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*Clinical Overview:*
# How Do I Treat the Adults I've Been Seeing with New Type 2 Diabetes?

By Alan D Jacknow, MD

## Introduction

Diabetes mellitus has rapidly become an epidemic in the Western world, especially in the United States. The number of patients who present with diabetes, along with the closely associated obesity and metabolic syndrome (syndrome X), has exploded—in part because of the contemporary American lifestyle. Approximately 7.9% of all Americans have diabetes (up from 4.9% just a decade ago).[1] Although diabetes is more prevalent among Americans aged 60 years or more, increase in incidence is most rapid in those under 30 years, especially in the Latino/Hispanic, African American, and Native American populations.[2]

Diabetes is the sixth largest killer in the United States,[3] and the overall risk of death among people with diabetes is about twice that among people without diabetes. However, the increased risk associated with diabetes is greater for younger people (that is, 3.6 times higher for people age 25 to 44 years versus 1.5 times higher for those age 65 to 74 years) and for women (that is, 2.7 times higher for women aged 45 to 64 years versus 2.0 times higher for men in that age group).[2] One million people are diagnosed with diabetes yearly, yet the estimate is that one of every three patients with diabetes remains undiagnosed.[1]

> **Treatment begins with self-management.**

## Case Example

A resident working in the walk-in clinic calls you at home about a patient who is being seen for the first time. A 58-year-old Latino/Hispanic male who has been feeling weak and tired for the last few months, the patient has difficulty sleeping because he has to wake up so often to urinate. He also complains of weight loss, thirst, and blurred vision, even though he got new glasses two weeks ago. He hasn't seen his physician for several years and takes no medication. Physical examination reveals an obese Latino/Hispanic male with blood pressure of 164/88 mm Hg, dry mouth, and skin with decreased turgor. The rest of the examination shows normal fundi, heart sounds, prostate, and feet. Blood glucose level, determined by fingerstick in the examination room, is 338 mg/dL (18.8 mmol/L).

## Discussion
### Diagnosis of Type 2 Diabetes

Although probable, Type 2 diabetes cannot be definitively diagnosed on the basis of this patient's presentation alone. The diagnosis of diabetes depends on any one of three criteria: 1) symptoms of diabetes and a casual blood glucose level of $\geq$200 mg/dL ($\geq$11.1 mmol/L); 2) fasting (no caloric intake for at least eight hours) blood glucose $\geq$125 mg/dL ($\geq$6.9 mmol/L); or 3) 2-hour blood glucose $\geq$200 mg/dL ($\geq$11.1 mmol/L) during an oral glucose tolerance test (OGTT). The OGTT should be performed as described by the World Health Organization, ie, using a glucose load containing the equivalent of 75 grams of anhydrous glucose dissolved in water.[5] A positive test result must be confirmed by any of these same three methods, but on another day, to authoritatively diagnose diabetes mellitus. Glycosylated hemoglobin ($HbA_{1c}$) levels are not currently used in diagnosis, although dramatically elevated levels provide presumptive evidence. The patient should be scheduled for a confirmatory test as soon as possible.

### Treatment of Type 2 Diabetes

Aside from gender, this patient typifies new-onset diabetic patients. He is obese and has not been in close contact with the health care system.

Treatment begins with self-management. He does not smoke, but smoking cessation would be a priority if he did. Smoking in cases of diabetes increases the risk of cardiovascular disease by 35%.[6] The basis of clinical management of Type 2 diabetes is emphasis on and frequent return to the basics of self-management: diet, increased physical activity, and home glucose monitoring. The patient should be referred to the basic diabetes classes offered at his care institution. If classes are successfully completed, diabetes self-care can improve glucose control and can decrease complications.[7]

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Because retinopathy can be present at diagnosis in a patient with Type 2 diabetes, the patient should be referred for retinal screening (dilated eye examination) too.[8]

The question of whether to treat this patient with diabetic medication at this time is difficult to answer. No long-term studies appear to evaluate this question. Although he presents with some acute hyperglycemic symptoms (such as blurred vision and nocturia), a three-month trial of lifestyle modification is recommended. If HbA$_{1c}$ level is not reduced below 7.0% of total hemoglobin, pharmaceutical treatment is indicated. Again, when a desirable medication is sought, few studies compare treatment regimens directly. But the results of the United Kingdom Prospective Diabetes Study (UKPDS)[9] strongly suggest that in obese patients, metformin (Glucophage) is the preferred drug for initiation of therapy. In a report from the UK Prospective Diabetes Study Group,[9] treatment with metformin resulted in a 39% lower risk of myocardial infarction when compared with conventional treatment (primarily diet) but not when compared with intensive treatment with sulfonylureas—even when the same level of glucose control was achieved.

Metformin rarely causes hypoglycemia, an important advantage over other standard agents, and metformin causes less weight gain.[9] Gastrointestinal side effects (nausea and bloating) are lessened by beginning with 500 mg daily. I like patients to start this regimen at bedtime, because the side effects seem better tolerated and because of the theoretical advantage to treating fasting blood glucose. I recommend gradually increasing dosage to a daily maximum of 2.55 g (850 mg three times daily). This regimen is contraindicated for patients with mild renal failure (creatinine clearance of <70 mL/min per 1.73 m$^2$), active congestive heart failure, pregnancy, and hepatic dysfunction because of risk of developing of lactic acidosis. For the same reason, metformin is routinely withheld for 48 hours before certain radiologic and surgical procedures. No studies appear to have compared cardiovascular complications from thiazolidinedione versus metformin.

If metformin is contraindicated, thiazolidinedione (glitazone) may be a useful alternative. Glitazone therapy may be used in patients with renal insufficiency and mild hepatic dysfunction. In fact, early studies[10-12] suggest that thiazolidinedione may be a treatment for fatty liver disease, a common cause of liver dysfunction in insulin-resistant patients. The major side effect of thiazolidinedione is fluid retention, but recent studies[13-15] suggest its safety for treating controlled congestive heart failure (class A or B). The first thiazolidinedione, Rezulin (Parke-Davis/Warner-Lambert), caused hepatic failure that resulted in several patient deaths[16,17] and was withdrawn from the market in 2000. For this reason, close monitoring of liver function is recommended, although few long-term liver problems have been reported.[18]

Most often used in the past as first-line therapy, sulfonylurea and insulin are today used more often in combined therapy for patients who do not have adequate glucose control from metformin or for whom metformin is contraindicated. Although sulfonylurea and insulin may still be used as first-line agents, they do not have the same positive cardiovascular effects as metformin. In addition, because insulin can control blood glucose more quickly, insulin is sometimes used at diagnosis to establish quick control and is then discontinued. High blood glucose levels have a stunting effect on pancreatic beta cells, so rapid control with insulin may maximize the effectiveness of lifestyle changes, metformin therapy, or both.

The UK Prospective Diabetes Study showed that excellent control of blood glucose (HbA$_{1c}$ level <7.0% of total hemoglobin; fasting blood glucose level 80-120 mg/dL [4.4-6.7 mmol/L]; postprandial blood glucose level <180 mg/dL [<10.0 mmol/L]) reduces cardiovascular events in diabetic patients.[9] We therefore recommend that treatment of diabetes include more use of combined medication therapy until these laboratory value goals are achieved.

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## Additional Forms of Therapy for Type 2 Diabetes

Two thirds of all diabetic patients die from cardiovascular disease, including cardiovascular accidents. Recent studies illustrate ways to decrease these risks. The Heart Protection Study[19] evaluated ability of statins to prevent heart attacks and showed that statins lower risk of myocardial infarction in diabetic patients by nearly 20%, regardless of initial cholesterol level.

The Heart Outcomes Prevention Evaluation (HOPE) study[20] analyzed use of angiotensin-converting-enzyme (ACE) inhibitors in diabetic patients who had at least one other cardiac risk factor. The study showed a 25% decrease in combined risk of myocardial infarction, stroke, or death from cardiovascular disease when ACE inhibitors were used, regardless of their effect on blood pressure and even when used for normotensive (or well-controlled hypertensive) diabetes.[20] This decrease in risk was achieved without increased adverse effects, and the

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same beneficial effect was seen in diabetic patients with decreased renal function (in a subgroup analysis, risk of cardiovascular disease increased with decreased baseline renal function (creatinine level >1.4 mg/dL [>123.8 mmol/L]).[20]

Blood pressure control is among the most important interventions currently available for preventing diabetic complications. According to the American Diabetes Association, blood pressure in diabetic patients should be aggressively treated to reach 130/80 mm Hg or lower,[21] a goal that frequently necessitates use of multiple antihypertensive drugs. The Hypertension Optimal Treatment (HOT) Trial[22] examined effects of 75 mg daily aspirin versus placebo in 18,790 hypertensive patients, including 1501 diabetic subjects. Aspirin significantly reduced cardiovascular events by 15% and myocardial infarction by 36%.[22] Fatal bleeding episodes, including intracerebral bleeding, were equal in the aspirin and placebo groups; nonfatal, minor bleeding episodes were more common in the aspirin group.[22]

As a result of these clinical trials,[19,20,22] we now recommend that men age 50 years and older and women age 60 years and older receive a statin, an ACE inhibitor, and aspirin without regard to baseline cholesterol and blood pressure levels. Because our hypothetical patient falls within these parameters, all three therapies should be started unless contraindicated. ❖

> **… blood pressure in diabetic patients should be aggressively treated to reach 130/80 mm Hg or lower …**

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