. Her body mass index (BMI) was 30. Her blood pressure was 144/88 mm Hg, but she had no abnormalities of the optic fundi, thyroid, lungs, heart, or abdomen. Her pedal pulses were decreased, and there were findings suggestive of diabetic neuropathy.

Laboratory results revealed a fasting plasma glucose (FPG) 178 mg/dL, glycosylated hemoglobin (A1c) 8.4%, and dyslipidemia. Her urine albumin of 45 mg/g creatinine was in the microalbuminuric range. There was no evidence of urinary tract infection, and hepatic and renal function tests were normal; however, an electrocardiogram revealed left ventricular hypertrophy.

The patient was referred for instruction in nutrition and self-monitoring blood glucose (SMBG). She was also advised to undergo cardiovascular evaluation before beginning an exercise program.

**Glucose Monitoring**

SMBG was recommended for this patient, even though she was not yet on pharmacologic treatment, and despite the fact that some clinicians have maintained there is no relationship between monitoring and glucose control. The efficacy of self-monitoring has been questioned and many patients judge it constraining.

Karter et al sought to evaluate the effectiveness of SMBG levels by using a cohort design. The study sample included 24,312 adult patients with diabetes. Compared with patients who performed SMBG less frequently, patients with type 1 diabetes who monitored ≥3 times daily and pharmacologically treated type 2 diabetes patients who monitored at least daily had lower A1c values of 1.0 and 0.6 percentage points, respectively. Even nonpharmacologically treated patients with type 2 diabetes who practiced SMBG (at any frequency) had a 0.4-percentage point lower A1c level than those not practicing SMBG at all (P<0.001). More frequent self-monitoring of blood glucose levels was associated with better glycemic control regardless of the type of diabetes or the type of therapy.
Unfortunately, A1c levels alone cannot determine whether glucose control is adequate. Two-hour postprandial glucose levels are frequently elevated even in patients with A1c values <7%; consequently, home monitoring must go hand-in-hand with A1c measurements. Furthermore, several epidemiologic studies have shown that elevated postchallenge glucose is associated with an increased risk for coronary heart disease and mortality. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study group assessed mortality in more than 22,000 Europeans, over a median follow-up of 8.8 years. Elevations in 2-hour postchallenge glucose values were a better predictor of all-cause mortality (including cardiovascular disease) than were fasting plasma glucose elevations.

Conclusions reached by the recent Cardiovascular Health Study corroborated these findings. In a community of 4014 community-dwelling adults, aged 65 years or older, the contributions of fasting and 2-hour postchallenge glucose levels to the risk of cardiovascular events were examined. Two-hour glucose levels were better than fasting glucose levels alone at identifying older adults at increased risk of major incident cardiovascular events. These and other studies support making postprandial glucose an important focus of treatment. The patient described here had both fasting and postprandial glucose elevations.

Unfortunately, this case illustrates one of the major problems associated with type 2 diabetes: at the time of diagnosis, many patients already have serious complications. Accordingly, the American Association of Clinical Endocrinologists (AACE) has recommended screening high-risk populations at age ≥30 years, including persons who have a family history of diabetes; are overweight or sedentary; are Latino/Hispanic, African American, Asian American, or Pacific Islander; or have cardiovascular disease, impaired glucose tolerance or impaired fasting glucose, hypertension, increased triglycerides or low high-density lipoprotein (HDL)-cholesterol levels, a history of gestational diabetes, delivered a baby weighing more than 9 pounds, or a history of polycystic ovary disease.

Screening for diabetes has gained importance since publication of the results of the Diabetes Prevention Program study, which randomized patients with impaired glucose tolerance (IGT), defined as a plasma glucose level of 140 to 199 mm Hg 2 hours after ingestion of 75 g of glucose, to usual care, intensive lifestyle changes, or metformin. The goals of the intensive lifestyle change were to achieve weight loss equal to 7% or greater of body weight and to exercise equivalent to brisk walking for 150 minutes each week. After an average follow-up time of 2.8 years, the subjects treated with the intensive lifestyle intervention had a 58% reduction in the progression from IGT to type 2 diabetes compared with the usual care subjects. The reduction in the metformin-treated patients was 31%. Thus, there is clear evidence that persons at high risk can prevent or delay the development of type 2 diabetes.

The American Diabetes Association (ADA) and the National Institutes of Health have now recommended screening similar to that advocated by the AACE. Screening should occur as part of healthcare office visits using either an FPG or an oral glucose tolerance test (OGTT). A recent AACE consensus conference on the insulin resistance syndrome noted that the OGTT is more sensitive than the FPG; thus, if a value in the impaired fasting glucose (IFG) range is obtained with an FPG, one should definitely consider performing an OGTT, because a substantial number of such patients already have diabetes.

**Pathophysiology**

The patient described in this case had insulin resistance, decreased insulin secretion, and glucose toxicity. Providing appropriate treatment for patients with diabetes requires an understanding of the pathophysiology of the disease. Weyer and colleagues followed a number of Pima Indians who progressed over several years from normal glucose tolerance to type 2 diabetes and compared them to Pima Indians who did not develop diabetes. Individuals who progressed to type 2 diabetes had both a greater degree of insulin resistance and impaired beta-cell insulin secretion compared with those who did not progress.

The investigators noted that among subjects who became more insulin resistant during the course of observation, those who increased their insulin secretion to compensate for the insulin resistance did not develop diabetes, while those who were not able to increase their insulin secretion progressed to IGT.
and then to type 2 diabetes. Patients with insulin resistance usually have the insulin resistance syndrome and an increased risk for atherosclerosis and other adverse events, even though they do not have diabetes.

Such studies indicate that most patients with type 2 diabetes develop insulin resistance many years before diabetes is diagnosed. Initially, increased endogenous insulin secretion can compensate for insulin resistance and maintain normal glucose tolerance. In persons who develop diabetes, endogenous insulin secretion ultimately declines, and the patient first develops postprandial hyperglycemia and then fasting hyperglycemia sufficient to diagnose diabetes. Thus, at the time of diagnosis, most patients with type 2 diabetes have both insulin resistance and an insulin secretory deficit, and treatment should address both of these defects. Indeed, in the United Kingdom Prospective Diabetes Study (UKPDS), the newly diagnosed patients entering the study had on average 50% of normal beta-cell function. (Figure 2)

**SUMMARY AND DISCUSSION—CASE 1**

**SULFONYLUREA TREATMENT**

Although many endocrinologists would choose metformin as the first line of therapy for this patient, sulfonylureas remain a commonly prescribed class of oral agents for initial pharmacologic therapy of individuals with type 2 diabetes.

One of the concerns with sulfonylureas is weight gain. In the UKPDS, patients treated with glyburide gained 3.7 pounds. Overweight patients in the metformin substudy treated with glyburide gained 4 to 7 pounds.10

Sulfonylurea therapy might be associated with a weight gain of 2 to 5 kg and may cause hypoglycemia. Some studies suggest that newer, once-a-day sulfonylurea agents such as glimepiride and glipizide gastrointestinal therapeutic system (GITS) may present less risk for hypoglycemia and weight gain compared with the older sulfonylureas.11-13

In a study of more than 21 000 patients, the number of episodes of severe hypoglycemia per 1000 person-years was 5.8 with glyburide and only 0.43 with glimepiride.14 In another trial, almost 600 type 2 diabetic patients were randomized to placebo and diet or glipizide GITS and diet. Discontinuation due to hypoglycemia was no greater in patients randomized to glipizide GITS than in patients randomized to placebo.15

Several studies revealed no clinically significant weight gain with glipizide GITS therapy.15-17 Observational studies confirmed trends noted during clinical development of glimepiride that suggested it was not associated with significant weight gain. For example, favorable effects of glimepiride on weight were observed in a study of more than 19 000 type 2 diabetes patients treated with glimepiride who had a mean weight loss of 1.4 kg.18

These benefits of the newer once-a-day sulfonylureas, such as glimepiride and glipizide GITS, might occur because they increase insulin levels in response to meals, but are less likely to produce significant fasting hyperinsulinemia. In a study by Schade and colleagues, glimepiride improved postprandial insulin and C-peptide responses without producing clinically meaningful increases in fasting insulin or C-peptide levels.12 No clinically notewor-
thy abnormal laboratory values or hypoglycemia (blood glucose <60 mg/dL) occurred.

A recent study by Korytkowski and colleagues compared glimepiride with placebo treatment in patients with type 2 diabetes.19 Fasting plasma insulin (66 ± 18 vs 84 ± 48 pmol/L, P <.05) and first-phase (19 ± 8 vs 32 ± 11 pmol/L, P <.04) and second-phase incremental insulin responses to glucose (48 ± 23 vs 72 ± 32 pmol/L, P <.02) improved with glimepiride therapy.

Two new insulin secretagogues, repaglinide and nateglinide, have been touted to improve the first-phase insulin response that is impaired in patients with type 2 diabetes. These agents have a quicker onset of action than the sulfonylureas and must be given before meals.

**Combination Therapy**

Monotherapy is unlikely to maintain target glucose levels in most patients with type 2 diabetes. After 3 years in the UKPDS study less than 50% of subjects had an A1c <7%, whether they were treated with diet, insulin, a sulfonylurea, or metformin.20 Therefore, whether therapy was initiated with either metformin or a sulfonylurea such as glimepiride or glipizide GITS, it is likely that the other agent would be required in a relatively short period of time.

We also must address this patient's other cardiovascular risk factors because diabetes is associated with a marked increased risk for coronary heart disease as noted by Haffner and colleagues.4 The National Cholesterol Education Program's Adult Treatment Panel III (ATP III) identifies diabetes as a coronary heart disease equivalent.21 Morgan et al corroborated the high incidence of cardiovascular disease among patients with diabetes.1

Treatment goals for diabetic patients, in addition to controlling glycemia (the AACE A1c goal is <6.5%), must focus on other cardiovascular risk factors, including hypertension, smoking, dyslipidemia, and the hypercoagulable state associated with diabetes. The ADA goal for blood pressure is <130/80 mm Hg. The lipid goals include low-density lipoprotein (LDL) cholesterol levels <100 mg/dL, H DL >45 mg/dL in men and >55 mg/dL in women, and triglycerides <150 mg/dL. This patient should have treatment for hypertension with an angiotensin-converting enzyme (ACE) inhibitor, and a statin should be initiated for her dyslipidemia.

**Case Study 2**

A 68-year-old Caucasian male had been treated for type 2 diabetes over a 25-year period by a general practitioner. He had required insulin for the past 3 years. His wife also had type 2 diabetes and required insulin.

The patient also had hypertension, reflux esophagitis, a history of peptic ulcer disease, with a gastrointestinal bleed, and was a heavy drinker. He had undergone a 3-vessel coronary artery bypass and had previously had 3 episodes of pancreatitis, an appendectomy, and a pilonidal cystectomy. He also had dyslipidemia and peripheral vascular disease, requiring a left femoral artery bypass. He had undergone amputation of his third through fifth toes on the right foot, had a left lower extremity graft with occlusion and re-opening, and subsequent amputation of the left fourth toe. This is the type of patient who should be referred much earlier in his disease to an endocrinologist for care. Unfortunately these patients are often referred only after several complications have occurred.

The patient weighed 225 lb and had a BMI of 31. His blood pressure was 156/96 mm Hg, and his pulse was 64. He fit the criteria of the metabolic syndrome.

**Treatment Recommendations**

His blood sugars were originally 200 mg/dL fasting, and 330 mg/dL after meals. It is likely that he rarely exercised. In addition to hemoglobin A1c, urine albumin, and a complete metabolic panel, one should obtain a lipid profile and creatinine clearance. Creatinine clearance findings should be used to determine whether he can be safely treated with metformin.

Laboratory results were as follows: hemoglobin A1c 12.2%; LDL cholesterol 180 mg/dL; HDL cholesterol 37 mg/dL; and triglycerides 295 mg/dL. The patient will require treatment for his dyslipidemia. His C-peptide was normal (3.2), but his urine albumin (250 mg/g creatinine) and fasting plasma glucose (200 mg/dL) were high. His electrolytes and liver enzymes were normal, and his creatinine clearance was slightly decreased at 79.
In 2001, the AACE Consensus Panel revised their parameters for glucose control, recommending an A1c of <6.5%, a preprandial (fasting) plasma glucose <110 mg/dL, and a 2-hour postprandial plasma glucose <140 mg/dL. This patient clearly required increased control and aggressive treatment.

UKPDS 34 showed that improved glycemic control can reduce the risk of all diabetes-related endpoints, MI (although this just missed achieving statistical significance; P = .052), albuminuria, retinopathy, and microvascular complications (Figure 3). Treating compromised individuals aggressively, however, should include a review of the cost of care. In other words, how much will it cost to reduce hemoglobin A1c by 1%? A sulfonylurea, such as glimepiride, will provide the least expensive route, and a thiazolidinedione the most expensive. Another way to approach this question is to determine the cost of monthly treatment with the highest dose of any of these medications (Table 1). Approaching treatment this way is important, especially when combination medication is required. Prescribing medications without taking costs into consideration can impair the ability of patients to adhere to therapy, especially when 2 or more medications must be taken (Table 2). Even when patients have access to managed care with a prescription benefit, their copays can be high or there might be limits to medication coverage.

This patient must also be treated for hypertension. An ACE inhibitor could be used. Alternatively, an angiotensin II receptor blocker (ARB) might benefit this patient. In the Reduction of Endpoints in nonsulin dependent diabetes mellitus in the Angiotensin II Antagonist Losartan (RENAAL) study, the ARB losartan reduced the risk that diabetic nephropathy would progress to renal failure in patients with type 2 diabetes and nephropathy. Losartan, in combination with other antihypertensive therapy (excluding ACE inhibitors), delayed the onset of the primary composite endpoint (a doubling of serum creatinine, end-stage renal disease, or death; P = .02) and delayed progression to end-stage renal disease (P = .002). Losartan also reduced proteinuria (P < .001), the rate of decline of renal function (P = .01), and the incidence of first hospitalization for heart failure (P = .005). These benefits were significantly beyond those solely attributable to the reduction of blood pressure.
Parving et al examined the effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. Irbesartan reduced the risk of progression to renal insufficiency. Renal protection from irbesartan in patients with type 2 diabetes and microalbuminuria was independent of its beneficial effect on blood pressure. In hypertensive patients with type 2 diabetes and microalbuminuria, treatment conferred a renoprotective effect.

In the Irbesartan Diabetic Nephropathy trial (IDNT), irbesartan reduced the incidence of the primary composite endpoint (doubling of serum creatinine, end-stage renal disease, and death) by 23% compared with amlodipine in hypertensive patients with nephropathy.

ACE inhibitors or ARBs appear to offer diabetic patients greater benefits than some other antihypertensive agents. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial compared treatment with enalapril or nisoldipine, each in 235 patients, for 5 years. Patients treated with the ACE inhibitor had fewer fatal and nonfatal MIs (9 vs 27). Similar differences were noted in the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) in which 380 hypertensive type 2 diabetics were treated with fosinopril, amlodipine, or both for 3 years. A cardiovascular endpoint occurred in 27 of the 141 patients on amlodipine, 14 of the 131 on fosinopril, but only in 4 of the 108 treated with both drugs.

The AACE and American Diabetes Association (ADA) guidelines recommend blood pressure goals of <130/85 and <130/80 mm Hg, respectively, in diabetic patients. The Hypertension Optimal Treatment (HOT) trial demonstrated the importance of achieving optimal blood pressure control, especially in diabetic patients. The HOT trial sought to determine the optimal target blood pressure in patients with hypertension. In patients with diabetes, cardiovascular events were reduced 51% at a blood pressure <80 mm Hg, compared with the target group at ≤90 mm Hg (P for trend = .005).

In the HOT study, hypertension was controlled with 1 agent in only one third of subjects. Nearly two thirds of all patients required at least 2 agents to control blood pressure. Some required 3 or more agents. The use of multiple drugs points out again why costs must be considered when prescribing medications for diabetic patients.

The patient in this case also required a cholesterol-lowering agent: His LDL cholesterol required a reduction of 80 mg/dL. An HMG-CoA reductase inhibitor (statin) should be the agent of first choice. It was also necessary to increase his HDL cholesterol level. Increasing HDL-C is possible with niacin; however, this agent can worsen glycemic control in some patients. His triglyceride level was 295, requiring a reduction of 145 mg/dL. Gemfibrozil or fenofibrate can improve both the hypertriglyceridemia and the low HDL-C, and statins are moderately effective in high doses in patients with elevated triglyceride and LDL levels. One needs to closely observe patients treated with the combination of a statin and a fibrate because of the risk of rhabdomyolysis with acute renal failure, which can occur with the combination. The ATP III guidelines recommend initial treatment in patients with triglycerides between 200 and 500 mg/dL with a statin to reduce LDL cholesterol. A triglyceride-lowering agent is added if triglycerides remain >200 mg/dL on statin treatment.

Glycemic Control

Glycemic control, which of course remains a major priority in this patient, would best be achieved by changing his insulin regimen. The

Table 2. Estimated Maximum Monthly Costs of Some Branded Antidiabetic Combination Therapies

<table>
<thead>
<tr>
<th>Combination</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea + Metformin</td>
<td>121.86</td>
</tr>
<tr>
<td>Repaglinide + Metformin</td>
<td>172.84</td>
</tr>
<tr>
<td>Nateglinide + Metformin</td>
<td>181.87</td>
</tr>
<tr>
<td>Sulfonylurea + Rosiglitazone or Pioglitazone</td>
<td>174.48</td>
</tr>
<tr>
<td>Metformin + Rosiglitazone or Pioglitazone</td>
<td>244.42</td>
</tr>
<tr>
<td>Metformin + sulfonylurea + Thiazolidinedione</td>
<td>270.38</td>
</tr>
</tbody>
</table>

source www.drugstore.com accessed 2/10/03. These are self-pay prices and do not take into account any discounts or insurance coverage. Assumed usual maximally effective doses of each oral agent component. Prices likely to vary from different retailers and over time and in different geographic areas or based on insurance coverage. Prices may be somewhat lower with some single pill combination medications.
UKPDS demonstrated a progressive decline in beta-cell function over time in patients with type 2 diabetes (Figure 4). Eventually, this decline results in a need for insulin in many type 2 patients. This patient's insulin regimen was altered to eliminate the 70/30 insulin and initiate 26 U of insulin glargine each day at bedtime. He had been taking 30 U of Humulin 70/30 or 21 U of neutral protamine Hagedorn (NPH) daily; however, because he was very poorly controlled on this regimen, a higher dose of glargine was employed. Rapid-acting insulin before meals was initiated, and the patient began calling in SMBG results regularly in order to have the basal and preprandial insulin doses adjusted as needed. Atorvastatin (10 mg qhs), perindopril (4 mg), and hydrochlorothiazide (12.5 mg) were also added to the regimen because his hypertension was difficult to control. Lasix was replaced with a low dose of a longer-acting hydrochlorothiazide. The effect of Lasix lasts approximately 6 hours and does not provide blood pressure control over a long enough period of time.

Diabetic education and nutritional instruction were initiated, not only for the patient, but also for his wife, the person responsible for the cooking in his family. She also had diabetes and would therefore benefit as well.

At the 4-week follow-up, his average FPG was reduced to 140 mg/dL, and his average 4 pm level had fallen to 160 mg/dL. There was no elevation of his liver enzymes or creatine phosphokinase. He had no myalgias, and his blood pressure had dropped to 140/90 mm Hg.

At his 3-month follow-up, his weight had decreased to 220 lb; his blood pressure was 138/84; and his average 4 pm home-monitored glucose level was further reduced to 120 mg/dL. His A1c level had dropped considerably to 7.8%; but his total cholesterol was still elevated at 230 mg/dL. His LDL was 140; HDL 37; and triglycerides 230. Atorvastatin was increased to 20 mg/d.

At the 6-month follow-up, he had lost another 5 lb. His blood pressure had dropped to 128/79 and was now within the AACE and ADA guidelines. Home-monitored FPG averaged 100 mg/dL, and the 4 pm level remained at 120 mg/dL. His A1c dropped further to 6.8%. His total cholesterol was now 196; LDL cholesterol level was 117; and HDL cholesterol level was 39. His triglycerides had finally reached 200.

**Summary**

This patient had every aspect of the metabolic syndrome. Now that criteria have been designated for this syndrome, they should be used and aggressive treatment should be provided without delay. As demonstrated in this patient, even late therapy can be helpful.

By the time endocrinologists see patients with diabetes, their insulin secretion has often already declined substantially. At least 50% of patients will have had the metabolic syndrome for quite some time prior to the diagnosis of diabetes. We should keep in mind several messages from the UKPDS trial:

- Sulfonylureas, metformin, and insulin reduce microvascular complications by improving glycemic control.
- There is no evidence that sulfonylureas or insulin increase cardiovascular risk.
- Combination therapy is usually needed to control glucose.

Furthermore, insulin therapy should be introduced if patients cannot achieve glycemic targets with combinations of oral antidiabetic agents that have complementary actions. Insulin therapy may be required, at least temporarily, at the outset in patients with marked and/or symptomatic hyperglycemia.

**CASE STUDY 3**

A 54-year-old, African American male with type 2 diabetes and hypertension presented for reevaluation. Treatment included ramipril, a thiazide, glimepiride, and metformin. He had been markedly overweight for 15 years, and had a BMI of 42. His blood pressure was 134/84 mm Hg. He had back-
ground retinopathy, 2+ ankle edema, and evidence of neuropathy. He had microalbuminuria and dyslipidemia. His A1c was 8.6%, indicating that his glucose levels were poorly controlled, despite his taking 2 oral agents.

Rosiglitazone was added to the regimen of our patient. Three months after the dose was titrated to 4 mg bid, the A1c had declined to 7.9%. This degree of glycemic lowering is what would be expected based on studies in which a thiazolidinedione had been added to 1 or more oral antidiabetic agents.

At this point, it is clear that the patient will require insulin to achieve adequate glycemic control. Many physicians hesitate to start insulin therapy. The complexity of initiating insulin, patient concern about inconvenience or discomfort of injections, patient and physician concerns about possible hypoglycemia or weight gain all inhibit implementation of insulin therapy.

Initiating insulin therapy with a bedtime dose of basal insulin has the advantage of offering a simple regimen that involves a single daily injection with no mixing and a simple titration. The result is good efficacy with little weight gain and a low risk for hypoglycemia. The bedtime insulin is intended to emulate the endogenous basal insulin that is steadily secreted between meals and overnight in nondiabetic individuals. Until recently, it has been difficult to replicate endogenous basal insulin using traditional intermediate and long-acting insulin preparations such as NPH, lente, and ultralente insulin. The recent availability of insulin glargine has provided a basal insulin that, in most type 2 diabetes patients, lasts up to 24 hours without peaks in the insulin profile that can increase the risk of hypoglycemia. Riddle, Rosenstock, and others have reported results of a treat-to-target study assessing the feasibility of achieving glycemic control with the addition of bedtime insulin glargine or NPH to the regimens of type 2 diabetic patients who had inadequate glycemic control despite taking 1 or 2 oral agents.9 The study was conducted in insulin-naïve patients who continued their prior oral therapy. The investigators used a simple weekly titration algorithm.

Fifty-seven percent of patients achieved A1c values of <7% with the addition of either NPH or glargine. Reduction in A1c was similar; both groups achieved an end-of-study mean A1c of 6.9%. Significantly more patients treated with insulin glargine (33% vs 27%; P < 0.5) achieved the main objective: A1c <7% without documented hypoglycemia (glucose <72 mg/dL). Overall, treatment with insulin glargine caused less nocturnal hypoglycemia than NPH insulin (532 vs 886 events; P < 0.002) in 40% vs 49% of subjects (P < 0.01). Severe hypoglycemia (requiring assistance) was similar and uncommon in the 2 groups (2.5% and 2.3% of subjects).

One can base a reasonable insulin implementation strategy for patients with type 2 diabetes on the above trial. When patients do not achieve target glycemia despite a combination of 2 or 3 oral agents with complementary mechanisms of action, one can administer a daily bedtime dose of NPH or insulin glargine. Because of the benefits of glargine noted above, it is being chosen with increased frequency. One can safely start with a nightly dose of 10 U in the vast majority of patients, and thus obviate the need for dose calculation. Patients are instructed that they need only perform a single morning fasting SMBG daily, unless they have signs or symptoms of hypoglycemia at other times of the day. Each week, they can report their 2 or 3 most recent SMBG values and a simple titration schedule can be used. Unless the patient reports episodes of hypoglycemia, the daily insulin dose is increased by 4 U for the next week if the fasting glucose is >140 mg/dL and by 2 U if the SMBG is >120 mg/dL. One continues these weekly adjustments, aiming for an FPG of <120 mg/dL, unless a patient has contraindications to trying to optimize glycemic control.

After the fasting glucose goal has been achieved and maintained long enough to be reflected in the A1c value (~3 months), one can consider adding rapid-acting insulin to the regimen if the A1c or preprandial or postprandial glucose level is significantly above target. Rapid-acting insulin can be added first to the main meal and, subsequently, to other meals if necessary.
What should one do about the oral antidiabetic medications after insulin has been added? Unless there are contraindications to its use, metformin should be continued based on studies demonstrating that combining metformin with insulin results in better glycemic control at the same or lower insulin doses than combining a placebo with insulin. Some studies have shown similar glycemic control, but at lower insulin doses. The addition of metformin may also result in less weight gain and lower cholesterol or LDL-cholesterol values.30

There is also evidence of benefit from combining insulin and thiazolidinediones. The glycemic effects of treatment with pioglitazone in combination with a stable insulin regimen were evaluated in patients with type 2 diabetes.31 Patients (n=566) who were receiving stable insulin regimens for >30 days but had A1c >8.0% and C-peptide >0.7 mcg/L were randomized to receive 15 mg pioglitazone, 30 mg pioglitazone, or placebo once daily in a 16-week multicenter, double-blind, placebo-controlled trial. At the end of double-blind treatment, patients receiving pioglitazone (15 mg or 30 mg) showed statistically significant mean decreases relative to baseline A1c (-1.0 and -1.3, respectively; P <.0001) and FPG (-34.5 mg/dL [-1.92 mmol/L] and -48.0 mg/dL [-2.67 mmol/L], respectively; P <.0001); these differences compared with placebo were also significant (P <.0001).

Postmarketing studies of the combination of thiazolidinediones and insulin have indicated the possibility of fluid accumulation that can lead to or exacerbate congestive heart failure. Therefore, patients should be observed for signs and symptoms of heart failure. The drug should be discontinued if any deterioration occurs in cardiac status. Patients with New York Heart Association Class III and IV cardiac status were not studied during clinical trials; therefore, rosiglitazone and pioglitazone are not recommended in such patients. The combination of insulin and thiazolidinediones may be problematic even among those with milder degrees of congestive heart failure.32

In this regard, it should be remembered that metformin is contraindicated in patients whose congestive heart failure requires pharmacologic therapy.

One might surmise that when insulin was added to the regimen of a patient with type 2 diabetes, any insulin secretagogues could be discontinued; however, a recent study from the UKPDS reported on patients who were randomly allocated to a conventional glucose-lowering protocol, primarily with diet, or an intensive protocol with a sulfonylurea or with insulin as in the main UKPDS study.33 For patients randomized to an intensive protocol with sulfonylurea, insulin was added automatically if the FPG remained >108 mg/dL despite maximal sulfonylurea doses.

Over 6 years, approximately 53% of patients treated with sulfonylurea required additional insulin therapy. Median A1c in the sulfonylurea ± insulin group was significantly lower (6.6%) than in the group taking insulin alone (7.1%; P =.0066), and significantly more patients in the sulfonylurea ± insulin group achieved an A1c <7% (47% vs 35%, respectively; P =.011). Weight gain was similar in the intensive therapy group, but major hypoglycemia occurred less frequently overall in the sulfonylurea ± insulin group compared with the insulin alone group (1.6% vs 3.2% per annum, respectively; P =.017). An editorial by Riddle suggested that the combination of a secretagogue and insulin might reduce both hypoglycemia and glycemic variability by enhancing the ratio of endogenous to exogenous insulin.34 Based on these papers, it seems reasonable to continue the insulin secretagogues when one initiates basal insulin therapy. There are no data addressing whether secretagogues continue to be beneficial after prandial rapid-acting insulin is added to the regimen.

SUMMARY

Type 2 diabetes is a serious, costly, and epidemic disorder. Early diagnosis and early therapy focused on improving glycemic control and treating other risk factors are essential. Medical nutrition therapy and appropriately prescribed exercise are cornerstones of treatment. Most patients with type 2 diabetes require multiple pharmacologic agents, including insulin.

REFERENCES


