in the clinic

Type 2 Diabetes

The content of **In the Clinic** is drawn from the clinical information and education resources of the **American College of Physicians** (ACP), including **PIER** (Physicians' Information and Education Resource) and **MKSAP** (Medical Knowledge and Self-Assessment Program). **Annals of Internal Medicine** editors develop **In the Clinic** from these primary sources in collaboration with the ACP's Medical Education and Publishing division and with the assistance of science writers and physician writers. Editorial consultants from **PIER** and **MKSAP** provide expert review of the content. Readers who are interested in these primary resources for more detail can consult http://pier.acponline.org, and other resources referenced within each issue of In the Clinic.

The information contained herein should never be used as a substitute for clinical judgment.

Editor
Christine Laine, MD, MPH

Science Writer
Jennifer F. Wilson

ACP American College of Physicians

Annals of Internal Medicine

American College of Physicians pier Physicians' Information and Education Resource

MKSAP Medical Knowledge Self-Assessment Program

in the clinic

Annals of Internal Medicine

It is nearly impossible to be a practicing internist in the United States and have a day of clinical work pass without encountering at least 1 patient with type 2 diabetes. Currently, over 20 million Americans and over 150 million persons worldwide have type 2 diabetes. Models estimate that this number will nearly double by the year 2050 so that about one third of adult Americans will have the disease[1–3]. Unfortunately, although researchers are gaining new insights into the pathophysiology of the disease, including its genetic basis[4], and therapeutic options are expanding[5], many people with type 2 diabetes develop complications of the disease. A recent national analysis of diabetes care in the United States shows that despite improvements in processes of care and intermediate outcomes over the past decade, there remains much room for improvements in diabetes care[6]. Among adult Americans with diabetes, 2 in 5 have suboptimal lipid control, 1 in 3 has poor blood pressure control, and 1 in 5 has poor glycemic control.

Diagnosis

What are the diagnostic criteria for type 2 diabetes in nonpregnant adults?

Type 2 diabetes is often present at least 4 to 7 years before diagnosis[7]. Definitive diagnosis of type 2 diabetes is important because it allows attempts to improve glycemic control and to implement other interventions to improve clinical outcomes. Clinicians should confirm the diagnosis with laboratory testing when a patient presents with symptoms compatible with type 2 diabetes (polyuria, polydipsia, and unexplained weight loss), with evidence of possible diabetes complications (vision problems, retinopathy, impotence, renal dysfunction, peripheral neuropathy, acanthosis nigricans, or frequent infections), or with elevated incidental blood glucose levels (≥126 mg/dL fasting or ≥200 mg/dL nonfasting). A fasting plasma glucose level that is 126 mg/dL or greater and is confirmed on repeated testing on another day is the current American Diabetes Association (ADA) preferred criterion for diagnosis (Table 1).

What alternative diagnoses should clinicians consider when a patient presents with hyperglycemia?

The differential diagnosis for type 2 diabetes is limited and includes type 1 diabetes, diabetes insipidus, and maturity-onset diabetes of the young. Clinicians should consider type 1 diabetes when patients are younger

Table 1: Diagnostic Tests For Diabetes

Test	*Threshold Value*	*Recommended Follow-up*	*Advantages*	*Disadvantages*
Fasting plasma glucose (FPG)	· ≥126 mg/dL suggests diabetes · 100–125 mg/dL suggests prediabetes	· Confirm by repeated test on another day	· Time since last meal easily defined · Preferred American Diabetes Association criterion for diagnosis	· Less convenient to draw than a random glucose level
Random plasma glucose	· ≥200 mg/dL in setting of symptoms indicates diabetes	· Confirm with FPG or OGTT performed on another day	· Convenient	· Lower sensitivity and specificity than other tests · Least acceptable test for diagnosis
2-h oral glucose tolerance test (OGTT)	· ≥200 mg/dL diagnostic for diabetes · 140–199 mg/dL suggests prediabetes	· Confirm with FPG on another day	· None	· Less convenient and more costly to administer than other tests
Glycosylated hemoglobin	· Hemoglobin A_{1c} value >6% is suggestive of diabetes but not diagnostic	· Perform confirmatory testing with fasting glucose or OGTT measurement	· Convenient	· No universally implemented standard · Not an accepted diagnostic criterion for diabetes

1. Centers for Disease Control and Prevention. Diabetes Surveillance, 2005. Atlanta, GA, Department of Health and Human Services, 2005.
2. Honeycutt AA, Boyle JP, Broglio KR, Thompson TJ, Hoerger TJ, Geiss LS, et al. A dynamic Markov model for forecasting diabetes prevalence in the United States through 2050. Health Care Manag Sci. 2003;6:155-64. [PMID: 12943151]
3. Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. Lifetime risk for diabetes mellitus in the United States. JAMA. 2003;290:1884-90. [PMID: 14532317]
4. Hattersley AT. Beyond the beta cell in diabetes. Nat Genet. 2006;38:12-3. [PMID: 16380722]
5. Comi RJ. Treatment of type 2 diabetes mellitus: a weighty enigma [Editorial]. Ann Intern Med. 2005;143:609-10. [PMID: 16230728]
6. Saaddine JB, Cadwell B, Gregg EW, Engelgau MM, Vinicor F, Imperatore G, et al. Improvements in diabetes processes of care and intermediate outcomes: United States, 1988-2002. Ann Intern Med. 2006;v144 :465-74. [PMID:16585660]
7. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care. 1992;15:815-9. [PMID: 1516497]

Diagnosis continued

than 40 years of age, have a history of ketoacidosis, or are of low or normal weight. Polyuria and polydipsia in the setting of confirmed normal plasma suggest diabetes insipidus. Strong familial transmission characterizes maturity-onset diabetes of the young, which is due to monogenetic defects in β-cell function. ◆

Diagnosis... Type 2 diabetes is common, and clinicians should consider the diagnosis when patients present with symptoms or signs of the disease or its complications. Fasting plasma glucose levels greater than 126 mg/dL on 2 occasions at least 1 day apart confirm the diagnosis and have the advantage of being relatively convenient to measure. However, random plasma glucose levels and oral glucose tolerance testing can also be used to establish the diagnosis of type 2 diabetes. Other forms of diabetes are much less common than type 2 diabetes, but clinicians should consider these alternatives and endocrinology consultation when the clinical picture is unclear.

CLINICAL BOTTOM LINE

Screening

Should we screen for type 2 diabetes?

The natural history of type 2 diabetes includes an asymptomatic phase that is detectable only through screening or incidental testing. Because complications can occur before clinical symptoms, some groups advocate screening all primary care patients for the disease. However, no direct evidence proves that screening improves health outcomes. Further research is needed to define the effect of delaying the onset of frank diabetes on long-term outcomes and resource utilization and to determine whether there are potential harms of early treatment in patients with diabetes identified through screening. In the absence of such evidence, there is a lack of consensus about whether to screen all primary care patients, regardless of their underlying risk. Organizations have tended to advocate focusing screening on patients at high risk for diabetes or its complications.

Which patients are likely to benefit most from diabetes screening?

Several evidence-based guidelines advocate focusing screening efforts on patients with elevated risk for type 2 diabetes (Table 2), particularly those with cardiovascular disease, hypertension, or dyslipidemia.

Intensive glycemic control in people with type 2 diabetes reduces intermediate markers of microvascular complications but has not been convincingly shown to reduce end-organ complications or macrovascular disease. Yet fair evidence from observational studies[8-11] and a decision model[12] suggests that detecting diabetes improves estimates of cardiovascular risk and provides an opportunity for earlier and more aggressive interventions, such as more aggressive hypertension and lipid control, to reduce cardiovascular events in

Table 2: Diabetes Screening Guidelines

Date	*Organization (Reference)*	*Recommendations*
2006	American Diabetes Association[13]	· For adults who do not have diabetes risk factors, consider screening every 3 y starting at age 45 y, particularly if body mass index >25 kg/m^2 · Screen adults < 45 y of age if they are overweight and have another diabetes risk factor
2003	U.S. Preventive Services Task Force[14]	· There is insufficient evidence to recommend for or against routine screening of asymptomatic adults · Fair evidence supports screening adults with hypertension or hyperlipidemia
2003	Canadian Diabetes Association[15]	· Evaluate all patients for type 2 diabetes risk annually · Screen patients without diabetes risk factors every 3 y starting at age 40 y · Consider earlier, more frequent screening for patients with diabetes risk factors

8. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979;241:2035-8. [PMID: 430798]
9. Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. Diabetes Care. 1979;2:120-6. [PMID: 520114]
10. Haffner SM, Lehto S, Ronnemaa T, Pyoraia K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339:229-34. [PMID: 9673301]
11. Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. BMJ. 2002;324:939-42. [PMID: 11964337]
12. Goyder EC, Irwig LM. Screening for type 2 diabetes mellitus: a decision analytic approach. Diabet Med. 2000;17:469-77. [PMID: 10975217]
13. Standards of medical care in diabetes--2006. Diabetes Care. 2006;29 Suppl 1:S4-42. [PMID: 16373931]
14. Screening for type 2 diabetes mellitus in adults: recommendations and rationale. Ann Intern Med. 2003;138:212-4. [PMID: 12558361]

Risk Factors for Type 2 Diabetes

- Age > 45 y
- First-degree relative with type 2 diabetes
- African-American, Hispanic, Asian, Pacific Islander, or Native-American ethnicity
- History of gestational diabetes or delivery of infant weighing ≥9 lbs
- Polycystic ovary syndrome
- Overweight, especially abdominal obesity
- Cardiovascular disease, hypertension, dyslipidemia, or other metabolic syndrome features

Screening continued

patients with diabetes and preven[illegible] common diabetes complications.

Although currently available guidelines (Table 2) differ in their recommendations for screening of patients with average cardiovascular risk and the ages at which to begin screening, they generally agree that clinicians should screen for diabetes in patients with elevated risk for cardiovascular disease. ◆

Screening... Pending direct evidence of the benefits of early treatment for patients with type 2 diabetes identified through routine screening, screening for diabetes seems prudent for middle-aged patients with risk factors for cardiovascular disease, such as hypertension or dyslipidemia. Professional groups differ with respect to recommendations for screening in people without elevated cardiovascular risk.

CLINICAL BOTTOM LINE

Prevention

Can we prevent type 2 diabetes?

Before people develop type 2 diabetes, they almost always have "prediabetes." This condition is defined by hyperglycemia that does not meet the diagnostic criteria for diabetes. Whether this condition is called "impaired fasting glucose" or "impaired glucose tolerance" depends on whether the hyperglycemia was detected on measurement of fasting plasma glucose levels or an oral glucose tolerance test. Both impaired fasting glucose and impaired glucose tolerance are risk factors for future diabetes and cardiovascular disease[13]. Patients with prediabetes should undergo monitoring and should modify their risk factors for diabetes and cardiovascular disease if possible.

Prediabetes is identified by either of the following criteria:

- Impaired fasting glucose: fasting plasma glucose level 100 to 125 mg/dL (5.6 to 6.9 mmol/L)
- Impaired glucose tolerance: plasma glucose level 140 to 199 mg/dL (7.8 to 11.0 mmol/L) 2 hours after 75 g of glucose

In addition to observational studies, clinical trials document that dietary changes and regular exercise prevent or delay the development of overt diabetes in individuals at high risk for the disease, such as those with prediabetes.

In a randomized, unblinded, controlled trial of 522 overweight Finnish patients with impaired glucose tolerance (mean age, 55 years), an intervention aimed at a 5% reduction in weight decreased the incidence of newly diagnosed type 2 diabetes over 3 years from 23% to 11%[16]. The intervention involved personal counseling sessions to encourage a reduction in total and saturated fat intake to less than 30% and 10% of energy consumed, respectively; an increase in fiber intake; and moderate exercise for at least 30 minutes per day.

The Diabetes Prevention Project, a randomized, controlled trial that involved 3234 U.S. patients with prediabetes (mean age, 51 years; mean body mass index, 34 kg/m²), showed that a lifestyle modification program aimed at a 7% weight loss reduced the cumulative incidence of diabetes over 3 years from 29% to 14%[17] compared with placebo. The lifestyle intervention involved personal and group counseling sessions to encourage a low-calorie, low-fat diet and at least 150 minutes of moderate exercise (such as brisk walking) per week.

In a randomized, controlled trial that involved 577 Chinese adults with impaired glucose tolerance randomly assigned to diet, exercise, both, or neither, the incidence of diabetes over 6 years was 68% among persons in the "neither" group, 44% in the diet group, 41% in the exercise group, and 46% in the "both" group[18]. All 3 interventions resulted in statistically significant reductions in the progression to diabetes.

Clinical trials also show that certain medications can prevent type 2 diabetes in high-risk patients.

In the medication arm of the Diabetes Prevention Project, the trial that involved 3234 patients with prediabetes[18], metformin (850 mg twice daily) reduced the cumulative incidence of diabetes from 29% to 22% over

15. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2003;27(suppl 2).
16. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344:1343-50. [PMID: 11333990]
17. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393-403. [PMID: 11832527]
18. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997;20:537-44. [PMID: 9096977]

Prevention continued

3 years. This reduction was significant but smaller than that observed with the lifestyle intervention in this trial.

In the randomized, double-blind, international Study to Prevent Non–Insulin-Dependent Diabetes Mellitus, which involved 1429 patients with impaired glucose tolerance, acarbose (100 mg three times daily) reduced the incidence of diabetes from 42% to 32% compared with placebo[19]. The relative risk reduction over 3 years was 25%.

The DREAM trial (Diabetes Reduction Assessment with ramiripril and rosiglitazone Medication) is a multinational study that, using a 2-by-2 factorial design, randomized 5269 adults without previous cardiovascular disease but with impaired fasting glucose, impaired glucose tolerance, or both to rosiglitazone 8 mg per day or placebo and to rosiglitazone up to 15 mg per day or placebo. After a median 3 years, 11.6% of patients who received rosiglitazone developed diabetes or died compared with 26.0% of patients who received placebo (hazard ratio, 0.40 [95% CI, 0.35 to 0.46]). In addition, patients who received rosiglitazone were more likely to achieve normoglycemia than patients in the placebo group (50.5% vs. 30.3%; P<0.001). Cardiovascular event rates were statistically similar in both groups[20]. Patients in the ramiripril group did not have a significantly reduced incidence of diabetes or death, but these patients were more likely to have regressed to normoglycemia than were those receiving placebo (42.5% vs. 38.2%; P=0.001)[21]. ◆

Prevention... High-quality evidence supports the recommendation of regular exercise, weight loss, and reduction in total and saturated dietary fat for patients with blood glucose levels that are higher than normal but that do not meet the diagnostic criteria for diabetes (prediabetes). In some circumstances, evidence supports the use of pharmacologic therapy (metformin, acarbose, or rosilgitazone) to reduce a patient's risk for type 2 diabetes. Clinicians should consider one of these interventions when they identify patients as having prediabetes.

CLINICAL BOTTOM LINE

Evaluation & Treatment

What should the initial evaluation of patients with newly diagnosed type 2 diabetes include?

The initial evaluation of a patient with newly diagnosed type 2 diabetes should include a detailed history, physical examination, and laboratory tests to establish baseline values of glycemic control, to assess risk factors for complications, and to screen for existing diabetes complications.

What are the components of non-drug therapy for patients with type 2 diabetes?

Diet and exercise with optimization of body weight are the cornerstones of the management of type 2 diabetes.

In a study of patients with newly diagnosed type 2 diabetes, diet initially improved hemoglobin A_{1c} (HbA_{1c}) levels by 2.25 percentage points[22]. However, control deteriorated over time and most patients eventually required drug therapy.

A meta-analysis of 14 randomized trials that compared exercise with no exercise and involved a total of 377 patients with type 2 diabetes showed that exercise significantly improved glycemic control, reduced visceral adipose tissue, and reduced plasma triglycerides even in the absence of weight loss[23].

Physicians should initiate diet and exercise regimens as the first line of treatment for type 2 diabetes unless severe hyperglycemia necessitates immediate drug therapy. Even when drug therapy is necessary, diet and exercise remain essential components of diabetes management. Physicians need to recognize that no single diet applies to all patients with type 2 diabetes; instead, they should offer education about sensible dietary principles and an individualized strategy for optimization of body mass index.

What is the role of home glucose monitoring for patients with type 2 diabetes?

Physicians should consider home blood glucose testing for patients with type 2 diabetes. Although no studies have assessed whether home blood glucose monitoring leads to more favorable outcomes for patients receiving oral therapy, home monitoring can be helpful to guide oral medication adjustment, is essential for sensible adjustment of insulin dosage, and is valuable in determining whether symptoms are due to hypoglycemia or hyperglycemia. Urine

Initial Laboratory Evaluation of Patients with Type 2 Diabetes

- Fasting blood glucose level
- Glycosylated hemoglobin level
- Fasting lipid profile
- Serum electrolyte, blood urea nitrogen, and creatinine levels
- Urine dipstick for overt proteinuria, with confirmation of positive result. If no dipstick proteinuria, screen for microalbuminuria with a spot urinary albumin–creatinine ratio (>30 mg albumin/g creatinine is positive result)
- Electrocardiography

19. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet. 2002;359:2072-7. [PMID: 12086760]
20. The DREAM Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired fasting glucose: a randomized controlled trail. Lancet. 2006; 368:1096-105. [PMID: 16997664]
21. The DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. N Engl J Med. 2006; 355:1551-62. [PMID: 16980380]
22. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837-53. [PMID: 9742976]

glucose testing is not recommended because it does not adequately reflect current glycemic status.

Patients should generally test before a meal to reflect fasting glucose levels as closely as possible. However, measurement of postprandial levels may be informative, particularly for patients with elevated glycosylated hemoglobin values despite normal fasting glucose levels. Some experts now advocate postprandial monitoring to limit after-meal glucose excursions on the basis of observational data suggesting that postprandial glucose levels are associated with a degree of cardiovascular risk independent of fasting glucose levels[24–25]. Currently, however, the only studies that show improved outcomes with interventions based on postprandial glucose levels have been done in patients with gestational diabetes.

What target for glycemic control should physicians aim for in patients with type 2 diabetes?

Quality improvement efforts often define an HbA_{1c} value less than 7% as optimal control. It is clear that "tight" glycemic control reduces the risk for microvascular diabetic complications[22,26], and recent evidence shows that control also reduces the risk for macrovascular complications in type 1 diabetes[27]. However, tight control may not benefit patients with a limited life expectancy, substantial comorbidity, or a high risk for adverse hypoglycemic events. Clinicians and patients should consider these factors when setting targets for control.

When should the treatment of type 2 diabetes include drugs?

If diet and exercise fail to achieve the desired level of glycemic control, pharmacologic intervention is indicated. Patient characteristics and preferences should be used to set treatment goals in the initial choice of pharmacologic agent. In patients with severe hyperglycemia or marked symptoms, pharmacologic therapy may begin at the time of diagnosis. Some suggest that patients with fasting glucose levels greater than 250 to 300 mg/dL are reasonable candidates, although there are no clear data in this area. Patient preferences and

Table 3: Oral Drug Therapies for Treating Type 2 Diabetes

Drug	*Mechanism*	*Hemoglobin A_{1c} Reduction*	*Notes*
Biguanides (metformin)	· Suppresses hepatic glucose production · Decreases intestinal absorption of glucose · Improves insulin sensitivity	· 1%–2% · May also reduce lipid and blood pressure levels, although blood pressure effect may not be clinically significant	· No weight gain · Gastrointestinal side effects · Increase in risk for lactic acidosis (avoid if creatinine level >1.4 mg/dL in women and >1.5 mg/dL in men, decompensated congestive heart failure, liver failure, or heavy alcohol use)
Sulfonylureas (glimepiride, glipizide, glyburide, acetohexamide, chlorpropamide)	· Increases pancreatic secretion of insulin	· 1%–2%	· Possible initial weight gain · Potential for hypoglycemia
Thiazolidinediones (rosiglitazone and pioglitazone)	· Increases sensitivity to insulin	· 1%–2% as monotherapy or when added to other agents	· Weight gain and edema · Avoid in New York Heart Association class III or class IV heart failure
α-Glucosidase inhibitors (acarbose and miglitol)	· Decreases postprandial hyperglycemia by reducing gastrointestinal carbohydrate absorption	· 0.5%–1.0%	· Gastrointestinal side effects · Acarbose contraindicated in cirrhosis and requires liver function monitoring
Meglitinides (repaglinide and nateglinide)	· Increases pancreatic secretion of insulin through a different glucose-binding site than used by sulfonylureas	· 0.5%–2%	· Compared with sulfonylureas: Shorter onset of action and half-life · Greater decrease in postprandial glucose level · Lower risk for hypoglycemia

23. Thomas DE, Elliot EJ, Naughton GA. Exercise for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2006 Jul 19; 3:CD002968. [PMID: 16855995]
24. Gerich JE. The importance of tight glycemic control. Am J Med. 2005;118:7S-11S. [PMID: 16224937]
25. Ceriello A. Postprandial hyperglycemia and diabetes complications: is it time to treat? Diabetes. 2005;54:1-7. [PMID: 15616004]
26. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28:103-17. [PMID: 7587918]