A 74-Year-Old Woman With Diabetes

Ms M, a 74-year-old woman with type 2 diabetes of 6 years’ duration, has a glycated hemoglobin (HbA1c) value of 7.4% despite taking 3 oral antidiabetic medications, as well as coexistent hypertension and abdominal obesity. She has no known microvascular or macrovascular complications of diabetes and is otherwise healthy. She is reluctant to commence insulin treatment as she dislikes the idea of injections and wonders if there are any alternate options if she is to get her HbA1c value below 7%. The natural history of type 2 diabetes, reasons why many patients begin requiring insulin over time, rationale for tight glycemic control, and therapeutic options for Ms M are discussed.

Ms M’s most recent BMI was 24.5 and her waist circumference was 36 inches. She is able to exercise only with short walks due to back pain. Her blood pressure over the past 6 months ranged from 130 to 140 mm Hg systolic and 70 to 75 mm Hg diastolic. Her most recent total cholesterol measurement 6 months ago was 153 mg/dL (3.96 mmol/L) with a high-density lipoprotein cholesterol (HDL-C) level of 101 mg/dL (2.61 mmol/L) and a calculated low-density lipoprotein cholesterol (LDL-C) level of 31 mg/dL (0.80 mmol/L). Her urine albumin–creatinine ratio was 30.6 about 2 years ago. However, all subsequent measurements have been in the 2.6 to 20.0 range. Her recent ophthalmologic examination findings were normal. She has no symptoms of peripheral neuropathy.

Ms M is retired. She has been widowed for 8 years. She has 3 children, one of whom has diabetes. She does not smoke. She drinks alcohol socially.

Her current medications include rosiglitazone (4 mg/d), valsartan (80 mg/d), hydrochlorothiazide (12.5 mg/d), estradiol (0.5 mg/d), glyburide (10 mg twice daily), and metformin (1000 mg twice daily). She is allergic to moexipril with the development of tongue swelling.

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Ms M remains very reluctant to begin taking insulin and if and when her HbA1C value increases to 7% or more she wonders whether she has any other options.

MS M: HER VIEW
Diabetes bothers me, even having it bothers me. I was diagnosed with diabetes in 1999. I had the shingles and after the shingles, my doctor diagnosed me with diabetes during some tests that she was doing about the shingles. One of my daughters had diabetes and we couldn’t find a history of how because no one in our family that we knew of, not blood relatives, had diabetes. So that was kind of a shock.

I don’t think that it has affected me. It hasn’t slowed me down in anything I do. I have to watch what I eat, sometimes that’s not easy, but I try anyway. I try to exercise, which is kind of hard because I have problems with my legs. I had a back operation and my legs are still kind of weak. But I walk every day, so that helps.

I check my sugars twice a week. In the morning they’re usually good, but sometimes at night they are high. I just don’t like needles and I just can’t see myself injecting insulin every morning. So I’m trying my best to stay away from having to do insulin. I’m taking 6 pills a day and one of them twice a day and right now I think I’m maximum on my medicine that she can give me. I am wondering if there are any alternatives besides taking the insulin? I would gladly welcome the news.

AT THE CROSSROADS: QUESTIONS FOR DR ABRAHAMSON
What is currently understood about the cause of type 2 diabetes? What is the evidence that tight control of hyperglycemia improves outcomes in type 2 diabetes, particularly in older individuals like Ms M? What are the comparative efficacies and outcomes of the available therapies for type 2 diabetes, including diet/exercise, oral agents, and insulin? When should a patient be prescribed insulin and why? What do you recommend for Ms M? How might her management be different in the future?

DR ABRAHAMSON: Ms M is a 74-year-old woman whose story demonstrates the natural history of type 2 diabetes and who is truly at a crossroads in terms of therapeutic decisions and recommendations. She was diagnosed with diabetes 6 years ago and since that time has required increasing numbers of medications to achieve and maintain target glucose and HbA1C concentrations. She now is taking maximum doses of glyburide and metformin and a near maximum dose of rosiglitazone. To understand the rationale for recommending additional or alternative therapy for Ms M it is important to understand the natural history of type 2 diabetes.

Causes of Type 2 Diabetes
Diabetes is the most common metabolic disorder, affecting more than 20 million people in the United States alone, of whom approximately 90% have type 2 diabetes. Type 2 diabetes is important particularly because of its significant morbidity and mortality, primarily from cardiovascular disease. The prevalence of type 2 diabetes is increasing at an alarming rate, particularly due to the rise in obesity, such that by 2025 it is estimated that 300 million people in the world will have this disorder, and the lifetime risk of developing type 2 diabetes will approximate 20%. The prevalence of type 2 diabetes increases with advancing age; for example, in 2004 the prevalence of diabetes among people aged 65 to 74 years was 16.7% vs 1.4% in people younger than 45 years.

In all age groups, type 2 diabetes is characterized by 2 major pathophysiological abnormalities: insulin resistance, which is associated with increased hepatic glucose production and reduced glucose clearance, and impaired beta cell insulin secretion (both basal and glucose-stimulated). In most individuals who develop diabetes, insulin resistance begins and progresses many years before the development of hyperglycemia. Its development can be correlated with obesity, in particular increases in visceral fat. Adipocytokines, such as tumor necrosis factor α, plasminogen activator inhibitor type 1, and interleukin 6, which are released from adipose tissue, impair insulin signaling, the fibrinolytic system, and endothelial function. Circulating concentrations of another adipose-specific protein, adiponectin, have been shown to be reduced in individuals with insulin resistance and obesity and correlate negatively with the degree of insulin resistance. Visceral fat is resistant to the antilipolytic effects of insulin and hence produces more free fatty acids, which in turn impair insulin-mediated glucose uptake in muscle and further impair insulin secretion, a phenomenon known as “lipotoxicity.” Visceral fat accumulation is also associated with the development of an abnormal lipid profile characterized by elevated triglyceride level, low HDL-C, and increased concentrations of small dense LDL-C particles that are highly atherogenic (which Ms M does not have), and an increased risk of hypertension (which Ms M has).

The distribution of body fat plays an important role in determining the presence or absence of insulin resistance. Peripheral subcutaneous fat deposition is not associated with insulin resistance and all of its consequent metabolic abnormalities, whereas visceral fat is. Indeed, BMI alone cannot be reliably used to identify individuals who are insulin resistant; a person whose BMI is less than 25 may still be insulin resistant if he or she has a predominance of visceral or central fat. Ms M has a BMI of 24.5, which is considered to be normal, but her waist circumference is 36 inches, suggesting that she has a predominance of visceral fat with its attendant risk for cardiovascular disease.

Impaired beta cell secretory function must be present before hyperglycemia develops. Impaired insulin secretion following intravenous or oral glucose administration has been demonstrated in individuals with impaired fasting glucose levels (ie, fasting glucose concentrations between 100 and 125 mg/dL [5.55 and 6.93 mmol/L]) and deteriorates further as glucose concentrations rise above this. As patients progress
from normal to impaired glucose tolerance to overt diabetes, postprandial sugars may increase before the fasting glucose concentration increases.\textsuperscript{10} By the time diabetes develops, the individual has lost as much as 50% of beta cell function.\textsuperscript{21} Rising glucose levels further compromise insulin secretion and insulin action, a phenomenon known as “glucose toxicity.”\textsuperscript{22} A summary of the natural history is shown in the FIGURE.

The progressive loss of beta cell secretory function means that patients with diabetes often require more medication over time to maintain the same level of glycemic control. In the United Kingdom Prospective Diabetes Study (UKPDS), in which individuals with newly diagnosed type 2 diabetes were followed up for a median of 11.1 years, fewer than 30% of participants were able to achieve and maintain an HbA1C value of less than 7% while taking only 1 antidiabetic medication, and more than 60% of participants in the trial required additional pharmacotherapy to achieve and maintain “optimal” glycemic control.\textsuperscript{23,24} Ms M’s clinical course mirrors this experience.

**Evidence That Tight Control of Diabetes Improves Outcomes**

In patients with type 1 diabetes, microvascular complications begin as early as 5 years after disease onset (and rarely, earlier) and increase with disease duration.\textsuperscript{25,26} Hence, screening for microvascular complications in this subset of individuals is recommended 5 years after diagnosis and annually thereafter. In type 2 diabetes, often asymptomatic at early stages, microvascular complications may be present at the time of diagnosis in up to 20% of individuals.\textsuperscript{27} While Ms M was diagnosed with diabetes 6 years ago and currently has no evidence of microvascular complications, there is no guarantee that she will not develop these complications with ongoing disease duration. Most individuals with type 2 diabetes will die of macrovascular complications of the disease, notably coronary artery disease (CAD).\textsuperscript{28}

In 1977, Jean Pirart, a Belgian diabetologist, published a retrospective analysis of 4400 patients whom he had personally followed for up to 25 years and demonstrated a correlation between glycemic control and development of the microvascular complications of the disease.\textsuperscript{29-31} The Diabetes Control and Complications Trial (DCCT) was the first large randomized controlled study to demonstrate a clear association between risk for the onset or progression of the microvascular complications of diabetes and glucose control in patients with type 1 diabetes.\textsuperscript{32} In this study a 2% difference in HbA1C value between the “routinely” treated patients and “intensively” treated patients (9.0% vs 7.1%) was associated with a 76% relative risk reduction for the development of retinopathy, a 54% relative risk reduction for the progression of retinopathy, and a 54% and 60% relative risk reduction for the onset or progression of nephropathy and neuropathy, respectively. A similar but smaller study in insulin-treated patients with type 2 diabetes demonstrated nearly identical results.\textsuperscript{33}

**Figure. Schematic of Progression From Normal Glucose Tolerance to Impaired Glucose Tolerance and Type 2 Diabetes Mellitus**

*Risk factors for development of type 2 diabetes mellitus:
- Genetics
- Perinatal Factors

*Insulin responsiveness:
- Insulin Resistant: Impaired Insulin-Mediated Peripheral Glucose Uptake (Skeletal Muscle, Adipose Tissue)
- Insulin Sensitive

*Beta cell function:
- Normal Insulin Secretion: Compensatory Hyperinsulinemia (Compensatory Increase in Beta Cell Secretion)
- Relative Insulin Deficiency: Impaired Suppression of Hepatic Glucose Output
- Progressive Beta Cell Failure

*Glucose tolerance:
- Normoglycemia
- Impaired Fasting Glucose Tolerance
- Impaired Glucose Tolerance
- Diabetes Mellitus

*Visceral fat accumulation is associated with altered secretion of adipocytokines that impair insulin sensitivity (eg, increased tumor necrosis factor $\alpha$, plasminogen activator inhibitor 1, and interleukin 6, and decreased adiponectin), and with increased free fatty acid production.*
The UKPDS was the first large randomized controlled study confirming the benefit of better glycemic control in participants with type 2 diabetes aged between 48 and 60 years who were treated with diet, oral agents, or insulin, or combinations of oral agents and/or insulin. In this study, a 1% difference in HbA1c value between the intensively and conventionally treated groups who were treated with sulfonylureas or insulin (median HbA1c value over 10 years, 7.0% vs 7.9%) was associated with an average 25% relative risk reduction for the onset or progression of microvascular complications of the disease, including the need for retinal photocoagulation. The risk of myocardial infarction was reduced a relative 16% in the more intensively treated group (P = .052), but cardiovascular outcomes did not differ between patients treated with sulfonylureas or insulin. In a separate analysis of the data from the study, each 1% decline in HbA1c value was associated with a 21% relative reduction in diabetes-related mortality, a 14% relative reduction in myocardial infarction, and a 37% relative reduction in microvascular complications (all statistically significant). No glycemic threshold for risk reduction of any end point was observed. In a subgroup of obese individuals treated with metformin as monotherapy, risk of myocardial infarction was reduced 39%, all-cause mortality was reduced 36%, and diabetes-related deaths were reduced by 42%. In evaluating the potential relationship between risk factors and development of CAD in this study, the authors also found that LDL-C, HDL-C, HbA1c value, systolic blood pressure, and smoking were all significant risk factors. Several epidemiological studies have also confirmed a relationship between glycemia and risk for CAD, including an increased risk for total CAD and CAD mortality in patients with impaired glucose tolerance. In a 17-year follow-up of the DCCT, those individuals (mean age, 45 years at follow-up) who had intensive treatment of diabetes during the 6.5 years of the randomized study experienced a 50% lower rate of cardiovascular events compared with the group without intensive treatment, even though tight glycemic control was not maintained after the study.

Unfortunately, no studies have evaluated the impact of intensive glycemic control in individuals older than 60 years. However, individuals who are otherwise healthy and have a “reasonable” life expectancy would be expected to experience benefits similar to younger patients, provided the risk of hypoglycemia is not excessive. The average life expectancy for a woman in the United States aged 74 years is 13 years. Given that Ms M has type 2 diabetes, hypertension, and central adiposity and no other serious comorbid conditions, her life expectancy could reasonably be estimated at 13 years. Therefore, I would argue that improving glucose control to reduce the risk for development of complications, providing it can be done safely, is warranted. This is consistent with guidelines for improving the care of the older person with diabetes mellitus in which individualization of treatment is recommended and based on the patient’s overall health, comorbid conditions, projected life expectancy, health care goals, and preferences for treatment.

**Treatment Goals**

The evidence linking tight glycemic control with reduced risk for complications has led to the publication of increasingly stringent targets for glucose control by various diabetes and endocrine organizations, including the American Diabetes Association and the American College of Endocrinology. The target HbA1c value set by the American Diabetes Association is less than 7%, while the American College of Endocrinology recommends that the target HbA1c value should be less than 6.5%. These targets are based on the data presented above, with the recognition that there are no data for an older population group. The overriding approach in managing patients with diabetes should be to provide each patient with the opportunity to achieve glucose levels as close to normal as possible without significantly increasing his or her risk for additional complications such as hypoglycemia, and taking into account the presence of comorbid conditions, expected longevity of the individual, and ability to adhere to therapeutic regimens including lifestyle changes. Ms M is an otherwise healthy, active woman with well-controlled hypertension and an excellent lipid profile, but her hyperglycemia is not ideally controlled. We do not know how high her fasting or post-prandial glucose concentrations are but know that there are therapies that can be used safely to improve glucose control and maintain an HbA1c value of less than 7%. We also do not know how long she has had diabetes but should recognize that microvascular complications of diabetes begin to occur within 5 years after development of disease and increase in prevalence thereafter.

**Treatment of Type 2 Diabetes**

Medical nutrition therapy and exercise form the cornerstone of all treatment programs for patients with type 2 diabetes, as they have for Ms M. Nutrition counseling, recommending modest weight loss by reducing calorie intake (conventionally achieved by reducing fat intake), facilitates improvement in glycemic control and may be associated with a reduction in the HbA1c value of up to 1%. Moderate-intensity exercise (such as walking or cycling 3-4 times per week and/or resistance training 2 times per week) may lead to a reduction in HbA1c value slightly more than 0.5%, but these interventions alone are usually not sufficient to ensure that patients reach the target HbA1c value of less than 7%. However, even small amounts of weight loss improve insulin sensitivity, and exercise not only reduces insulin resistance but is beneficial for the comorbid conditions often associated with type 2 diabetes (eg, hypertension and hyperlipidemia) and improves psychological well-being.

Since most patients with type 2 diabetes present with or have HbA1c concentrations exceeding 8%, medical therapy with oral antidiabetic drugs is usually required. Classes of
oral agents include insulin secretagogues (sulfonylureas and glinides), insulin sensitizers (metformin and thiazolidinediones), and drugs that delay the absorption of carbohydrate from the gastrointestinal tract (α-glucosidase inhibitors). These various classes of agents, their mechanism of action, and effect on glycemic control are summarized in Table 1. Comprehensive reviews are available.48-51

Two new classes of insulin secretagogues are also listed in Table 1. Exenatide is an analogue of exendin 4, a peptide found in the saliva of the Gila monster that has similar actions to glucagon-like peptide-1 (GLP-1). It inhibits glucagon secretion and stimulates endogenous insulin secretion via a mechanism different from sulfonylureas. The US Food and Drug Administration has approved its use in combination with sulfonylureas and/or metformin.51,52 More recently, the Food and Drug Administration approved sitagliptin, an insulin secretagogue, for use in type 2 diabetes as monotherapy or in combination with metformin or a thiazolidinedione.53-55 This drug inhibits the enzyme dipeptidyl peptidase type IV (DPP-IV), which degrades endogenously secreted incretins like GLP-1. This effectively prolongs the action of the incretins, which enhance insulin secretion in a glucose-dependent manner and inhibit glucagon secretion.

Outcome data from the UKPDS found that patients treated with sulfonylureas, metformin, or insulin all demonstrated an HbA1c reduction of 1%,51,52 but clinical experience with this drug is limited. However, the mean HbA1c concentration in the studies in which this regimen was tested was greater than 9% and most patients enrolled in these studies did not achieve target HbA1c concentrations of less than 7%.67 Hence, addition of insulin is often necessary if patients are going to achieve therapeutic targets. Studies of exenatide have demonstrated an HbA1c reduction of 1%, but clinical experience with this drug is limited.

In Ms M’s situation, adding metformin to glyburide resulted in an improvement in glycemic control for a period of time. A third oral agent was needed after approximately 18 months as glycemic control had deteriorated, probably

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**Table 1. Major Classes of Oral Antihyperglycemic Drugs and Incretins Used in Clinical Practice**

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Reduction in HbA1c %</th>
<th>Common Adverse Effects</th>
<th>Approximate Cost Per Month of Dose Indicated*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stimulate insulin secretion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.5-2.0</td>
<td>Weight gain, hypoglycemia</td>
<td>Glyburide: 5 mg twice daily, $16</td>
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<td></td>
<td></td>
<td></td>
<td>Glimepiride: 4 mg daily, $15</td>
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<td></td>
<td>Glipizide XL: 10 mg daily, $22</td>
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<tr>
<td>Non-sulfonylurea insulin secretagogues</td>
<td>1.0-2.0</td>
<td>Weight gain, hypoglycemia</td>
<td>Repaglinide: 2 mg 3 times daily, $111</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nateglinide: 120 mg 3 times daily, $115</td>
</tr>
<tr>
<td>Exenatide</td>
<td>1.0</td>
<td>Nausea, vomiting, weight loss, hypoglycemia (when used with sulfonylurea)</td>
<td>10 µg twice daily, $209</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>0.8</td>
<td>Nasopharyngitis, headache</td>
<td>100 mg daily, $164</td>
</tr>
<tr>
<td><strong>Decrease insulin resistance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin (acts at hepatic level)</td>
<td>1.5-2.0</td>
<td>Flatulence and diarrhea, lactic acidosis (rare), vitamin B12 deficiency (rare)</td>
<td>1000 mg twice daily, $56</td>
</tr>
<tr>
<td>Thiazolidinediones (act at peripheral level)</td>
<td>0.6-1.9</td>
<td>Weight gain, edema (contraindicated in class 3 or 4 CHF)</td>
<td>Pioglitazone: 30 mg daily, $163</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Rosiglitazone: 4 mg daily, $106</td>
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<tr>
<td>Delay carbohydrate absorption from gastrointestinal tract</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>0.5-1.0</td>
<td>Flatulence and diarrhea</td>
<td>Acarbose: 100 mg 3 times daily, $87</td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; DPP-IV, dipeptidyl peptidase type IV; HbA1c, glycated hemoglobin.
because of progressive loss of beta cell function. This addition, as expected, led to a further reduction in HbA1c concentration but will be not enough to sustain the level below 7%. As discussed above, she likely will need insulin to achieve optimal control.

**When to Prescribe Insulin**

Over time, many patients with type 2 diabetes will require insulin therapy since beta cell secretory dysfunction is progressive and currently no therapies reverse this. In nondiabetic individuals, basal insulin is secreted at all times to suppress hepatic glucose production between meals and overnight. At mealtime, ingestion of food stimulates acute release of insulin, which is maintained as long as glucose levels are elevated. The secreted insulin ensures that hepatic glucose production is suppressed, glucose is disposed of, and serum glucose levels are maintained in a narrow range until they return to premeal concentrations. As glucose levels decline toward normal fasting levels, secretion of insulin decreases too, ensuring that hypoglycemia does not occur. The ultimate goal of treatment is to mimic this level of control, but such control is difficult to achieve in practice.

Indications for insulin therapy in type 2 diabetes include inability to achieve target glucose (fasting and/or postprandial) and HbA1c concentrations despite taking oral agents (monotherapy or combination therapy); if symptoms are severe (especially at the time of diagnosis) or if patients present with ketoacidosis; and in women who are planning to become pregnant or who may become pregnant while presenting with ketoacidosis; and in women who are planning to become pregnant or who may become pregnant while taking oral medications. For individuals who are thought to become pregnant or who may become pregnant while taking oral medications. For individuals who are thought to have type 2 diabetes and who began insulin treatment at the time of diagnosis, the decision regarding use of oral agents can be deferred until the etiology of the type of diabetes is confirmed and/or glycemic control is as close to normal as possible, at which stage use of oral antidiabetic agents may be considered. The decision to initiate insulin therapy in patients inadequately controlled with oral antidiabetic medications is often delayed, as with Ms M, for a number of reasons, including physician reluctance to prescribe insulin, patient reluctance to start insulin because of fear of the injections (as is the case with Ms M), concern about hypoglycemia, or because there is a perception that insulin therapy implies severe disease. The risk of hypoglycemia can be minimized by starting insulin at a relatively low dose; titrating the dose against blood glucose concentrations; using more "physiologic" insulins; and ensuring that patients understand the relationship between glucose control, insulin therapy, ingestion of food, and exercise. The "clinical inertia" associated with the decision to proceed to insulin treatment can be overcome by appropriate referral to diabetes centers with professional staff who are adept at facilitating the initiation of insulin treatment and ongoing care. There are no absolute contraindications to insulin in a patient with diabetes—indeed, when used appropriately (ie, the correct dose) it is more effective than oral medications in lowering glucose concentrations. Long- or intermediate-acting insulins provide basal insulin requirements for patients with diabetes and are administered once or twice daily. Addition of basal insulin at night is indicated for patients taking oral medications whose fasting glucose levels are elevated. An appropriate starting dose is 10 units or 0.1 unit per kilogram. The dose of basal insulin is titrated until target fasting glucose concentrations are achieved. Use of the long-acting basal insulin analogue glargine at night is associated with less frequent hypoglycemia when compared with neutral protamine Hagedorn (NPH) insulin. In a “treat to target” study, which included patients aged 30 to 70 years, addition of a basal insulin to regimens with 2 oral medications led to a further 1.6% reduction of HbA1c with almost 60% of patients reaching an HbA1c concentration of less than 7%. Nearly one quarter more patients studied achieved this goal without documented nocturnal hypoglycemia than those treated with NPH insulin (33.2% vs 26.7%), and neither treatment had episodes of severe hypoglycemia. Nearly 40% of those treated in this study did not reach target HbA1c concentrations, probably because their postprandial glucose concentrations were elevated and the basal insulin did not reduce glycemic postmeal excursions.

In individuals whose postprandial glucose concentrations are elevated, rapid- or short-acting insulin is necessary even if their fasting glucose concentrations are within goal. Similar results have been reported with another basal insulin analogue called detemir. Based on clinical experience, oral agents including sensitizers and secretagogues are usually continued when basal insulin alone is used. However, after prandial insulin has been added, insulin secretagogues are generally stopped but insulin sensitizers are continued. Many articles address dose titration. In brief, basal and prandial insulin coverage can be achieved by using a mixture of intermediate- and rapid- or short-acting insulin twice daily, using premixed combinations of insulin, or mixing the 2 types of insulin prior to administration, or by using rapid- or short-acting insulin prior to each meal with a long-acting basal insulin such as glargine, which can be given at night or in the morning. The insulins commonly used are listed in Table 2.

**Recommendations for Ms M**

Ms M has had type 2 diabetes for at least 5 years and her glycemic control is not ideal despite taking 3 oral medications. She is not checking her blood glucose levels often and it is difficult to determine whether her fasting or postprandial glucose concentrations or both are elevated. Self-monitoring of blood glucose and HbA1c measurements provide complementary information about glucose control and hence regular self-monitoring of her blood glucose level...
should be encouraged as part of Ms M’s management plan. Both the fasting and postprandial glucose concentrations contribute to the HbA1C level; as HbA1C declines below 8%, postprandial glucose excursions contribute more than the fasting glucose to the HbA1C level. Furthermore, acute glucose swings (ie, postprandial glucose excursions) are more closely associated with activation of oxidative stress (which plays an important role in the pathogenesis of the chronic complications of diabetes) than are chronic elevations in glucose.

If Ms M’s fasting glucose level is elevated, I think she should start a basal insulin such as glargine or detemir or NPH insulin. If her fasting glucose is within target and her postprandial glucose concentrations are elevated, she would be a candidate for either rapid-acting insulin prior to meals (which can be administered subcutaneously or via inhalation) or to a trial of therapy with the GLP-1 receptor agonist exenatide, which would be administered twice daily before breakfast and supper, starting with a dose of 5 µg twice daily and increasing to 10 µg twice daily after 1 month if the 5-µg dose is tolerated.

In summary, Ms M is at a crossroads in that her HbA1C concentration is barely at target level, and to maintain optimal control she must be prepared to take either a drug that lowers her postprandial glucose level (such as prandial insulin or exenatide) or one that lowers the fasting glucose level using a basal insulin analogue such as glargine or detemir. Blood glucose monitoring—checking sugars fasting and 2 hours after meals—would be the next step in her management prior to deciding which therapeutic approach to take. To help Ms M enhance her ability to adhere to her diet, exercise, and medication regimen; monitor her fasting and postprandial glucose levels and understand adverse effects such as hypoglycemia; and consider insulin injections if necessary, Ms M would benefit from a team approach that includes certified diabetes educators. Finally, use of alternate site home glucose testing may make it easier for Ms M to test her blood glucose level more frequently to allow more meaningful adjustments to doses of medications including insulin or addition of other medications if she does not achieve her therapeutic goals.

QUESTIONS AND DISCUSSION

A PHYSICIAN: My question has to do with flogging the poor beta cells in this disease. Is there any evidence that using a secretogogue hastens that decline by overstimulating those cells? Also, as you look at some of these newer agents being developed like GLP-1 analogues and DPP-IV inhibitors, do they have any real advantage other than being more physiologic over the currently available secretagogues or could you use them even in combination?

DR ABRAHAMSON: We don’t really know if use of conventional insulin secretagogues (like sulfonylureas) hastens the decline in beta cell secretory function or if the decline in beta cell function can be accounted for by the natural history of type 2 diabetes. We do know that hyperglycemia further impairs insulin secretion, so normalization of plasma glucose concentrations would be beneficial to the beta cell. We also know that in short-term studies, intensive insulin therapy use was associated with more improvement of beta cell function when compared with sulfonylureas. Regardless of whether sulfonylureas hasten burnout of the beta cell, it is important to realize when these medications are ineffective and to proceed to the next step in therapy to maintain glucose concentrations within target.

The second part of the question raises some interesting new concepts in the treatment of type 2 diabetes. Incretins (of which GLP-1 is an example) are gastrointestinal hormones secreted by L cells in the small intestine when food enters the stomach. These hormones stimulate insulin via specific receptors on the beta cell (not sulfonylurea receptors), suppress glucagon secretion, suppress hepatic glucose production, delay gastric emptying, and increase satiety. Exenatide is an analogue of exendin 4 that has similar effects to GLP-1. It lowers postprandial glucose concentrations via mechanisms noted above. In addition, there are some data from animal studies suggesting that this compound may preserve beta cell function and/or may cause differentiation of pancreatic ductal cells in to beta cells. If this is true, we may have a class of agents whose use is not associated with the inexorable decline of beta cell function that is associated with use of sulfonylureas and metformin for that matter.
A physician: Ms M is a 74-year-old woman who lives extremely well with a bad back. She seems quite obsessed with the medical regimen she’s on and you’re proposing that she be on a more complicated one. Her HbA1c is on the lower end of the people we see who are diabetic in our primary care practices. I’m wondering whether I should put so much attention into her and less into the others, or more into the others and let her lapse a little bit.

Dr Abrahamson: Another very valid question. Ms M, as you say, is an otherwise healthy 74-year-old female with a bad back. I would argue that we should do what we can to prevent complications, and since we have tools that can be used safely to facilitate this, we should use them. I don’t think we would be making things more complicated by adding a basal insulin or a drug that lowers postprandial glucose concentrations. In fact, after adding one of these agents, we could rationalize and reduce her other antidiabetic medications. I would also reassure her that the need for additional therapy is not her “fault” but related to the natural history of diabetes. And finally, I would reiterate that starting patients on insulin in a primary care physician’s office can be difficult and time-consuming and referral to a facility with experts who can do this should be encouraged. Indeed, diabetes educators often do a better job getting patients on to insulin than physicians do! Parenthetically, she also has the metabolic syndrome—diabetes, hypertension, and an increased waist circumference, factors that increase her risk for cardiovascular disease.

A physician: What is the relative role of weight loss?

Dr Abrahamson: A small amount of weight loss can go a long way toward improving glyemic control, as it is associated with improvements in insulin sensitivity. I think it is important to counsel patients about weight loss and discuss achievable goals with them rather than set unrealistic expectations that increase frustration and anxiety. Large amounts of weight loss, such as that seen after bariatric surgery, can lead to normalization of glucose tolerance.

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