2. Classification and Diagnosis of Diabetes

American Diabetes Association

Diabetes Care 2015;38(Suppl. 1):S8–S16 | DOI: 10.2337/dc15-S005

CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to β-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive insulin secretory defect on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as in the treatment of HIV/AIDS or after organ transplantation)

This section reviews most common forms of diabetes but is not comprehensive. For additional information, see the American Diabetes Association (ADA) position statement "Diagnosis and Classification of Diabetes Mellitus" (1).

Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, with individuals not necessarily fitting clearly into a single category. For example, some patients cannot be clearly classified as having type 1 or type 2 diabetes. Clinical presentation and disease progression may vary considerably in both types of diabetes.

The traditional paradigms of type 2 diabetes occurring only in adults and type 1 diabetes only in children are no longer accurate, as both diseases occur in both cohorts. Occasionally, patients with type 2 diabetes may present with diabetic ketoacidosis (DKA). Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia and occasionally with DKA. The onset of type 1 diabetes may be variable in adults and may not present with the classic symptoms seen in children. However, difficulties in diagnosis may occur in children, adolescents, and adults, with the true diagnosis becoming more obvious over time.

DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on A1C criteria or plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT) (1,2) (**Table 2.1**).

The same tests are used to both screen for and diagnose diabetes. Diabetes may be identified anywhere along the spectrum of clinical scenarios: in seemingly low-risk individuals who happen to have glucose testing, in symptomatic patients, and in higher-risk individuals whom the provider tests because of a suspicion of diabetes. The same tests will also detect individuals with prediabetes.

A1C

The A1C test should be performed using a method that is certified by the NGSP and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Although point-of-care (POC) A1C assays may be NGSP certified, proficiency testing is not mandated for performing the test, so use of POC assays for diagnostic purposes may be problematic and is not recommended.

The A1C has several advantages to the FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and less day-to-day perturbations during stress and illness. These advantages must be balanced by

Suggested citation: American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In Standards of Medical Care in Diabetes—2015. *Diabetes Care 2015;38(Suppl. 1):S8–S16*

Table 2.1—Criteria for the diagnosis of diabetes

A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

greater cost, the limited availability of A1C testing in certain regions of the developing world, and the incomplete correlation between A1C and average glucose in certain individuals.

It is important to take age, race/ethnicity, and anemia/hemoglobinopathies into consideration when using the A1C to diagnose diabetes.

Age

The epidemiological studies that formed the framework for recommending A1C to diagnose diabetes only included adult populations. Therefore, it remains unclear if A1C and the same A1C cut point should be used to diagnose diabetes in children and adolescents (3–5).

Race/Ethnicity

A1C levels may vary with patients' race/ethnicity (6,7). For example, African Americans may have higher A1C levels than non-Hispanic whites despite similar fasting and postglucose load glucose levels. A recent epidemiological study found that, when matched for FPG, African Americans (with and without diabetes) had higher A1C levels than non-Hispanic whites, but also had higher levels of fructosamine and glycated albumin and lower levels of 1,5-anhydroglucitol, suggesting that their glycemic burden (particularly postprandially) may be higher (8).

Hemoglobinopathies/Anemias

Interpreting A1C levels in the presence of certain hemoglobinopathies and anemia may be problematic. For patients with an abnormal hemoglobin but normal red cell turnover, such as those with the sickle cell trait, an A1C assay without interference from abnormal hemoglobins should be used. An updated list of interferences is available at www.ngsp.org/interf.asp. In conditions associated with increased red cell turnover, such as pregnancy (second and third trimesters), recent blood loss or transfusion, erythropoietin therapy, or hemolysis, only blood glucose criteria should be used to diagnose diabetes.

Fasting and 2-Hour Plasma Glucose

In addition to the A1C test, the FPG and 2-h PG may also be used to diagnose diabetes (**Table 2.1**). The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. National Health and Nutrition Examination Survey (NHANES) data indicate that an A1C cut point of ≥6.5% identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of ≥126 mg/dL (7.0 mmol/L) (9). Numerous studies have confirmed that, compared with these A1C and FPG cut points, the 2-h PG value diagnoses more people with diabetes. Of note, the lower sensitivity of A1C at the designated cut point may be offset by the test's ease of use and facilitation of more widespread testing.

Unless there is a clear clinical diagnosis (e.g., a patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥200 mg/dL), it is recommended that the same test be repeated immediately using a new blood sample for confirmation because there will be a greater likelihood of concurrence. For example, if the A1C is 7.0% and a repeat result is 6.8%, the diagnosis of diabetes is confirmed. If two different tests (such as A1C and FPG) are both above the diagnostic threshold, this also confirms the diagnosis. On the other hand, if a patient has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated. The diagnosis is made on the basis of the confirmed test. For example, if a patient meets the diabetes criterion of the A1C (two results ≥6.5%), but not FPG (<126 mg/dL [7.0 mmol/L]), that person should nevertheless be considered to have diabetes.

Since all the tests have preanalytic and analytic variability, it is possible that an abnormal result (i.e., above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point. This scenario is least likely for A1C, more likely for FPG, and most likely for the 2-h PG, especially if the glucose samples are collected at room temperature and not centrifuged promptly. Barring laboratory error, such patients will likely have test results near the margins of the diagnostic threshold. The health care professional should follow the patient closely and repeat the test in 3–6 months.

CATEGORIES OF INCREASED RISK FOR DIABETES (PREDIABETES)

Recommendations

- Testing to assess risk for future diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and who have one or more additional risk factors for diabetes. For all patients, particularly those who are overweight or obese, testing should begin at age 45 years. **B**
- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. **C**
- To test for prediabetes, the A1C, FPG, and 2-h PG after 75-g OGTT are appropriate. **B**
- In patients with prediabetes, identify and, if appropriate, treat other cardiovascular disease (CVD) risk factors. **B**
- Testing to detect prediabetes should be considered in children and adolescents who are overweight or obese and who have two or more additional risk factors for diabetes. **E**

Description

In 1997 and 2003, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus (10,11) recognized a group of individuals whose glucose levels did not meet the criteria for diabetes but were too high to be considered

Table 2.2—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and have additional risk factors:
   - physical inactivity
   - first-degree relative with diabetes
   - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - women who delivered a baby weighing >9 lb or were diagnosed with GDM
   - hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - women with polycystic ovary syndrome
   - A1C ≥5.7%, IGT, or IFG on previous testing
   - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - history of CVD
2. For all patients, particularly those who are overweight or obese, testing should begin at age 45 years.
3. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

normal. "Prediabetes" is the term used for individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and indicates an increased risk for the future development of diabetes. IFG and IGT should not be viewed as clinical entities in their own right but rather risk factors for diabetes (**Table 2.2**) and CVD. IFG and IGT are associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

Diagnosis

In 1997 and 2003, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus (10,11) defined IFG as FPG levels 100–125 mg/dL (5.6–6.9 mmol/L) and IGT as 2-h PG after 75-g OGTT levels 140–199 mg/dL (7.8–11.0 mmol/L). It should be noted that the World Health Organization (WHO) and numerous diabetes organizations define the IFG cutoff at 110 mg/dL (6.1 mmol/L).

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes demonstrated a strong, continuous association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with an A1C between 5.5–6.0% had a substantially increased risk of diabetes (5-year incidence from 9 to 25%). An A1C range of 6.0–6.5% had a 5-year risk of developing diabetes between 25–50% and a relative risk 20 times higher compared with an A1C of 5.0% (12). In a community-based study of African American and non-Hispanic white adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (13). Other analyses suggest that an A1C of 5.7% is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (14).

Hence, it is reasonable to consider an A1C range of 5.7–6.4% as identifying individuals with prediabetes. As with those with IFG and/or IGT, individuals with an A1C of 5.7–6.4% should be informed of their increased risk for diabetes and CVD and counseled about effective strategies to lower their risks (see Section 5. Prevention or Delay of Type 2 Diabetes). Similar to glucose measurements, the continuum of risk is curvilinear, so as A1C rises, the diabetes risk rises disproportionately (12). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C >6.0%).

Table 2.3 summarizes the categories of prediabetes. For recommendations regarding risk factors and screening for prediabetes, see p. S12 ("Testing for Type 2 Diabetes and Prediabetes in Asymptomatic Adults" and "Testing for Type 2 Diabetes and Prediabetes in Children and Adolescents").

TYPE 1 DIABETES

Recommendation

- Inform the relatives of patients with type 1 diabetes of the opportunity to be tested for type 1 diabetes risk, but only in the setting of a clinical research study. **E**

Immune-Mediated Diabetes

This form, previously called "insulin-dependent diabetes" or "juvenile-onset diabetes," accounts for 5–10% of diabetes and is due to cellular-mediated autoimmune destruction of the pancreatic β-cells. Autoimmune markers include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to GAD (GAD65), autoantibodies to the tyrosine phosphatases IA-2 and IA-2β, and autoantibodies to zinc transporter 8 (ZnT8). Type 1 diabetes is defined by the presence of one or more of these autoimmune markers. The disease has strong HLA associations, with linkage to the *DQA* and *DQB* genes. These HLA-DR/DQ alleles can be either predisposing or protective.

The rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Children and adolescents may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis with infection or other stress. Adults may retain sufficient β-cell function to prevent ketoacidosis for many years; such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes

Table 2.3—Categories of increased risk for diabetes (prediabetes)*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4%

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life.

Autoimmune destruction of β-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are not typically obese when they present with type 1 diabetes, obesity should not preclude the diagnosis. These patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac disease, autoimmune hepatitis, myasthenia gravis, and pernicious anemia.

Idiopathic Diabetes

Some forms of type 1 diabetes have no known etiologies. These patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian ancestry. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited, lacks immunological evidence for β-cell autoimmunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may come and go.

Testing for Type 1 Diabetes

The incidence and prevalence of type 1 diabetes is increasing (15). Type 1 diabetic patients often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and some are diagnosed with life-threatening ketoacidosis. Several studies suggest that measuring islet autoantibodies in relatives of those with type 1 diabetes may identify individuals who are at risk for developing type 1 diabetes. Such testing, coupled with education about diabetes symptoms and close follow-up in an observational clinical study, may enable earlier identification of type 1 diabetes onset. There is evidence to suggest that early diagnosis may limit acute complications (16) and extend long-term endogenous insulin production (17).

A recent study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in three pediatric cohorts from Finland, Germany, and the U.S. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% within 15 years (16,18). These findings are highly significant because, while the German group was recruited from offspring of parents with type 1 diabetes, the Finnish and American groups were recruited from the general population. Remarkably, the findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both "sporadic" and genetic cases of type 1 diabetes.

While there is currently a lack of accepted screening programs, one should consider referring relatives of those with type 1 diabetes for antibody testing for risk assessment in the setting of a clinical research study (http://www2.diabetestrialnet.org). Widespread clinical testing of asymptomatic low-risk individuals is not currently recommended due to lack of approved therapeutic interventions. Higher-risk individuals may be tested, but only in the context of a clinical research setting. Individuals who test positive will be counseled about the risk of developing diabetes, diabetes symptoms, and DKA prevention. Numerous clinical studies are being conducted to test various methods of preventing type 1 diabetes in those with evidence of autoimmunity (www.clinicaltrials.gov).

TYPE 2 DIABETES

Recommendations

- Testing to detect type 2 diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and who have one or more additional risk factors for diabetes. For all patients, particularly those who are overweight or obese, testing should begin at age 45 years. **B**
- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. **C**
- To test for diabetes, the A1C, FPG, and 2-h PG after 75-g OGTT are appropriate. **B**
- In patients with diabetes, identify and, if appropriate, treat other CVD risk factors. **B**
- Testing to detect type 2 diabetes should be considered in children and adolescents who are overweight or obese and who have two or more additional risk factors for diabetes. **E**

Description

This form, previously referred to as "non-insulin-dependent diabetes" or "adult-onset diabetes," accounts for ~90–95% of all diabetes. Type 2 diabetes encompasses individuals who have insulin resistance and usually relative (rather than absolute) insulin deficiency. At least initially, and often throughout their lifetime, these individuals may not need insulin treatment to survive.

There are various causes of type 2 diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other known causes of diabetes. Most, but not all, patients with type 2 diabetes are obese. Obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.

Ketoacidosis seldom occurs spontaneously in type 2 diabetes; when seen, it usually arises in association with the stress of another illness such as infection. Type 2 diabetes frequently goes undiagnosed for many years because hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice the classic diabetes symptoms. Nevertheless, such patients are at an increased risk of developing macrovascular and microvascular complications.

Whereas patients with type 2 diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these patients would be expected to result in even higher insulin values had their β-cell function been normal. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal.

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently

in women with prior GDM, in those with hypertension or dyslipidemia, and in certain racial/ethnic subgroups (African American, American Indian, Hispanic/Latino, and Asian American). It is often associated with a strong genetic predisposition, more so than type 1 diabetes. However, the genetics of type 2 diabetes is poorly understood.

Testing for Type 2 Diabetes and Prediabetes in Asymptomatic Adults

Prediabetes and diabetes meet criteria for conditions in which early detection is appropriate. Both conditions are common and impose significant clinical and public health burdens. There is often a long presymptomatic phase before the diagnosis of type 2 diabetes. Simple tests to detect preclinical disease are readily available. The duration of glycemic burden is a strong predictor of adverse outcomes. There are effective interventions that prevent progression from prediabetes to diabetes (see Section 5. Prevention or Delay of Type 2 Diabetes) and reduce the risk of diabetes complications (see Section 8. Cardiovascular Disease and Risk Management and Section 9. Microvascular Complications and Foot Care).

Approximately one-quarter of people with diabetes in the U.S. are undiagnosed. Although screening of asymptomatic individuals to identify those with prediabetes or diabetes might seem reasonable, rigorous clinical trials to prove the effectiveness of such screening have not been conducted and are unlikely to occur. A large European randomized controlled trial compared the impact of screening for diabetes and intensive multifactorial intervention with that of screening and routine care (19). General practice patients between the ages of 40–69 years were screened for diabetes and randomized by practice to intensive treatment of multiple risk factors or routine diabetes care. After 5.3 years of follow-up, CVD risk factors were modestly but significantly improved with intensive treatment compared with routine care, but the incidence of first CVD events or mortality was not significantly different between the groups (19). The excellent care provided to patients in the routine care group and the lack of an unscreened control arm limit our ability to prove that screening and early intensive treatment impact outcomes. Mathematical modeling studies suggest that screening, beginning at age 30 or 45 years and independent of risk factors, may be cost-effective (<$11,000 per quality-adjusted life-year gained) (20).

Additional considerations regarding testing for type 2 diabetes and prediabetes in asymptomatic patients include the following:

Age

Testing recommendations for diabetes in asymptomatic adults are listed in **Table 2.2**. Age is a major risk factor for diabetes. Testing should begin at age 45 years for all patients, particularly those who are overweight or obese.

BMI and Ethnicity

Testing should be considered in adults of any age with BMI $\geq$25 kg/m^2 and one or more additional risk factors for diabetes. However, recent data (21) and evidence from the ADA position statement "BMI Cut Points to Identify At-Risk Asian Americans for Type 2 Diabetes Screening" (22) suggest that the BMI cut point should be lower for the Asian American population. For diabetes screening purposes, the BMI cut points fall consistently between 23–24 kg/m^2 (sensitivity of 80%) for nearly all Asian American subgroups (with levels slightly lower for Japanese Americans). This makes a rounded cut point of 23 kg/m^2 practical. In determining a single BMI cut point, it is important to balance sensitivity and specificity so as to provide a valuable screening tool without numerous false positives. An argument can be made to push the BMI cut point to lower than 23 kg/m^2 in favor of increased sensitivity; however, this would lead to an unacceptably low specificity (13.1%). Data from the WHO also suggest that a BMI $\geq$23 kg/m^2 should be used to define increased risk in Asian Americans (23).

Evidence also suggests that other populations may benefit from lower BMI cut points. For example, in a large multiethnic cohort study, for an equivalent incidence rate of diabetes, a BMI of 30 kg/m^2 in non-Hispanic whites was equivalent to a BMI of 26 kg/m^2 in African Americans (24).

Medications

Certain medications, such as glucocorticoids, thiazide diuretics, and atypical antipsychotics (25), are known to increase the risk of diabetes and should be considered when ascertaining a diagnosis.

Diagnostic Tests

The A1C, FPG, and 2-h PG after 75-g OGTT are appropriate for testing. It should be noted that the tests do not necessarily detect diabetes in the same individuals. The efficacy of interventions for primary prevention of type 2 diabetes (26–32) has primarily been demonstrated among individuals with IGT, not for individuals with isolated IFG or for those with prediabetes defined by A1C criteria.

Testing Interval

The appropriate interval between tests is not known (33). The rationale for the 3-year interval is that with this interval, the number of false-positive tests that require confirmatory testing will be reduced and individuals with false-negative tests will be retested before substantial time elapses and complications develop (33).

Community Screening

Ideally, testing should be carried out within a health care setting because of the need for follow-up and treatment. Community testing outside a health care setting is not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. Community testing may also be poorly targeted; i.e., it may fail to reach the groups most at risk and inappropriately test those at very low risk or even those who have already been diagnosed.

Testing for Type 2 Diabetes and Prediabetes in Children and Adolescents

In the last decade, the incidence and prevalence of type 2 diabetes in adolescents has increased dramatically, especially in ethnic populations (15). Recent studies question the validity of A1C in the pediatric population, especially among certain ethnicities, and suggest OGTT or FPG as more suitable diagnostic tests (34). However, many of these studies do not recognize that diabetes diagnostic criteria are based on long-term health outcomes, and validations are not currently available in the pediatric population (35). The ADA acknowledges the limited data supporting A1C for diagnosing diabetes in children and adolescents. However, aside from rare instances, such as cystic fibrosis and hemoglobinopathies, the ADA continues to recommend A1C in this cohort (36,37). The modified recommendations of the ADA consensus report "Type 2 Diabetes in Children and Adolescents" are summarized in **Table 2.4**.

Table 2.4—Testing for type 2 diabetes or prediabetes in asymptomatic children*

Criteria • Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
Plus any two of the following risk factors: • Family history of type 2 diabetes in first- or second-degree relative • Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) • Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) • Maternal history of diabetes or GDM during the child's gestation
Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age
Frequency: every 3 years

*Persons aged ≤18 years.

GESTATIONAL DIABETES MELLITUS

Recommendations

- Test for undiagnosed type 2 diabetes at the first prenatal visit in those with risk factors, using standard diagnostic criteria. **B**
- Test for GDM at 24–28 weeks of gestation in pregnant women not previously known to have diabetes. **A**
- Screen women with GDM for persistent diabetes at 6–12 weeks postpartum, using the OGTT and clinically appropriate nonpregnancy diagnostic criteria. **E**
- Women with a history of GDM should have lifelong screening for the development of diabetes or prediabetes at least every 3 years. **B**
- Women with a history of GDM found to have prediabetes should receive lifestyle interventions or metformin to prevent diabetes. **A**

Definition

For many years, GDM was defined as any degree of glucose intolerance that was first recognized during pregnancy (10), regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy. This definition facilitated a uniform strategy for detection and classification of GDM, but it was limited by imprecision.

The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age, resulting in an increase in the number of pregnant women with undiagnosed type 2 diabetes (38). Because of the number of pregnant women with undiagnosed type 2 diabetes, it is reasonable to test women with risk factors for type 2 diabetes (**Table 2.2**) at their initial prenatal visit, using standard diagnostic criteria (**Table 2.1**). Women with diabetes in the first trimester would be classified as having type 2 diabetes. GDM is diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes.

Diagnosis

GDM carries risks for the mother and neonate. Not all adverse outcomes are of equal clinical importance. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (39), a large-scale (~25,000 pregnant women) multinational cohort study, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM. GDM diagnosis (**Table 2.5**) can be accomplished with either of two strategies:

1. "One-step" 75-g OGTT or
2. "Two-step" approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive

Different diagnostic criteria will identify different degrees of maternal hyperglycemia and maternal/fetal risk, leading some experts to debate, and disagree on, optimal strategies for the diagnosis of GDM.

One-Step Strategy

In the 2011 Standards of Care (40), the ADA for the first time recommended that all pregnant women not known to have prior diabetes undergo a 75-g OGTT at 24–28 weeks of gestation, based on a recommendation of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (41). The IADPSG defined diagnostic cut points for GDM as the average glucose values (fasting, 1-h, and 2-h PG) in the HAPO study at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean glucose levels of the study population. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to ~15–20%), primarily because only one abnormal value, not two, became sufficient to make the diagnosis. The ADA recognized that the anticipated increase in the incidence of GDM would have significant impact on the costs, medical infrastructure capacity, and potential for increased "medicalization" of pregnancies previously categorized as normal, but recommended these diagnostic criteria changes in the context of worrisome worldwide increases in obesity and diabetes rates with the intent of optimizing gestational outcomes for women and their offspring.

The expected benefits to these pregnancies and offspring are inferred from intervention trials that focused on women with lower levels of hyperglycemia than identified using older GDM diagnostic criteria and that found modest benefits including reduced rates of large-for-gestational-age births and preeclampsia (42,43). It is important to note that 80–90% of women being treated for mild GDM in two randomized controlled trials (whose glucose values overlapped with the thresholds recommended by the IADPSG) could be managed with lifestyle therapy alone. Data are lacking on how the treatment of lower levels of hyperglycemia affects a mother's risk for the development of type 2 diabetes in the future and her offspring's risk for obesity, diabetes, and other metabolic dysfunction. Additional well-designed clinical studies are needed to determine the optimal intensity of monitoring and treatment of women with GDM diagnosed by the one-step strategy.

Two-Step Strategy

In 2013, the National Institutes of Health (NIH) convened a consensus development conference on diagnosing GDM. The 15-member panel had representatives from obstetrics/gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields to consider diagnostic criteria (44). The panel recommended the two-step approach of screening with a 1-h 50-g

Table 2.5—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

If the plasma glucose level measured 1 h after the load is ≥140 mg/dL* (7.8 mmol/L), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

	Carpenter/Coustan (56)	or	NDDG (57)
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

NDDG, National Diabetes Data Group.
*The ACOG recommends a lower threshold of 135 mg/dL (7.5 mmol/L) in high-risk ethnic populations with higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).

glucose load test (GLT) followed by a 3-h 100-g OGTT for those who screen positive, a strategy commonly used in the U.S.

Key factors reported in the NIH panel's decision-making process were the lack of clinical trial interventions demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large new group of women with GDM, including medicalization of pregnancy with increased interventions and costs. Moreover, screening with a 50-g GLT does not require fasting and is therefore easier to accomplish for many women. Treatment of higher threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births, and shoulder dystocia, without increasing small-for-gestational-age births (45). The American College of Obstetricians and Gynecologists (ACOG) updated its guidelines in 2013 and supported the two-step approach (46).

Future Considerations

The conflicting recommendations from expert groups underscore the fact that there are data to support each strategy. The decision of which strategy to implement must therefore be made based on the relative values placed on factors that have yet to be measured (e.g., cost-benefit estimation, willingness to change practice based on correlation studies rather than clinical intervention trial results, relative role of cost considerations, and available infrastructure locally, nationally, and internationally).

As the IADPSG criteria have been adopted internationally, further evidence has emerged to support improved pregnancy outcomes with cost savings (47) and may be the preferred approach. In addition, pregnancies complicated by GDM per IADPSG criteria, but not recognized as such, have comparable outcomes to pregnancies diagnosed as GDM by the more stringent two-step criteria (48). There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policymakers. Longer-term outcome studies are currently underway.

MONOGENIC DIABETES SYNDROMES

Monogenic defects that cause β-cell dysfunction, such as neonatal diabetes and MODY, represent a small fraction of patients with diabetes (<5%). These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years).

Neonatal Diabetes

Diabetes diagnosed in the first 6 months of life has been shown not to be typical autoimmune type 1 diabetes. This so-called neonatal diabetes can either be transient or permanent. The most common genetic defect causing transient disease is a defect on ZAC/HYAMI imprinting, whereas permanent neonatal diabetes is most commonly a defect in the gene encoding the Kir6.2 subunit of the β-cell K_{ATP} channel. Diagnosing the latter has implications, since such children can be well managed with sulfonylureas.

Maturity-Onset Diabetes of the Young

MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action. It is inherited in an autosomal dominant pattern. Abnormalities at six genetic loci on different chromosomes have been identified to date. The most common form is associated with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1α. A second form is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule. Glucokinase converts glucose to glucose-6-phosphate, the metabolism of which, in turn, stimulates insulin secretion by the β-cell. The less common forms of MODY result from mutations in other transcription factors, including HNF-4α, HNF-1β, insulin promoter factor (IPF)-1, and NeuroD1.

Diagnosis

Readily available commercial genetic testing now enables a true genetic diagnosis. It is important to correctly diagnose one of the monogenic forms of diabetes because these children may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal treatment regimens and delays in diagnosing other family members (49).

The diagnosis of monogenic diabetes should be considered in children with the following findings:

- Diabetes diagnosed within the first 6 months of life
- Strong family history of diabetes but without typical features of type 2 diabetes (nonobese, low-risk ethnic group)

- Mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), especially if young and nonobese
- Diabetes with negative autoantibodies and without signs of obesity or insulin resistance

CYSTIC FIBROSIS–RELATED DIABETES

Recommendations

- Annual screening for cystic fibrosis–related diabetes (CFRD) with OGTT should begin by age 10 years in all patients with cystic fibrosis who do not have CFRD. **B** A1C as a screening test for CFRD is not recommended. **B**
- Patients with CFRD should be treated with insulin to attain individualized glycemic goals. **A**
- In patients with cystic fibrosis and IGT without confirmed diabetes, prandial insulin therapy should be considered to maintain weight. **B**
- Annual monitoring for complications of diabetes is recommended, beginning 5 years after the diagnosis of CFRD. **E**

CFRD is the most common comorbidity in people with cystic fibrosis, occurring in about 20% of adolescents and 40–50% of adults. Diabetes in this population is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality from respiratory failure. Insulin insufficiency related to partial fibrotic destruction of the islet mass is the primary defect in CFRD. Genetically determined function of the remaining β-cells and insulin resistance associated with infection and inflammation may also play a role. While screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with abnormal glucose tolerance, there appears to be no benefit with respect to weight, height, BMI, or lung function compared with those with normal glucose tolerance <10 years of age. The use of continuous glucose monitoring may be more sensitive than OGTT to detect risk for progression to CFRD, but this likely needs more evidence.

Encouraging data suggest that improved screening (50,51) and aggressive insulin therapy have narrowed the gap in mortality between cystic fibrosis patients with and without diabetes and have eliminated the sex difference in mortality (52). Recent trials comparing insulin with oral repaglinide showed no significant difference between the groups. However, another study compared three different groups: premeal insulin aspart, repaglinide, or oral placebo in cystic fibrosis patients with abnormal glucose tolerance. Patients all had weight loss; however, in the insulin-treated group, this pattern was reversed, and they gained 0.39 (± 0.21) BMI units ($P = 0.02$). Patients in the repaglinide-treated group had initial weight gain, but this was not sustained by 6 months. The placebo group continued to lose weight (53). Insulin remains the most widely used therapy for CFRD (54).

Recommendations for the clinical management of CFRD can be found in the ADA position statement "Clinical Care Guidelines for Cystic Fibrosis–Related Diabetes: A Position Statement of the American Diabetes Association and a Clinical Practice Guideline of the Cystic Fibrosis Foundation, Endorsed by the Pediatric Endocrine Society" (55).

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