

Diabetes Mellitus: Diagnosis and Screening

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Based on etiology, diabetes is classified as type 1 diabetes mellitus, type 2 diabetes mellitus, latent autoimmune diabetes, maturity-onset diabetes of youth, and miscellaneous causes. The diagnosis is based on measurement of A1C level, fasting or random blood glucose level, or oral glucose tolerance testing. Although there are conflicting guidelines, most agree that patients with hypertension or hyperlipidemia should be screened for diabetes. Diabetes risk calculators have a high negative predictive value and help define patients who are unlikely to have diabetes. Tests that may help establish the type of diabetes or the continued need for insulin include those reflective of beta cell function, such as C peptide levels, and markers of immune-mediated beta cell destruction (e.g., autoantibodies to islet cells, insulin, glutamic acid decarboxylase, tyrosine phosphatase [IA-2 α and IA-2 β]). Antibody testing is limited by availability, cost, and predictive value. (*Am Fam Physician*. 2010;81(7):863-870. Copyright © 2010 American Academy of Family Physicians.)

► See related editorial on page 843.

Prevention, timely diagnosis, and treatment are important in patients with diabetes mellitus. Many of the complications associated with diabetes, such as nephropathy, retinopathy, neuropathy, cardiovascular disease, stroke, and death, can be delayed or prevented with appropriate treatment of elevated blood pressure, lipids, and blood glucose.¹⁻⁴

In 1997, the American Diabetes Association (ADA) introduced an etiologically based classification system and diagnostic criteria for diabetes,⁵ which were updated in 2010.¹ Type 2 diabetes accounts for approximately 90 to 95 percent of all persons with diabetes in the United States, and its prevalence is increasing in adults worldwide.⁶ With the rise in childhood obesity, type 2 diabetes is increasingly being diagnosed in children and adolescents.⁶

The risk of diabetes is increased in close relatives suggesting a genetic predisposition, although no direct genetic link has been identified.⁷ Type 1 diabetes accounts for 5 to 10 percent of persons with diabetes⁶ and is characterized by insulin deficiency that is typically an autoimmune-mediated condition.

Latent autoimmune diabetes in adults includes a heterogeneous group of conditions that are phenotypically similar to type 2 diabetes, but patients have autoantibodies

that are common with type 1 diabetes. Diagnostic criteria include age of 30 years or older; no insulin treatment for six months after diagnosis; and presence of autoantibodies to glutamic acid decarboxylase, islet cells, tyrosine phosphatase (IA-2 α and IA-2 β), or insulin.

Patients with maturity-onset diabetes of youth typically present before 25 years of age, have only impaired insulin secretion, and have a monogenetic defect that leads to an autosomal dominant inheritance pattern. These patients are placed in a subcategory of having genetic defects of beta cell.⁸

The old terminology of prediabetes has now been replaced with “categories of increased risk for diabetes.” This includes persons with impaired fasting glucose, impaired glucose tolerance, or an A1C level of 5.7 to 6.4 percent.^{1,9,10}

Diagnostic Criteria and Testing

The 1997 ADA consensus guidelines lowered the blood glucose thresholds for the diagnosis of diabetes.⁵ This increased the number of patients diagnosed at an earlier stage, although no studies have demonstrated a reduction in long-term complications. Data suggest that as many as 5.7 million persons in the United States have undiagnosed diabetes.⁶ *Table 1* compares specific diagnostic tests for diabetes.¹¹⁻¹⁴

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Patients with a sustained blood pressure of greater than 135/80 mm Hg should be screened for diabetes.	A	34, 42
Patients with hypertension or hyperlipidemia should be screened for diabetes.	B	33
Risk calculators can be used to determine which patients do not need screening for diabetes.	C	13
A1C value of greater than 6.5 percent on two separate occasions is diagnostic for diabetes.	C	18
Patients at increased risk of diabetes should be counseled on effective strategies to lower their risk, such as weight loss and exercise.	C	9, 10

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

TESTS TO DIAGNOSE DIABETES

Blood Glucose Measurements. The diagnosis of diabetes is based on one of three methods of blood glucose measurement (Table 2).¹ Diabetes can be diagnosed if the patient has a fasting blood glucose level of 126 mg per dL (7.0 mmol per L) or greater on two separate occasions. The limitations of this test include the need for an eight-hour fast before the blood draw, a 12 to 15 percent day-to-day variance in fasting blood glucose values, and

a slightly lower sensitivity for predicting microvascular complications.^{15,16}

Diabetes can also be diagnosed with a random blood glucose level of 200 mg per dL (11.1 mmol per L) or greater if classic symptoms of diabetes (e.g., polyuria, polydipsia, weight loss, blurred vision, fatigue) are present. Lower random blood glucose values (140 to 180 mg per dL [7.8 to 10.0 mmol per L]) have a fairly high specificity of 92 to 98 percent; therefore, patients with these values should undergo more definitive testing. A low sensitivity of 39 to 55 percent limits the use of random blood glucose testing.¹⁵

The oral glucose tolerance test is considered a first-line diagnostic test. Limitations include poor reproducibility and patient compliance because an eight-hour fast is needed before the 75-g glucose load, which is followed two hours later by a blood draw.¹⁷ The criterion for diabetes is a serum blood glucose level of greater than 199 mg per dL (11.0 mmol per L).

In 2003, the ADA lowered the threshold for diagnosis of impaired fasting glucose to include a fasting glucose level between 100 and 125 mg per dL (5.6 and 6.9 mmol per L). Impaired glucose tolerance continues

Table 1. Comparison of Diagnostic Tests for Diabetes

Test	Sensitivity (%)	Specificity (%)	PPV*	NPV*	Medicare reimbursement†
OGTT (two hour)	Reference standard				\$19
Random blood glucose level ^{11‡}					
≥ 140 mg per dL (7.8 mmol per L)	55	92	30.5	97	\$6
≥ 150 mg per dL (8.3 mmol per L)	50	95	39.9	96.7	
≥ 160 mg per dL (8.9 mmol per L)	44	96	41.2	96.4	
≥ 170 mg per dL (9.4 mmol per L)	42	97	47.2	96.3	
≥ 180 mg per dL (10.0 mmol per L)	39	98	55.5	96	
A1C levels (%) ^{12§}					
6.1	63.2	97.4	60.8	97.6	\$14, serum test or point-of-care test
6.5	42.8	99.6	87.2	96.5	
7.0	28.3	99.9	94.7	95.6	
Diabetes Risk Calculator ^{13,14}	78.2 to 88.2	66.8 to 74.9	6.3 to 13.6	99.2 to 99.3	Free

NPV = negative predictive value; OGTT = oral glucose tolerance test; PPV = positive predictive value.

*—Calculated based on prevalence of 6 percent.

†—Based on 2009 rates.

‡—Reference standard was OGTT.

§—Reference standard was fasting blood glucose measurement.

Information from references 11 through 14.

Table 2. Diagnostic Criteria for Diabetes Mellitus

<i>Diabetes type</i>	<i>Blood glucose levels</i>	<i>Special tests</i>
Categories of increased risk (formerly prediabetes)	Fasting glucose test: 100 to 125 mg per dL (5.6 to 6.9 mmol per L) Two-hour OGTT (75-g load): 140 to 199 mg per dL (7.8 to 11.0 mmol per L) A1C measurement: 5.7 to 6.4 percent	—
Type 1, type 2, LADA, MODY	Fasting glucose test: \geq 126 mg per dL (7.0 mmol per L) Two-hour OGTT (75-g load): \geq 200 mg per dL (11.1 mmol per L) Random glucose test: \geq 200 mg per dL with symptoms A1C measurement: \geq 6.5 percent	Type 1 diabetes: decreased C peptide, presence of GADA and ICA LADA: increased C peptide, presence of GADA and ICA, tyrosine phosphatase antibody (IA-2), anti-insulin antibody MODY: genetic testing
Gestational diabetes	OGTT (100-g load): Fasting, 95 mg per dL (5.3 mmol per L) One hour, 180 mg per dL (10.0 mmol per L) Two hour, 155 mg per dL (8.6 mmol per L) Three hour, 140 mg per dL Need at least two abnormal results OGTT (75-g load): Fasting, 95 mg per dL One hour, 180 mg per dL Two hour, 155 mg per dL	One-hour Glucola OGTT (50-g load): 140 mg per dL (7.8 mmol per L), confirm diagnosis with 75- or 100-g OGTT

GADA = anti-glutamic acid decarboxylase antibody; ICA = anti-islet cell antibody; LADA = latent autoimmune diabetes in adults; MODY = maturity-onset diabetes of youth; OGTT = oral glucose tolerance test.

Information from reference 1.

to be defined as a blood glucose level between 140 and 199 mg per dL (7.8 and 11.0 mmol per L) two hours after a 75-g load. Patients meeting either of these criteria are at significantly higher risk of progression to diabetes and should be counseled on effective strategies to lower their risk, such as weight loss and exercise.^{1,9}

A1C. A1C measurement has recently been endorsed by the ADA as a diagnostic and screening tool for diabetes.¹ One advantage of using A1C measurement is the ease of testing because it does not require fasting. An A1C level of greater than 6.5 percent on two separate occasions is considered diagnostic of diabetes.¹⁸ Lack of standardization has historically deterred its use, but this test is now widely standardized in the United States.¹⁹ A1C measurements for diagnosis of diabetes should be performed by a clinical laboratory because of the lack of standardization of point-of-care testing. Limitations of A1C testing include low sensitivity, possible racial disparities, and interference by anemia and some medications.¹⁵

TESTS TO IDENTIFY TYPE OF DIABETES

Tests that can be used to establish the etiology of diabetes include those reflective of beta cell function (e.g., C peptide) and markers of immune-mediated beta cell destruction (e.g., insulin, islet cell, glutamic acid

decarboxylase, IA-2 α and IA-2 β autoantibodies). *Table 3* presents the characteristics of these tests.²⁰⁻²⁷

C peptide is linked to insulin to form proinsulin and reflects the amount of endogenous insulin. Patients with type 1 diabetes have low C peptide levels because of low levels of endogenous insulin and beta cell function. Patients with type 2 diabetes typically have normal to high levels of C peptide, reflecting higher amounts of insulin but relative insensitivity to it. In a Swedish study of patients with clinically well-defined type 1 or 2 diabetes, 96 percent of patients with type 2 diabetes had random C peptide levels greater than 1.51 ng per mL (0.50 nmol per L), whereas 90 percent of patients with type 1 diabetes had values less than 1.51 ng per mL.²⁰ In the clinically undefined population, which is the group in which the test is most often used, the predictive value is likely lower.

Antibody testing is limited by availability, cost, and predictive value, especially in black and Asian patients. Prevalence of any antibody in white patients with type 1 diabetes is 85 to 90 percent,⁵ whereas the prevalence in similar black or Hispanic patients is lower (19 percent in both groups in one study).²⁸ In persons with type 2 diabetes, the prevalence of islet cell antibody is 4 to 21 percent; glutamic acid decarboxylase antibody, 7 to 34 percent; IA-2, 1 to 2 percent; and any antibody,

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11.6 percent.^{24,25,29} In healthy persons, the prevalence of any antibody marker is 1 to 2 percent³⁰; thus, overlap of the presence of antibodies in various types of diabetes and patients limits the utility of individual tests.

Screening

As with any condition, a rationale for screening should first be established. Diabetes is a common disease that is associated with significant morbidity and mortality. It has an asymptomatic stage that may be present for up to seven years before diagnosis. The disease is treatable, and testing is acceptable and accessible to patients. Early treatment of diabetes that was identified primarily by symptoms improves microvascular outcomes.³¹ However, it is not clear whether universal screening reduces diabetes-associated morbidity and mortality. *Table 4* presents screening guidelines from several organizations.^{1,8,32-38}

TYPE 1 DIABETES

Screening for type 1 diabetes is not recommended because there is no accepted treatment for patients who

are diagnosed in the asymptomatic phase. The Diabetes Prevention Trial identified a group of high-risk patients based on family history and positivity to islet cell antibodies. However, treatment did not prevent progression to type 1 diabetes in these patients.³⁹

TYPE 2 DIABETES

Medications and lifestyle interventions may reduce the risk of diabetes, although 20 to 30 percent of patients with type 2 diabetes already have complications at the time of presentation.⁴⁰ Although a recent analysis suggests that screening for and treating impaired glucose tolerance in persons at risk of diabetes may be cost-effective, the data on screening for type 2 diabetes are less certain.⁴¹ It is unclear whether the early diagnosis of type 2 diabetes through screening programs, with subsequent intensive interventions, provides an incremental benefit in final health outcomes compared with initiating treatment after clinical diagnosis.

Guidelines differ regarding who should be screened for type 2 diabetes. The U.S. Preventive Services Task

Table 3. Characteristics of Special Tests for the Diagnosis of Diabetes Mellitus

Test	Type of diabetes			Medicare reimbursement*
	Type 1	Type 2	LADA	
C peptide	< 1.51 ng per mL (0.5 nmol per L): PPV of 96 percent for diagnosis in adults and children ²⁰	< 1.51 ng per mL: NPV of 96 percent for diagnosis in adults and children ²⁰	Not available	\$30
GADA	60 percent prevalence in adults and children ²¹ 73 percent prevalence in children ²²	7 to 34 percent prevalence in adults and children ^{23,24} NPV of 94 percent for requiring insulin at six years in adults ²⁵	Presence: PPV of 92 percent for requiring insulin at three years in persons 15 to 34 years of age ²⁶ Absence: NPV of 49 percent for requiring insulin at three years in persons 15 to 34 years of age ²⁶	\$28
IA-2 α and IA-2 β †	40 percent prevalence in adults and children ²¹ 86 percent prevalence in children ²⁷	2.2 percent prevalence in adults ²⁵	PPV of 75 percent for requiring insulin at three years in persons 15 to 34 years of age ²⁶	Cost not available
ICA	75 to 85 percent prevalence in adults and children ²¹ 84 percent prevalence in children ²²	4 to 21 percent prevalence in adults ²⁴	PPV of 86 percent for requiring insulin at three years in persons 15 to 34 years of age ²⁶	\$28

GADA = anti-glutamic acid decarboxylase antibody; ICA = anti-islet cell antibody; LADA = latent autoimmune diabetes in adults; NPV = negative predictive value; PPV = positive predictive value.

*—Based on 2009 rates.

†—Tyrosine phosphatase antibodies.

Information from references 20 through 27.

Table 4. Practice Guidelines for Diabetes Mellitus Screenings

Organization	Recommendations
Diabetes	
AACE ³²	All persons 30 years or older who are at risk of having or developing type 2 diabetes should be screened annually.
ADA ^{8*}	<p>Testing to detect type 2 diabetes should be considered in asymptomatic adults with a BMI of 25 kg per m² or greater and one or more additional risk factors for diabetes.</p> <p>Additional risk factors include physical inactivity; hypertension; HDL cholesterol level of less than 35 mg per dL (0.91 mmol per L) or a triglyceride level of greater than 250 mg per dL (2.82 mmol per L); history of CV disease; A1C level of 5.7 percent or greater; IGT or IFG on previous testing; first-degree relative with diabetes; member of a high-risk ethnic group; in women, history of gestational diabetes or delivery of a baby greater than 4.05 kg (9 lb), or history of PCOS; other conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans).</p> <p>In persons without risk factors, testing should begin at 45 years of age.</p> <p>If test results are normal, repeat testing should be performed at least every three years.</p>
CTFPHC ³³	There is fair evidence to recommend screening patients with hypertension or hyperlipidemia for type 2 diabetes to reduce the incidence of CV events and CV mortality.
USPSTF ³⁴	<p>All adults with a sustained blood pressure of greater than 135/80 mm Hg should be screened for diabetes.</p> <p>Current evidence is insufficient to assess balance of benefits and harms of routine screening for type 2 diabetes in asymptomatic, normotensive patients.</p>
Gestational diabetes	
AACE ³²	<p>In all pregnant women, fasting glucose should be measured at the first prenatal visit (no later than 20 weeks' gestation). A 75-g OGTT should be performed if the fasting glucose concentration is greater than 85 mg per dL (4.7 mmol per L).</p>
ACOG ^{35,36*}	<p>All pregnant women should be screened through history, clinical risk factors, or laboratory testing.</p> <p>Women at low-risk may be excluded from glucose testing.</p> <p>Low-risk criteria include age younger than 25 years, BMI of 25 kg per m² or less, no history of abnormal OGTT result, no history of adverse obstetric outcomes usually associated with gestational diabetes, no first-degree relative with diabetes, not a member of a high-risk ethnic group.</p> <p>Women with gestational diabetes should be screened six to 12 weeks postpartum and should receive subsequent screening for the development of diabetes.</p>
ADA ^{1,8*}	<p>Risk assessment should be performed at the first prenatal visit.</p> <p>Women with clinical characteristics consistent with a high risk of gestational diabetes (e.g., marked obesity, personal history of gestational diabetes, glycosuria, strong family history of diabetes) should undergo glucose testing as soon as possible. If glucose test results are negative, retesting should be performed at 24 to 28 weeks' gestation.</p> <p>Testing may be excluded in low-risk women (see ACOG criteria above). All other women should receive Glucola test or OGTT at 24 to 28 weeks' gestation.</p> <p>Women with gestational diabetes should be screened for diabetes six to 12 weeks postpartum and should receive subsequent screening for the development of diabetes.</p>
CTFPHC ³⁷	There is poor evidence to recommend for or against screening using Glucola testing in the periodic health examination of pregnant women.
USPSTF ³⁸	<p>Evidence is insufficient to assess the balance of benefits and harms of screening for gestational diabetes, either before or after 24 weeks' gestation.</p> <p>Physicians should discuss screening with patients and make case-by-case decisions.</p>

AACE = American Association of Clinical Endocrinologists; ACOG = American College of Obstetricians and Gynecologists; ADA = American Diabetes Association; BMI = body mass index; CTFPHC = Canadian Task Force on Preventive Health Care; CV = cardiovascular; HDL = high-density lipoprotein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test; PCOS = polycystic ovary syndrome; USPSTF = U.S. Preventive Services Task Force.

*—Expert consensus process, rather than an explicitly evidence-based process, was used to develop guidelines and practice parameters.

Information from references 1, 8, and 32 through 38.

Table 5. Diagnostic Criteria for Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

Parameter	Diabetic ketoacidosis			Hyperglycemic hyperosmolar state
	Mild	Moderate	Severe	
Plasma glucose	> 250 mg per dL (13.9 mmol per L)	> 250 mg per dL	> 250 mg per dL	> 600 mg per dL (33.3 mmol per L)
Arterial pH	7.25 to 7.30	7.00 to 7.24	< 7.00	> 7.30
Serum bicarbonate	15 to 18 mEq per L (15 to 18 mmol per L)	10 to 15 mEq per L (10 to 15 mmol per L)	< 10 mEq per L (10 mmol per L)	> 15 mEq per L (15 mmol per L)
Urine ketones	Positive	Positive	Positive	Small
Serum ketones	Positive	Positive	Positive	Small
Serum osmolality	Variable	Variable	Variable	> 320 mOsm per kg
Anion gap	> 10 mEq per L	> 12 mEq per L	> 12 mEq per L	< 12 mEq per L
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

Adapted with permission from Umpierrez GE, Murphy MB, Kitabchi AE. Diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. Diabetes Spectrum. 2002;15(1):30.

Force (USPSTF) recommends limiting screening to adults with a sustained blood pressure of greater than 135/80 mm Hg.^{34,42} The American Academy of Family Physicians concurs, but specifically includes treated and untreated patients.⁴³ The Canadian Task Force on Preventive Health Care recommends screening all patients with hypertension or hyperlipidemia.³³ The ADA recommends screening a much broader patient population based on risk.¹

There are several questionnaires to predict a patient's risk of diabetes. The Diabetes Risk Calculator was developed using data from the National Health and Nutrition Examination Survey III and incorporates age, height, weight, waist circumference, ethnicity, blood pressure, exercise, history of gestational diabetes, and family history.^{13,14} For diagnosis of diabetes, it has a positive predictive value (PPV) of 14 percent and a negative predictive value (NPV) of 99.3 percent. The tool is most valuable in helping define which patients are very unlikely to have diabetes.¹³

GESTATIONAL DIABETES

Whether patients should be screened for gestational diabetes is unclear. The USPSTF states that there is insufficient evidence to recommend for or against screening.³⁴ The ADA and the American College of Obstetricians and Gynecologists recommend risk-based testing, although most women require testing based on these inclusive guidelines.³⁶ The Glucola test is the most commonly used screening test for gestational diabetes and includes glucose testing one hour after a

50-g oral glucose load. An abnormal Glucola test result (i.e., blood glucose level of 140 mg per dL or greater) should be confirmed with a 75-g or 100-g oral glucose tolerance test. Whether screening and subsequent treatment of gestational diabetes alter clinically important perinatal outcomes is unclear. Untreated gestational diabetes is associated with a higher incidence of macrosomia and shoulder dystocia.⁴⁴ A randomized controlled trial found that treatment led to a reduction in serious perinatal complications, with a number needed to treat of 34. Treatment did not reduce risk of cesarean delivery or admission to the neonatal intensive care unit, however.⁴⁴

New-Onset Symptomatic Hyperglycemia

Patients may initially present with diabetic ketoacidosis or hyperglycemic hyperosmolar state (Table 5),⁴⁵ both of which are initially managed with insulin because they are essentially insulin deficiency states. Both groups of patients may present with polyuria, polydipsia, and signs of dehydration. Diagnostic criteria of diabetic ketoacidosis include a blood glucose level greater than 250 mg per dL (13.9 mmol per L), pH of 7.3 or less, serum bicarbonate level less than 18 mEq per L (18 mmol per L), and moderate ketonemia. However, significant ketosis has also been shown to occur in up to one third of patients with hyperglycemic hyperosmolar state.⁴⁶

Although diabetic ketoacidosis typically occurs in persons with type 1 diabetes, more than one half of newly diagnosed black patients with unprovoked diabetic ketoacidosis are obese and many display classic features

of type 2 diabetes—most importantly with a measurable insulin reserve.⁴⁷ Thus, the presentation does not definitively determine the type of diabetes a patient has. Presence of antibodies, particularly glutamic acid decarboxylase antibody, predicts a higher likelihood of lifelong insulin requirement. There is, however, an overlap of presence of antibodies in type 1 and type 2 diabetes, and among patients with type 2 diabetes who may not require insulin.⁴⁸

A Swedish population-based study showed that among the 9.3 percent of young adults with newly diagnosed diabetes that could not be classified as type 1 or type 2, the presence of glutamic acid decarboxylase antibody was associated with a need for insulin within three years (odds ratio = 18.8; 95% confidence interval, 1.8 to 191).²⁶ The PPV for insulin treatment was 92 percent in those with the antibody. It should be noted that among patients who were negative for antibodies, 51 percent also needed insulin within three years. In contrast, the United Kingdom Prospective Diabetes Study found that only 5.7 percent of patients without glutamic acid decarboxylase antibody eventually needed insulin therapy, giving the test an NPV of 94 percent.²⁵ With these conflicting data, clinical judgment using a patient's phenotype, history, presentation, and selective laboratory testing is the best way to manage patients with diabetes.

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Author disclosure: Nothing to disclose.

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