

Diagnostic and Therapeutic Considerations in Adults with Diabetes Mellitus

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Introduction

Diabetes is a costly disease from both a clinical and a pecuniary perspective. In the United States, diabetes affects approximately one in 17 persons¹ and is the primary cause of blindness, end stage renal disease, and lower extremity amputation among individuals age 18 to 65 years.² In addition to the well-known multi-organ system effects on patients, diabetes-related costs are estimated to be more than \$100 billion annually in the United States.³ Inpatient hospital costs to manage long-term sequelae of diabetes constitute most of this expense.^{4,5} Whereas diabetes-associated costs represent 15% of all health care expenditures in the United States, patients with diabetes only account for 3% of the country's total population.⁶ Thus, effective management of the diabetic patient is critical to avoid severe clinical ramifications as well as the potential financial burden of the disease.

Cost considerations in addition to potential therapeutic advantages should encourage managed care providers, primary care practitioners, employers of diabetic patients, and/or pharmaceutical companies to work together to incorporate cooperative disease management approaches in the treatment of patients with diabetes.⁷⁻¹¹ In the 1920s, Dr. Elliot P. Joslin (1869-1962) initiated a broad team approach to diabetic patient care by integrating the nursing staff in clinical education and treatment efforts.¹² Today, disease management can unite comprehensive services and expertise from a variety of health care providers, all of whom are focused upon the disease entity of the patient.^{13,14} These interdisciplinary efforts may be cost effective, especially in patients with chronic disorders such as diabetes, although only a subpopulation of high-risk individuals may experience dramatic cost savings.¹³

The team approach for diabetic management using

nonphysician providers has some support in the literature and is being examined closely in other contexts. For example, dietitians have effectively provided organized, medical nutrition therapy to elderly adults with diabetes.¹⁵ In addition, pharmacists are currently engaged in a federal demonstration project to provide disease management services to diabetic patients using educational protocols.¹⁶ Such efforts are important because research has noted that effective and comprehensive treatment of the diabetic patient is reduced as a physician's patient load grows larger.¹⁷

Significant barriers, however, preclude broad-based educational and clinical efforts in diabetes. Although the health care providers in this case study provided care for the patient consistent with American Diabetes Association (ADA) guidelines, multiple studies have reported that primary care physicians often do not comply with the ADA guidelines for diabetes management,¹⁸⁻²¹ which emphasizes the need for educational systems (ie, support groups focusing on diabetes) or other mechanisms such as a computerized reminder for physicians and patients.²²⁻²⁵ As the health care dollar becomes further extended, such difficulties are exacerbated by additional pressure on physicians to see a

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greater number of patients. In addition, many patients do not comply with the therapeutic regimen and alter their self-care behavior on the basis of individual economic, educational, and cultural circumstances.²⁶ Further, although educational efforts for diabetic patients have been associated with positive clinical benefits over the past decade,²⁷ such provider services have not traditionally been reimbursed by insurers.²⁸ Federal government reimbursement policies for complex outpatient claims (eg, diabetic patient-related services) were revised in 1998 and now subject physicians to significantly detailed administrative reviews, adding costs to the providers who treat these outpatients.²⁹ Finally, although more efficient provision of care and education through disease management teams may be clinically beneficial to the patient and contain costs, whether such efforts actually attain cost reductions is still debatable.^{30,31} In recognition of the difficulties associated with care provision, at least 23 states have adopted legislation that requires health insurers and managed care plans to pay for diabetes self-management education and treatment supplies.³²

Overall, diabetes represents a significant challenge for providers and patients. A focus on care using an effective team approach, integration of the patient into the health care treatment process, and reinforcement of the importance of the treatment regimen are essential in order to limit the potentially devastating ramifications of diabetes. In the current health delivery climate, however, efforts to allocate more resources to the educational and therapeutic processes are necessary to continue the progress in treating diabetes.

CASE ONE PRESENTATION: COMBINATION THERAPY FOR TYPE 2 DIABETES

Initial Presentation

A 48-year-old Hispanic woman with a 10-year history of type 2 diabetes presents to her primary care physician with difficulty maintaining her target blood glucose level.

History

The patient has been treated with diabetes medications since the time of her diagnosis. Therapy was initiated with a sulfonylurea agent and was changed to twice-daily insulin injections 2 years prior to the current presentation. Her current insulin dose is 40 U of neutral protamine Hagedorn (NPH) insulin with 8 U of regular insulin before breakfast and 20 U of NPH insulin with 12 U of regular insulin before dinner.

Despite twice-daily self-monitoring, the patient's preprandial blood glucose levels range from 100 to 240 mg/dL and average approximately 190 mg/dL. In

addition, her office-measured HbA_{1c} levels range from 10% to 12%. The patient generally does not become hypoglycemic. However, on days when she increases her exercise and decreases her caloric intake, the patient's blood glucose level falls to near 100 mg/dL and she experiences occasional symptoms of hypoglycemia. These days of increased activity occur approximately once per week and cannot be predicted by the patient.

The patient has gained 30 lb since beginning insulin therapy. She cooks for her family and has difficulty controlling her caloric intake, despite receiving diabetes education and individual dietary instruction. She also does not exercise consistently.

Originally from El Salvador, the patient has lived in the United States for 20 years and works as a housekeeper. She is married and has four children; one daughter was diagnosed with gestational diabetes at age 25 years. The patient's mother showed no signs of diabetes, but her father had heart disease. The patient does not smoke or drink. At age 40 years she underwent a cholecystectomy; at age 43 years she was diagnosed with hypothyroidism, for which she takes oral levothyroxine (0.125 mg/day).

Physical Examination

Physical examination reveals an obese woman in no acute distress. The patient is 5'2" tall and weighs 210 lb. Her blood pressure is 140/80 mm Hg, pulse is 80 bpm, and respiration is clear. Cardiac examination reveals a normal sinus rhythm. Pulses are 1+ in the lower extremities with no bruits. Lower extremities show no signs of foot ulcers or edema. Patellar reflexes are 1+ and Achilles tendon reflexes are absent. Although the patient shows a slight decrease in vibration sense, neurologic examination reveals normal sensation to 5.07 monofilament testing. The abdomen is obese but nontender and without hepatosplenomegaly; the cholecystectomy scar is well healed. Examination of the patient's head, eyes, ears, nose, and throat reveals scattered microaneurysms in the ocular fundi. The thyroid gland is not palpable.

Laboratory Testing

Laboratory studies reveal a fasting plasma glucose level of 195 mg/dL, an HbA_{1c} concentration of 11.5%, and a serum creatinine level of 1.1 mg/dL. Liver function tests and complete blood count are within normal limits. Thyroid-stimulating hormone level is 2 µU/mL. Lipid levels are as follows: total cholesterol, 281 mg/dL; triglyceride, 380 mg/dL; high-density lipoprotein (HDL) cholesterol, 25 mg/dL; and low-density lipoprotein (LDL) cholesterol, 180 mg/dL. Urine dipstick test is negative for protein. The albumin:creatinine ratio is 48.

QUESTION

- **What are the known benefits of tight glycemic control in diabetic patients?**

DISCUSSION

Benefits of Tight Glycemic Control

Accumulated data from recent landmark diabetes trials have proven that tight glycemic control is advantageous in both type 1 and type 2 diabetes.

Diabetes Control and Complications Trial. In 1993, the results of the Diabetes Control and Complications Trial (DCCT) were published.³³ In this study, 1441 patients with type 1 diabetes were divided into two groups and followed for up to 10 years. One group received conventional therapy (median HbA_{1c} level, 9%) and the other group received intensive therapy (median HbA_{1c} level, 7.2%). The results showed a marked reduction in the development and progression of microvascular complications (ie, retinopathy, nephropathy) as well as neuropathic complications. Unfortunately, because of the close follow-up required to achieve and maintain tight glycemic control in patients with type 1 diabetes, similar results have been difficult to achieve outside a research setting. In the DCCT, tight control was associated with a three-fold increase in the rate of severe hypoglycemia (defined as hypoglycemia requiring assistance from another form of treatment). However, maintaining near euglycemia is possible in patients with type 1 diabetes if the risks of both hyperglycemia and hypoglycemia are counterbalanced. This counterbalance generally requires a motivated and knowledgeable patient.

United Kingdom Prospective Diabetes Study. In September 1998, the results of the United Kingdom Prospective Diabetes Study (UKPDS) were published.^{34,35} The overall design of this study of more than 5000 patients with new-onset type 2 diabetes is quite complex and the data extensive. In essence, patients were randomized to a variety of treatment arms and studied for up to 15 years; treatments varied from intensive control (median HbA_{1c} level, 7.0%) to conventional control (median HbA_{1c} level, 7.9%). The initial treatment groups compared diet and exercise, sulfonylureas, metformin, insulin, and combination treatment with metformin plus a sulfonylurea agent (after initial treatment with sulfonylurea alone). In some patients, acarbose was also added.

Regardless of the therapy, tighter control lowered the risks of microvascular complications. Every 1% fall in HbA_{1c} level was associated with significant benefit, down to an HbA_{1c} level of 6%. No specific threshold was found for onset of complications, and no increase in macrovascular disease risk was detected with any of

the treatments. In fact, based on epidemiologic data, a fall in HbA_{1c} level was associated with improved macrovascular outcomes. The patients in this study showed a gradual drift upward in glycemic control over time, illustrating the progressive nature of type 2 diabetes. Because this trial was undertaken in a variety of clinical practice settings around the United Kingdom (ie, the patients were not followed in intensive research settings), the results should be applicable to the general practices of most physicians.

QUESTIONS

- **What treatment approaches should be considered to improve blood glucose levels in the patient in this case study?**
- **What are important considerations in changing this patient's drug therapy?**

DISCUSSION

Treatment Options for Glycemic Management

This case study represents a common scenario for primary care physicians in this era of expanded treatment options for patients with diabetes. At the time of this patient's initial diagnosis and treatment, the medical options were largely limited to sulfonylurea agents and insulin. When an oral sulfonylurea agent failed to control the patient's glycemia, she was switched to insulin. This patient's inadequate glycemic control while on insulin may reflect one of the following or a combination of factors, including poor compliance with overall diabetes treatment recommendations (eg, dietary restrictions, exercise), inadequate follow-up and treatment adjustment by her physician, and a relative insensitivity to insulin, as might be expected in an obese patient.

At her current presentation, the patient clearly needs improved glycemic control. Her HbA_{1c} level is far above the levels shown by the DCCT and UKPDS trials to be linked to increased microvascular and neuropathic complications. In fact, she already shows evidence of diabetic complications. The patient displays some degree of retinopathy on physical examination, and her mildly elevated urine albumin:creatinine ratio indicates microalbuminuria—evidence that nephropathic changes are beginning to occur. The recognition of this patient's marked hyperglycemia clearly demonstrates ample room for glycemic improvement and, therefore, possible prevention of further diabetic complications. Options for improving glycemic control include increasing the patient's compliance with dietary restrictions and exercise recommendations, increasing her insulin dose, and adding one or more of the currently available oral antidiabetic medications.

Improved Compliance with Nonpharmacologic Measures

At this point, the underlying mechanism of the diabetes, the primary goals of treatment, and the rationale for different treatment approaches, including dietary changes, exercise, and medication, should be reviewed with the patient. Diet and exercise—the cornerstone for treatment in all patients with type 2 diabetes—must be stressed at every visit regardless of the medications a patient may be taking. This patient should be seen by a dietitian and a diabetes educator to help her make any practicable lifestyle changes, namely, a 20% reduction in her caloric intake and an increase in her exercise level to include walking for 30 minutes five times per week.

Options for Drug Therapy

Increasing insulin dose. While increasing a patient's insulin dose can often improve glycemic control, an association with hypoglycemia and weight gain has also been demonstrated. However, the patient in this case study has already gained 30 lb and is unable to comply with an insulin regimen of appropriate complexity to lower her blood glucose levels.

Addition of one drug. The addition of a single pharmacotherapeutic agent to insulin therapy may help to regulate a patient's diabetes.

Troglitazone. Studies have shown that adding troglitazone, an insulin sensitizer, to a diabetes treatment regimen provides the best chance of lowering HbA_{1c} levels.^{36,37} In the patient in this case study, the addition of troglitazone may allow her to reduce her insulin dosage to one injection per day and possibly to stop insulin therapy altogether. Patients who are taking troglitazone with monthly liver function testing should be monitored for the first 8 months of use because some patients may develop an idiosyncratic hepatotoxicity to the troglitazone. The use of troglitazone as monotherapy or with metformin does not result in weight gain.

Metformin. The addition of metformin to this patient's current treatment may slightly improve her glycemic control but would not simplify her insulin regimen. Metformin therapy is also unlikely to lead to any changes in blood glucose levels that could not be achieved by increasing her insulin dose alone.³⁸ Improving glycemic control with the addition of metformin, however, may not produce the same weight gain that simply increasing her insulin dose would produce.

Sulfonylurea agent. Adding a sulfonylurea agent to a patient who is on twice-daily insulin injections would have a minimal impact on glycemic control and should be avoided. In addition, when used with insulin, sulfonylureas promote weight gain. In the patient in this

case study, the sulfonylurea agent would simply further increase the need for insulin with minimal improvement in outcome.³⁹

Acarbose. Although adding acarbose to this patient's current medication regimen may lower her HbA_{1c} level by 0.5%, this decrease would not be adequate given the degree of her hyperglycemia.

Repaglinide. A short-acting insulin secretagogue, repaglinide is the newest agent available for the treatment of type 2 diabetes. Repaglinide may be used in patients who are attempting to adhere to diet and exercise but require enhancement of insulin secretion, often in addition to metformin and/or troglitazone. Although fixed doses were used in the clinical trials,⁴⁰ patients may be allowed to titrate the dose before meals based on their premeal blood glucose level and the anticipated quantity of carbohydrate intake. This technique uses repaglinide as a form of premeal, ultrarapid-acting insulin and allows patients to match their degree of hyperinsulinemia with the anticipated rise in blood glucose levels. Use of repaglinide in this manner necessitates multiple daily doses and, in turn, requires a diligent and compliant patient.

Addition of more than one drug. Combining troglitazone with metformin is effective at lowering blood glucose levels. After a patient's insulin dose has been reduced by troglitazone, metformin can often be added to help patients eliminate the need for insulin. This combination leads to less weight gain compared with the combination of a sulfonylurea agent with troglitazone and is preferred in many instances. A triple combination of a sulfonylurea agent or repaglinide with troglitazone and metformin can also be attempted, which would allow three complementary mechanisms of action. If necessary, an evening dose of NPH insulin can be continued to maintain the fasting glucose level in the 80 to 120 mg/dL range.

Relative Costs of Drug Therapies

The costs and benefits of each drug treatment option should be carefully considered for every patient. An economic analysis performed in the UKPDS demonstrated that although drug costs were higher in patients receiving intensive therapy, these costs were more than offset by the decrease in hospitalizations of well-controlled patients.^{34,35}

On an individual cost basis, generic sulfonylurea agents are the least expensive. Metformin, acarbose, and repaglinide are all more expensive; troglitazone is the most expensive of all available agents. Although insulin itself is fairly inexpensive, patients on insulin must perform self-monitoring of blood glucose levels

more often than patients on oral agents, and the price of testing strips adds to the cost of treatment.

QUESTION

- **Based on this patient's findings on physical examination and laboratory testing, what diabetes-related conditions require immediate attention and management?**

DISCUSSION

Management of Diabetes-Related Conditions

The clinical assessment of the diabetic patient in this case study revealed several areas of immediate concern, including early signs of retinopathy and nephropathy. This visit, therefore, provides an opportunity for her physician to apply specific interventions that could prevent further development of diabetic complications.

Retinopathy. Because physicians, including diabetologists, tend to underdiagnose diabetic retinopathy when looking through nondilated pupils, this patient should be sent immediately to an ophthalmologist for a formal dilated retinal examination.⁴¹ The presence of any retinopathy could signify more clinically severe disease and warrants prompt referral.

In addition to controlling blood glucose levels, UKPDS findings demonstrated that tight control of hypertension can also decrease the development and progression of retinopathy.⁴² This effect is additive to the improvement seen with good glycemic control. The ADA recommendation to maintain blood pressure below 130/85 mm Hg⁴³ would be an appropriate target for this patient.

Microalbuminuria. An albumin:creatinine ratio above 30 can signify microalbuminuria. Repeat measurement is necessary to confirm an initially elevated level. The finding of two out of three ratios that exceed 30 within 3 months confirms the diagnosis for microalbuminuria. To prevent diabetic nephropathy from deteriorating, patients with microalbuminuria should be treated with an angiotensin-converting enzyme (ACE) inhibitor. When renal function is impaired or if adequate ACE inhibitor therapy fails to halt worsening proteinuria, the patient should be referred to a nephrologist.

Macrovascular disease. Patients with type 2 diabetes have a markedly increased risk for macrovascular disease, particularly women who lose the ordinary cardioprotective effects of estrogen prior to menopause. Ideally, LDL levels should be less than 100 mg/dL in all patients. Because the patient in this case study has no known coronary artery disease, currently published recommendations suggest that her LDL cholesterol level should be reduced to below 130 mg/dL.⁴³ For sev-

eral months, a modified diet and exercise regimen should be undertaken. Physicians who lack cultural information specific to individual patients may not be able to provide concrete dietetic and other behavioral suggestions and should consult appropriate sources.

Although important for weight control and management of her diabetes, diet and exercise alone are unlikely to produce substantial increases in this patient's HDL cholesterol level given the magnitude of its current derangement, which increases her risk for developing macrovascular disease. Therefore, this patient will likely require an HMG-CoA reductase inhibitor for lipid management. Atorvastatin is often effective in diabetic patients because it has the greatest effect on lowering LDL and triglyceride levels and on raising HDL cholesterol levels.

Family Counseling

Although all of this patient's children and any siblings are at risk for developing type 2 diabetes, the patient's daughter is at greatest risk because of her history of gestational diabetes. The daughter should be screened yearly with a fasting plasma glucose concentration test to determine whether she has diabetes or is developing impaired glucose tolerance. All living first-degree relatives of the patient, especially relatives who are overweight, should receive guidance regarding lifestyle modification and weight loss to help prevent the development of diabetes. In addition, they should be screened for lipid disorders as well as hypertension; any abnormalities that are revealed should be treated aggressively.

ADDITION OF TROGLITAZONE AND FOLLOW-UP

Troglitazone is added to the patient's insulin regimen at a dose of 200 mg/day with breakfast, and her primary care physician explains that monthly liver function testing will begin as a consequence of this addition to her treatment regimen. The patient is referred to a dietitian for review of her dietary objectives and for suggestions for adhering to her diet and exercise regimen. Her physician also arranges for a consultation with an ophthalmologist to evaluate her retinopathy. Finally, the patient is instructed to monitor her blood glucose levels before each meal and at bedtime and informed that she will be contacted by a nurse in the physician's office to report these levels. After 2 weeks on troglitazone, the patient reports that her fasting blood glucose levels have fallen to 100 mg/dL and that her predinner blood glucose levels are 120 mg/dL.

Because the patient is responding well to the troglitazone, as evidenced by a fall in her blood glucose levels, her evening insulin dose is decreased to avoid fasting

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hypoglycemia. The patient is advised to contact the physician's office if her blood glucose levels fall to 100 mg/dL or below or if she develops symptoms of hypoglycemia.

After 8 weeks on troglitazone with 12 U of NPH plus 4 U of regular insulin before breakfast and 8 U of NPH plus 6 U of regular insulin before dinner, the patient's preprandial blood glucose levels have stabilized at 90 to 130 mg/dL. Her weight, however, is unchanged. The dose of troglitazone is increased to 400 mg/day.

Three months after beginning treatment with troglitazone, the patient's laboratory results are as follows: fasting plasma glucose concentration, 125 mg/dL; HbA_{1c} level, 8.2%; total cholesterol level, 260 mg/dL; triglyceride level, 280 mg/dL; HDL cholesterol level, 28 mg/dL; and LDL cholesterol level, 176 mg/dL. Her albumin:creatinine ratio is 15, and her liver function tests are normal.

QUESTION

- **What further management is appropriate for this patient?**

DISCUSSION

Further Adjustments in Therapy to Gain Glycemic Control

Ideally, this patient's HbA_{1c} level should be reduced to 7%. At this point her troglitazone dose should be increased to 600 mg/day and her insulin dose further decreased based on her blood glucose values. It is often beneficial to wait up to 6 months for the full impact of troglitazone to take effect. At each subsequent office visit, the patient's diet and exercise regimen should be monitored.

Treatment of Hyperlipidemia

As expected, the patient's lipid values did not fall to the target range with diet alone. At this point, she should be started on atorvastatin, 20 mg at dinnertime.

Monitoring

With the improvement in her glycemic control, the patient's albumin:creatinine ratio has improved and should be measured once more to be certain the improvement persists. If the patient's blood pressure continues to be slightly elevated and develops into persistent hypertension, she should be prescribed an ACE inhibitor. In several recent studies, ACE inhibitors have been shown to significantly aid in preventing or reducing the progression of diabetic nephropathy.⁴⁴ However, the patient should be made aware that the development of a persistent cough is common in women taking ACE

inhibitors and that she must be monitored in order to avoid complications resulting from an increased potassium level.

ADDITION OF METFORMIN AND CLINICAL COURSE

The patient's troglitazone dose is increased to 600 mg/day (200 mg/day for the first month, 400 mg/day the second month). Her liver function tests continue to be normal. Her insulin is eventually decreased to 10 U of NPH insulin at bedtime only, and her HbA_{1c} level falls to 7.8%. Although this control is adequate, the patient desires to discontinue insulin therapy. She also has experienced a 10-lb weight gain since adding the troglitazone 4 months ago. Therefore, a single 850-mg dose of metformin is added at dinnertime. While taking metformin plus troglitazone, the patient is able to discontinue her use of insulin and maintain an HbA_{1c} level below 8%. The patient experiences a weight loss of 6 lb over 3 months.

SUMMARY

The physician has taken advantage of the new agents available for treating this type 2 diabetic patient with good effect. Recognizing the role insulin resistance may have played in the patient's difficulty with glycemic control, the physician prescribed troglitazone, which heightens insulin sensitivity. The patient's glycemic control improved fairly well, but she was unable to lose weight, so metformin was initiated. The combined action of these two medications plus the mild anorectic effect of metformin led to weight loss and further improvement in glycemic control, to the extent that the patient was able to stop using insulin. However, this patient will always need a statin medication because her HDL level is so low.

The synergistic effect of available diabetes treatment modalities should be recognized and utilized by physicians. Perhaps the most important recent development in diabetes treatment is the ability to affect insulin sensitivity as well as to boost insulin levels (the only previous option). By addressing both arms of the pathogenesis of diabetes—insulin resistance and relative insulinopenia—physicians have a powerful strategy to control the disease and prevent its complications.

CASE TWO PRESENTATION: NEW-ONSET TYPE 1 DIABETES Initial Presentation

A 46-year-old man with an 8-month history of diabetes presents to his primary care physician for a routine check-up. The physician is concerned that the patient is not hitting his target blood glucose levels.

Medical History

At the time of initial diagnosis, the patient was a previously healthy man with no recognition of prior hyperglycemia. After the patient reported nocturia, increased urination, and a weight loss of 4 lb without effort, his physician ordered routine laboratory tests that revealed a fasting blood glucose level of 213 mg/dL. The physician suspected a diagnosis of diabetes and prescribed glyburide (5 mg/day).

The patient responded well, with improved blood glucose levels and no reports of adverse events. After meeting with a dietitian and attending several diabetes education classes, he became compliant with a strict diet and exercise regimen. However, he subsequently began to have frequent hypoglycemic reactions. Although the physician reduced the patient's glyburide dose to 2.5 mg/day, the patient still had occasional hypoglycemic episodes.

The patient's blood glucose levels continued to fluctuate, and his HbA_{1c} level remained around 9%, well above the upper limits of normal. In an effort to avoid hypoglycemia, the patient's physician then prescribed metformin (500 mg/twice daily). Again, however, the patient remained hyperglycemic, with average self-monitored blood glucose values around 200 mg/dL. Although the metformin dose was increased to 1000 mg twice daily, his blood glucose levels remained high. In response to the patient's continued poor glycemic control, his physician added troglitazone (400 mg/day) to the treatment regimen. When the initial dose of troglitazone failed to reduce the patient's blood glucose levels to an acceptable range, the dose was increased to 600 mg/day.

While on troglitazone, the patient's liver function was monitored monthly and remained normal. In spite of both agents, his preprandial blood glucose levels have remained 160 to 190 mg/dL.

Social and Family History

The patient is a married corporate executive with two children. He does not smoke and drinks alcohol moderately at social functions. He follows an ADA diet and exercises five times per week on a treadmill. He reports having a maternal great aunt with type 2 diabetes, but none of his first-degree relatives have been diagnosed with the disease. His family is originally from Great Britain. Both of his parents are alive, and the patient's grandparents lived into their 80s. His father has hypertension and his mother has hypothyroidism; the patient has one younger sister whom he reports to be healthy.

Physical Examination

Physical examination reveals a pleasant man in no

acute distress. He is 6' tall and weighs 176 lb. His blood pressure is 110/70 mm Hg, pulse is 60 bpm and regular, and respiration is clear. Cardiac examination reveals a normal sinus rhythm but no murmurs; pulses are 2+ bilaterally without bruits. Examination of his extremities shows no edema, foot ulcers, or bony deformities, and his nails are well trimmed. Lower extremity reflexes are 2+ bilaterally, with normal sensation to 5.07 monofilament testing. His abdomen appears soft, nontender, and without signs of hepatosplenomegaly. Examination of the patient's head, eyes, ears, nose, and throat reveals no signs of diabetic retinopathy. Thyroid examination is normal.

Laboratory Testing

Routine laboratory studies reveal a fasting plasma glucose level of 220 mg/dL, an HbA_{1c} concentration of 9.4%, a serum creatinine level of 0.7 mg/dL, a total cholesterol level of 189 mg/dL, a triglyceride level of 98 mg/dL, and an HDL cholesterol level of 48 mg/dL.

QUESTION

- **Given this patient's initial baseline characteristics and his poor response to treatment, should the diagnosis be reconsidered?**

DISCUSSION

Diagnostic Considerations

At initial presentation, it is sometimes difficult to determine if a patient older than age 30 years has type 1 or type 2 diabetes. Other forms of secondary diabetes (pancreatic diabetes, steroidogenic diabetes, endocrine diabetes) seem highly unlikely according to the available information.

In the initial clinical evaluation of patients, factors favoring a diagnosis of type 2 diabetes include obesity, a first-degree family history of type 2 diabetes, ancestry from a high-risk ethnic population (eg, Hispanic, African American, American Indian), a history of gestational diabetes, or previous delivery of an infant weighing more than 9 lb. Other features suggestive of type 2 diabetes include hypertension, triglyceride levels greater than 250 mg/dL, and HDL cholesterol levels less than 45 mg/dL.⁴⁵ If a patient in this age-group does not have ketonemia and is able to hydrate orally, it is usually safe to assume that they have type 2 diabetes and to treat them with oral agents.

In most cases, new-onset type 1 diabetes typically evolves more slowly in adults than in children.⁴⁶ Consequently, patients do not immediately worsen, even when treated with oral agents. Nevertheless, patients with atypical features should be followed carefully, and physicians should be aware of the potential for worsening

Table 1. Differential Characteristics of Type 1 and Type 2 Diabetes

Characteristic	Type 1 Diabetes	Type 2 Diabetes
Percentage of total diabetes patients	10%–15%	85%–90%
Age of onset	Usually < age 30 years; 50% < age 20 years	Usually > age 30 years; prevalence increasing at younger ages
Tendency for ketoacidosis	Yes	No
Body habitus	Normal	80%–85% obese
Requires insulin for glucose control	Yes	Yes, but only in 70%–85% of cases at diagnosis
Presence of ICAs or anti-GAD autoantibodies	Yes, but only in 70%–85% of cases at diagnosis	No
Family history	Weak (4%–10% risk with a first-degree relative)	Strong (40% lifetime risk with a family history; higher in some ethnic groups)
Ethnic groups most affected	Northern Europeans	Native Americans, Hispanics, African Americans, some Asian groups
Failure of oral medications	Immediate or within 1–2 years; does not respond well to combined oral agents after sulfonylureas fail	Usually after 3–20 years; usually responds to combined oral therapy after monotherapy fails

GAD = glutamic acid decarboxylase; ICA = islet cell antibodies.

hyperglycemia caused by progressive β cell failure.⁴⁷ Although initial evaluation has been demonstrated to result in misclassification in up to 10% of cases, appropriate monitoring and follow-up eventually result in the correct diagnosis without risk to the patient.⁴⁸

The patient in this case study does not have a family history of type 2 diabetes, is not from a high-risk ethnic population, and is not obese. He does not have hypertension, hypertriglyceridemia, or low HDL levels. Therefore, physicians should have significant concern that despite his age at onset he has type 1 diabetes.

QUESTIONS

- **What are the pathophysiologic and genetic characteristics of type 1 and type 2 diabetes?**
- **What laboratory tests are available to differentiate type 1 and type 2 diabetes?**

DISCUSSION

Pathophysiology and Genetics of Diabetes

Type 1 diabetes. Patients with type 1 diabetes represent 10% to 15% of the diabetic population (Table 1). Type 1 patients are insulin deficient because of islet cell loss that is progressive but variable among individuals. Type 1 diabetes is often associated with specific human leukocyte antigen (HLA) types; these patients develop insulinitis (inflammation of the islet cells) and autoimmune destruction of pancreatic β cells. Patients with type 1 diabetes are unable to utilize glucose for cellular metabolism and resort to alternate energy sources. In

the absence of exogenous insulin, patients develop keto-sis and eventually become dependent on insulin for survival. Although type 1 diabetes can occur at any age, 50% of cases develop before patients reach age 20 years.

The genetics of type 1 diabetes have been extensively studied. Although a genetic predisposition exists from birth, only a small percentage of these predisposed individuals actually develop the disease. In addition to the genetic predisposition, inciting environmental factors (eg, rubella, the coxsackievirus B) trigger the autoimmune process aimed at the β cells. In the white population, genetic studies indicate that 95% of patients with type 1 diabetes possess DR3 and/or DR4 class II HLA haplotypes. However, because approximately 45% of the general population also has DR3 or DR4 HLA genes, the presence of one or both of these genes is not helpful in predicting type 1 diabetes. Although the absence of these genes could help to exclude the possibility that a patient develops type 1 diabetes, these tests are not considered practical for differentiating the type of diabetes or for screening populations.

One or more of three autoantibodies—*islet cell antibodies (ICAs)*, *insulin autoantibodies (IAAs)*, and *anti-glutamic acid decarboxylase (anti-GAD) antibodies*, also called *64K antigens*—are present months to years before onset of type 1 diabetes. All three autoantibodies are often positive at the time of diagnosis. Anti-GAD antibodies tend to develop the earliest and persist the longest.⁴⁹ These antibodies are markers of the autoimmune attack on the β cells.

Type 2 diabetes. Patients with type 2 diabetes represent 85% to 90% of the diabetic population. While type 2 diabetes occurs more frequently in adults, it has been shown to occur at any age with increasing frequency in adolescents. In some populations, as many as 16% of patients with adolescent diabetes have type 2 rather than type 1 diabetes. Type 2 patients are usually ketosis-resistant. Under severe physiologic stress, however, patients may develop ketoacidosis and later revert back to a more classic picture of type 2 diabetes. In the United States, most patients with type 2 diabetes have insulin resistance with early compensatory hyperinsulinemia as dominant pathophysiologic features. Most of these patients are overweight, a factor that exacerbates their genetic predisposition to insulin resistance. Over time, a relative insulin deficiency develops as β -cell function is lost. A relative insulin deficiency probably representing a second genetic predisposition must develop in patients with insulin resistance as the primary adverse event. Otherwise, the patient simply remains hyperinsulinemic with normal glucose values.

A strong hereditary link is associated with type 2 diabetes. Whereas only about 5% of first-degree relatives in a family with type 1 diabetes develop the disease, 30% to 40% of relatives in a family with type 2 diabetes are diagnosed with the same disease. However, other than families with specific and unusual enzymatic defects (eg, the glucokinase gene defect seen in patients with maturity-onset diabetes of youth), the identification of a single genetic lesion for type 2 diabetes has been elusive.⁴⁹ Ongoing research in this area should help to further elucidate the underlying genetics of type 2 diabetes.

Laboratory Differentiation

As mentioned previously, a clinical diagnosis should usually suffice in identifying the type of diabetes relevant to a given patient. Unfortunately, no standardized laboratory techniques are available for differentiating type 1 and type 2 diabetes in routine clinical practice. Insulin and C-peptide levels are usually measurable at the time of disease recognition in both types of diabetes. Although tests have been developed to measure β -cell responsiveness (eg, glucagon-stimulated C-peptide), they remain primarily research tools.

Because type 1 diabetes is an autoimmune disease and is accompanied by immune-mediated β cell damage, one developing diagnostic approach is to search for immune markers of the disease. Assays are available in certain reference laboratories for all three of the antibodies produced by individuals with type 1 diabetes (ie, ICAs, IAAs, and anti-GAD). Antibody test results are not always positive at the time of diagnosis, and

antibody titers often decrease after diagnosis. Anti-GAD antibodies may remain measurable for a longer period of time than ICAs or IAAs. Although testing for anti-GAD antibodies has gained some favor because of their persistence, even this method may carry a 25% false-negative rate as well as a significant false-positive rate⁵⁰ and cannot be recommended for routine care.

Testing for immune markers may, however, be of some value in confirming cases of type 1 diabetes in adults with features atypical for type 2 diabetes and cases in which making the differential diagnosis early in the clinical observation period is particularly important. Early identification of patients with slowly progressive type 1 diabetes, followed by insulin therapy rather than oral agent therapy, could delay or prevent progression of the autoimmune damage.⁵¹ However, this theory remains unproven in clinical trials.

FURTHER LABORATORY TESTING AND DIAGNOSIS

The primary care physician of the patient in this case study is concerned that in only 8 months the patient has already failed therapy with three separate classes of oral antidiabetic agents. After consultation with a diabetologist, the physician recommends further laboratory tests in an attempt to refine the diagnosis of diabetes. Antibody testing is negative for ICAs and IAAs. The patient's fasting C-peptide level is 0.2 ng/mL.

QUESTION

- **Does this new information allow for a definitive diagnosis of type 1 diabetes in this patient such that a more appropriate treatment regimen may be initiated?**

DISCUSSION

Confirming the Diagnosis

In the patient in this case study, the new laboratory findings do not confirm the original diagnosis. Within the first 5 years after diagnosis, nearly all patients with type 2 diabetes experience significant endogenous insulin production. Therefore, both fasting C-peptide and insulin levels are measurable. However, C-peptide levels usually fall below 0.5 ng/mL in most patients with type 1 diabetes shortly after diagnosis. The fact that, in a short period of time, this patient failed therapy with three separate classes of oral antidiabetic agents suggests a significant β -cell defect, a feature that was confirmed by his measured fasting C-peptide level. The sulfonylureas left him hyperglycemic most of the time, as evidenced by his elevated HbA_{1c} level. The episodes of hypoglycemia resulted from inappropriate sulfonylurea stimulation of residual β -cell insulin at

times when minimal insulin was required. This inappropriate stimulation can be related to exercise or long intervals between meals. Agents that improved insulin sensitivity in the liver (metformin) or muscles (troglitazone) failed to restore euglycemia because of the lack of insulin that they require for effectiveness.

Thus, the clinical features in this case should cause the physician to question the more typical diagnosis of type 2 diabetes in an individual presenting at age 46 years. Regardless of antibody status, this patient should be considered to have type 1 diabetes.

INITIATION OF INSULIN THERAPY

All oral antidiabetic agents are stopped, and the patient is started on twice-daily injections of NPH and regular insulin. He is instructed to monitor his blood glucose levels four times daily—before each meal and at bedtime.

QUESTION

- **What educational pointers are important to impart to this patient?**

DISCUSSION

Educating the Patient About Insulin Therapy

Several factors specific to the use of insulin should be discussed with patients preparing to begin insulin therapy for the first time. At the time of diagnosis or at the time of a major change in therapy, the physician must bear in mind that the patient may be very anxious and may have a limited capacity for immediately comprehending all the factors that influence the use and effectiveness of insulin therapy. Therefore, while certain basic points must be emphasized, including a brief explanation of the pathophysiology of type 1 diabetes, the physician should refrain from overwhelming the patient with information.

Defining control and reviewing patient goals. Because patients sometimes have difficulty comprehending the complexities of managing diabetes, control in terms of blood glucose values and HbA_{1c} levels must be defined. Reviewing the benefits of good glycemic control is vital in promoting compliance with treatment modalities and self-care requirements. A quick review of the DCCT treatment protocols and findings can help the patient relate insulin therapy and good glycemic control to the reduced risk of complications. In the patient in this case study, explaining how the salient features of the laboratory data led the physician to alter the treatment regimen should help the patient understand why insulin therapy is required to gain better glycemic control. In addition, an explana-

tion of the importance of β -cell function and its probable decline may help the patient prepare for the possibility of increasing insulin requirements.

The patient's present status and goals for glycemic control should also be reviewed at this time. Patients should understand the acceptable ranges for blood glucose and HbA_{1c} levels. For example, patients not affected by coronary artery disease may have target preprandial blood glucose levels below 130 mg/dL, bedtime blood glucose levels between 100 and 160 mg/dL, and an HbA_{1c} concentration at or below 7%. The primary care physician should explain what these levels mean to the patient and how they should be monitored. At a later date, the patient is likely to benefit from a full diabetes education course that reviews self-management skills and the essentials of diabetes pathology, pathophysiology, and treatment.

Providing instructions for insulin administration. In the best-case scenario, the physician thoroughly motivates the patient to begin insulin therapy as a step toward achieving good glycemic control. When patients arrive at the office or clinic for their first day on an insulin regimen, however, anxieties may persist. Patients must be allowed to vent their feelings, fears, and questions regarding insulin therapy. Allaying these fears may help to increase the patient's ability to concentrate and learn.

Next, the patient must be taught insulin preparation and administration. The patient should be instructed to administer the injection into the subcutaneous fat of the abdominal region. This site will provide the most rapid and consistent absorption of insulin. To reduce the risk of lipohypertrophy and lipodystrophy, the physician should stress the rotation of sites within the abdominal region. Other sites (ie, the thigh) may be options for some patients at certain times of the day. For example, some patients benefit from bedtime insulin administered in the thigh when they are not active because this site offers the slowest rate of insulin absorption. Because many individuals experience increased blood glucose values in the morning, this site may provide better control for patients who use insulin with peak action during these hours.

Once patients have administered their injections, they usually experience relief and are ready to learn more about the action of insulin. They need to learn the onset, peak, and duration of action of each type of insulin to be administered. At this point, physicians should also discuss each insulin dose's specific correlation to blood glucose results.

Recommendations for beginning insulin therapy. When starting a patient on a treatment regimen that includes insulin, physicians should consider the

Table 2. Typical Intensive Insulin Injection Regimens*†

Before Breakfast	Before Lunch	Before Dinner	Before Bedtime
R/Li plus NPH/L	—	R/Li	NPH/L
R/Li plus UL	R/Li	R/Li plus UL‡	—
R/Li plus NPH/L	R/Li	R/Li	NPH/L
R/Li plus UL	R/Li	R/Li	NPH/L
R	R	R	NPH/L
Li plus R	Li plus R	Li plus R	NPH/L

L = Lente insulin; Li = insulin lispro; NPH = neutral protamine Hagedorn insulin; R = regular insulin; UL = Ultralente insulin.

*A subcutaneous infusion pump may be used instead of injections in some patients.

†Regular insulin is usually given approximately 30 minutes before meals. Insulin lispro is given immediately before meals (no more than 10 minutes before eating).

‡Ultralente insulin may be given before bedtime instead of with the dinner dose with this regimen.

patient's present degree of illness, anxiety level about starting injections, ability to draw and inject insulin properly, and willingness to perform self-monitoring tests. The acuteness of the patient's condition immediately preceding the initiation of insulin treatment dictates whether or not an aggressive regimen is needed immediately. If the patient is stable during this time, insulin dosage may be increased more slowly. Because the patient in this case is not acutely ill, a conservative approach may be taken.

Next, physicians should take into account the degree of a patient's insulin resistance, which influences the level of initial dosage. Patients with type 1 diabetes tend to require 0.5 to 1 U/kg/day and are less insulin resistant than patients with type 2 diabetes. Because insulin resistance is generally a primary component of the pathophysiology of type 2 diabetes, those patients require an average initial dose of 1 to 1.5 U/kg/day. Factors that increase insulin resistance include obesity, certain classes of medications (eg, glucocorticoids, proteinase inhibitors, high-dose thiazide diuretics), nicotinic acid, and both acute and chronic infections. Additionally, any factor or condition that increases the release of stress hormones will promote insulin resistance.

In type 1 patients who are insulin resistant, initial dosages of 0.5 to 0.75 U/kg/day are recommended. In type 1 patients who are not acutely ill, however, a lower initial insulin dosage of 0.3 to 0.5 U/kg/day in a split/mixed regimen can be prescribed. In split/mixed regimens, mixtures of intermediate and rapid-acting insulin

are given twice daily (before breakfast and dinner). **Table 2** outlines recommendations for such regimens.

Regular insulin should be injected 30 to 45 minutes before meals, and patients must monitor their blood glucose levels before each meal and at bedtime. This frequent blood glucose monitoring assists in determining the patterns of high and low glucose levels that dictate changes in the dosage of the individual insulins. For example, a pattern of increased bedtime glucose values would indicate the need for an increase in the predinner dose of regular insulin. In some cases, rapid-acting insulin adjustments (also referred to as *sliding scales*) can be used before meals. The use of these adjustments varies according to prevailing blood glucose levels and depends on the patient's ability to follow instructions. In general, since episodes of hypoglycemia tend to frighten patients, physicians should initially attempt to avoid using regimens that cause hypoglycemia. Until the blood glucose levels and insulin dosages have stabilized, daily personal or telephone contact with the patient is advised.

In the case study patient, whose body weight is 176 lb, one could cautiously begin insulin therapy with a dosage of 24 U/day, two thirds before breakfast and one third before dinner. The morning dose is typically two thirds intermediate-acting insulin and one third rapid-acting insulin. The initial evening dose is often equal parts intermediate- and rapid-acting insulin. Thus, this patient could receive 16 U in the morning (10 U intermediate, 6 U rapid) and 8 U at dinner (4 U intermediate, 4 U rapid).

QUESTION

- **What factors impact the effectiveness of the various insulin therapies?**

DISCUSSION

Maximizing Insulin Therapy Effectiveness

Devising an insulin regimen. The various insulin time courses (Table 1) invite a variety of insulin regimens, outlined in Table 2. When initiating insulin therapy, the least complicated regimen may be recommended. As therapy proceeds, however, and patients begin to react to the introduction of insulin, more complex regimens are often needed for improved control and safety.^{52,53}

For example, for most patients, human NPH insulin peaks in 6 to 8 hours. If given before dinner at 6:00 PM, the peak effect occurs between midnight and 2:00 AM, and the risk of hypoglycemia increases. Additionally, the duration of insulin action on this regimen may be inadequate to maintain good morning coverage, which results in hyperglycemia before breakfast. Therefore, a three-shot regimen with the evening intermediate

insulin before bedtime (ie, 10:00 PM) is generally safer and more effective.

Unfortunately, significant interindividual and intra-individual variations in the rate of insulin absorption complicate the formulation of effective insulin regimens. Therefore, the specific regimen must be tailored to the patient and his or her specific responses to treatment. If a peak is not evident to cover the appropriate problem time interval, an alternate insulin preparation or regimen should be prescribed.

Choosing an insulin preparation. Generally, rapid-acting insulins are absorbed more predictably than longer-acting insulins in which the peak of action may vary considerably from day to day. Therefore, insulin regimens relying on frequent injections of short-acting insulin often render more reproducible and reliable results. Additionally, such regimens allow for more frequent dosage adjustments according to change in food intake or exercise.

Supplemental monitoring of blood glucose levels may be of value when patients do not experience consistent results or when insulin therapy does not bring their blood glucose levels into their target ranges. For example, when using an evening dose of intermediate-acting insulin, occasional monitoring of blood glucose levels between 2:00 AM and 3:00 AM may be helpful to determine the optimal time for administering the dose. Careful analysis of glucose patterns in relation to meals, exercise, and insulin injections is necessary to determine when insulin adjustments are required.

Used alone, lispro can often wear off before the next meal, causing preprandial hyperglycemia. In these cases, one can have the patient mix lispro and regular insulin. The lispro component should be increased if the patient's blood glucose level is too high in order to quickly reduce blood glucose levels into an acceptable range. In addition, lispro is often used with intermediate-acting insulins.

CLINICAL COURSE AND CONCLUSION

Initially, the patient's insulin requirements are low—4 U of NPH insulin plus 2 U of regular insulin in the morning and 3 U of NPH plus 4 U of regular insulin before dinner. After 3 months on this regimen, his HbA_{1c} concentration is 7.6%.

Over time, the patient begins to require increasing doses of insulin. He is very compliant with his treatment regimen. This regimen evolves to contain multiple injections, including an evening dose of NPH insulin and a preprandial dose of regular and lispro insulin. His blood glucose levels generally remain between 70 and 145 mg/dL, with an HbA_{1c} concentration of 6.8%

to 7.6%. His physician emphasizes that if the patient continues to experience such good glycemic control, he has an exceedingly good chance of being free of serious diabetic complications throughout his life. HP

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