



American Diabetes Association

2. Classification and Diagnosis of Diabetes

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CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune β -cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of β -cell insulin secretion frequently on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
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 with glucocorticoid use, 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).

Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Classification is important for determining therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis. 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), particularly ethnic minorities (2). Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia, and approximately one-third present with DKA (3). The onset of type 1 diabetes may be more variable in adults, and they may not present with the classic symptoms seen in children. Although difficulties in distinguishing diabetes type may occur in all age-groups at onset, the true diagnosis becomes more obvious over time.

In October 2015, the ADA, JDRF, the European Association for the Study of Diabetes, and the American Association of Clinical Endocrinologists convened the Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis Research Symposium (4). The goals of the symposium were to discuss the genetic and environmental determinants of type 1 and type 2 diabetes risk and progression, to determine appropriate therapeutic approaches based on disease pathophysiology and stage, and to define research gaps hindering a personalized approach to treatment. The experts agreed that in both type 1 and type 2 diabetes, various genetic and environmental factors can result in the progressive loss of β -cell mass and/or function that manifests clinically as hyperglycemia. Once hyperglycemia occurs, patients with all forms of diabetes are at risk for developing the same complications, although rates of progression may differ. They concluded that the identification of individualized therapies for diabetes in the future will require better characterization of the many paths to β -cell demise or dysfunction.

Characterization of the underlying pathophysiology is much more developed in type 1 diabetes than in type 2 diabetes. It is now clear from studies of first-degree relatives of patients with type 1 diabetes that the persistent presence of two or

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more autoantibodies is an almost certain predictor of clinical hyperglycemia and diabetes. The rate of progression is dependent on the age at first detection of antibody, number of antibodies, antibody specificity, and antibody titer. Glucose and A1C levels rise well before the clinical onset of diabetes, making diagnosis feasible well before the onset of DKA. Three distinct stages of type 1 diabetes can be identified (Table 2.1) and serve as a framework for future research and regulatory decision making (4,5).

The paths to β -cell demise and dysfunction are less well defined in type 2 diabetes, but deficient β -cell insulin secretion frequently in the setting of insulin resistance appears to be the common denominator. Characterization of subtypes of this heterogeneous disorder have been developed and validated in Scandinavian and Northern European populations, but have not been confirmed in other ethnic and racial groups. Type 2 diabetes is primarily associated with insulin secretory defects related to inflammation and metabolic stress among other contributors including genetic factors. Future classification schemes for diabetes will likely focus on the pathophysiology of the underlying β -cell dysfunction and the stage of disease as indicated by glucose status (normal, impaired, or diabetes) (4).

DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on 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) or A1C criteria (1,6) (Table 2.2).

FPG, 2-h PG after 75-g OGTT, and A1C are equally appropriate for diagnostic 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 (7,8) has primarily been demonstrated among individuals with impaired glucose tolerance (IGT), not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by A1C criteria.

The same tests may be used to screen for and diagnose diabetes and to detect individuals with prediabetes. Diabetes may be identified anywhere along the spectrum of clinical scenarios: in seemingly low-risk individuals who happen to have glucose testing, in individuals tested based on diabetes risk assessment, and in symptomatic patients.

Fasting and 2-Hour Plasma Glucose

The FPG and 2-h PG may be used to diagnose diabetes (Table 2.2). The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. Numerous studies have confirmed that, compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with diabetes.

A1C

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

The A1C has several advantages compared with the FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and less day-to-day perturbations during stress and illness. However, these

advantages may be offset by the lower sensitivity of A1C at the designated cut point, greater cost, limited availability of A1C testing in certain regions of the developing world, and the imperfect correlation between A1C and average glucose in certain individuals. National Health and Nutrition Examination Survey (NHANES) data indicate that an A1C cut point of $\geq 6.5\%$ (48 mmol/mol) identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of ≥ 126 mg/dL (7.0 mmol/L) (9).

When using A1C to diagnose diabetes, it is important to recognize that A1C is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia including age, race/ethnicity, and anemia/hemoglobinopathies.

Age

The epidemiological studies that formed the basis for recommending A1C to diagnose diabetes included only adult populations. Therefore, it remains unclear if A1C and the same A1C cut point should be used to diagnose diabetes in children and adolescents (9,10).

Race/Ethnicity

A1C levels may vary with race/ethnicity independently of glycemia (11,12). For example, African Americans may have higher A1C levels than non-Hispanic whites despite similar fasting and post-glucose load glucose levels (13). Though there is some conflicting data, African Americans may also have higher levels of fructosamine and glycated albumin and lower levels of 1,5-anhydroglucitol, suggesting that their glycemic burden (particularly postprandially) may be higher (14,15). The association of A1C with risk for complications appears to be similar in African Americans and non-Hispanic whites (16).

Table 2.1—Staging of type 1 diabetes (4,5)			
	Stage 1	Stage 2	Stage 3
Stage	<ul style="list-style-type: none">• Autoimmunity• Normoglycemia• Presymptomatic	<ul style="list-style-type: none">• Autoimmunity• Dysglycemia• Presymptomatic	<ul style="list-style-type: none">• New-onset hyperglycemia• Symptomatic
Diagnostic criteria	<ul style="list-style-type: none">• Multiple autoantibodies• No IGT or IFG	<ul style="list-style-type: none">• Multiple autoantibodies• Dysglycemia: IFG and/or IGT• FPG 100–125 mg/dL (5.6–6.9 mmol/L)• 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L)• A1C 5.7–6.4% (39–47 mmol/mol) or $\geq 10\%$ increase in A1C	<ul style="list-style-type: none">• Clinical symptoms• Diabetes by standard criteria

Table 2.2—Criteria for the diagnosis of diabetesFPG ≥ 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

A1C $\geq 6.5\%$ (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

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.

Hemoglobinopathies/Red Blood Cell Turnover

Interpreting A1C levels in the presence of certain hemoglobinopathies may be problematic. For patients with an abnormal hemoglobin but normal red blood 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 blood cell turnover, such as pregnancy (second and third trimesters), hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only blood glucose criteria should be used to diagnose diabetes.

Confirming the Diagnosis

Unless there is a clear clinical diagnosis (e.g., patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥ 200 mg/dL [11.1 mmol/L]), a second test is required for confirmation. It is recommended that the same test be repeated without delay using a new blood sample for confirmation because there will be a greater likelihood of concurrence. For example, if the A1C is 7.0% (53 mmol/mol) and a repeat result is 6.8% (51 mmol/mol), 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 $\geq 6.5\%$ [48 mmol/mol]) 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 likely for FPG and 2-h PG if the glucose samples remain at room temperature and are not centrifuged promptly. Because of the potential for preanalytic variability, it is critical that samples for plasma glucose be spun and separated immediately after they are drawn. If patients 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**

- Screening for prediabetes and risk for future diabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults. **B**
- Testing for prediabetes and risk for future diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥ 25 kg/m² or ≥ 23 kg/m² in Asian Americans) and who have one or more additional risk factors for diabetes. **B**
- For all people, 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, fasting plasma glucose, 2-h plasma glucose after 75-g oral glucose tolerance test, and A1C are equally appropriate. **B**
- In patients with prediabetes, identify and, if appropriate, treat other cardiovascular disease risk factors. **B**
- Testing for 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 the Diagnosis and Classification of Diabetes Mellitus (17,18) recognized a group of individuals whose glucose levels did not meet the criteria for diabetes but were too high to be considered normal. “Prediabetes” is the term used for individuals with IFG and/or IGT and/or A1C 5.7–6.4% (39–47 mmol/mol). Prediabetes should not be viewed as a clinical entity in its own right but rather as an increased risk for diabetes (**Table 2.3**) and cardiovascular disease (CVD). Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

Diagnosis

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (17,18) defined IFG as FPG levels between 100 and 125 mg/dL (between 5.6 and 6.9 mmol/L) and IGT as 2-h PG after 75-g OGTT levels between 140 and 199 mg/dL (between 7.8 and 11.0 mmol/L). It should be noted that the World Health Organization (WHO) and numerous other 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 as defined by A1C criteria 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 A1C between 5.5 and 6.0% (between 37 and 42 mmol/mol)

Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m² or ≥23 kg/m² in Asian Americans) adults who have one or more of the following risk factors:
 - A1C ≥5.7% (39 mmol/mol), IGT, or IFG on previous testing
 - first-degree relative with diabetes
 - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
 - women who were diagnosed with GDM
 - history of CVD
 - 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
 - physical inactivity
 - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans).
2. For all patients, 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.

had a substantially increased risk of diabetes (5-year incidence from 9 to 25%). An A1C range of 6.0–6.5% (42–48 mmol/mol) had a 5-year risk of developing diabetes between 25 and 50% and a relative risk 20 times higher compared with A1C of 5.0% (31 mmol/mol) (19). 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 (20). Other analyses suggest that A1C of 5.7% (39 mmol/mol) or higher is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (21), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up (22).

Hence, it is reasonable to consider an A1C range of 5.7–6.4% (39–47 mmol/mol) as identifying individuals with prediabetes. Similar to those with IFG and/or IGT, individuals with A1C of 5.7–6.4% (39–47 mmol/mol) 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 (19). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C >6.0% [42 mmol/mol]).

Table 2.4 summarizes the categories of prediabetes and **Table 2.3** the criteria for prediabetes testing. The ADA diabetes risk test is an additional option for screening (**Fig. 2.1**). For recommendations regarding risk factors and screening for prediabetes, see pp. S17–S18 (“Screening and Testing for Type 2 Diabetes and Prediabetes in Asymptomatic Adults” and “Screening and Testing for Type 2 Diabetes and Prediabetes in Children and Adolescents”).

TYPE 1 DIABETES

- Recommendations**
- Blood glucose rather than A1C should be used to diagnose the acute onset of type 1 diabetes in individuals with symptoms of hyperglycemia. **E**
 - Screening for type 1 diabetes with a panel of autoantibodies is currently recommended only in the setting of a research trial or in first-degree family members of a proband with type 1 diabetes. **B**
 - Persistence of two or more autoantibodies predicts clinical diabetes

Table 2.4—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% (39–47 mmol/mol)

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

and may serve as an indication for intervention in the setting of a clinical trial. Outcomes may include reversion of autoantibody status, prevention of glycemic progression within the normal or prediabetes range, prevention of clinical diabetes, or preservation of residual C-peptide secretion. **A**

Diagnosis

In a patient with classic symptoms, measurement of blood glucose is sufficient to diagnose diabetes (symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose ≥200 mg/dL [11.1 mmol/L]). In these cases, knowing the blood glucose level is critical because, in addition to confirming that symptoms are due to diabetes, it will inform management decisions. Some providers may also want to know the A1C to determine how long a patient has had hyperglycemia.

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 and autoantibodies to GAD (GAD65), insulin, the tyrosine phosphatases IA-2 and IA-2β, and 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

ARE YOU AT RISK FOR

TYPE 2 DIABETES?



Diabetes Risk Test

1 How old are you?

Less than 40 years (0 points)
 40–49 years (1 point)
 50–59 years (2 points)
 60 years or older (3 points)

Write your score
in the box.



2 Are you a man or a woman?

Man (1 point) Woman (0 points)

3 If you are a woman, have you ever been diagnosed with gestational diabetes?

Yes (1 point) No (0 points)

4 Do you have a mother, father, sister, or brother with diabetes?

Yes (1 point) No (0 points)

5 Have you ever been diagnosed with high blood pressure?

Yes (1 point) No (0 points)

6 Are you physically active?

Yes (0 points) No (1 point)

7 What is your weight status?
(see chart at right)

Height	Weight (lbs.)		
4' 10"	119-142	143-190	191+
4' 11"	124-147	148-197	198+
5' 0"	128-152	153-203	204+
5' 1"	132-157	158-210	211+
5' 2"	136-163	164-217	218+
5' 3"	141-168	169-224	225+
5' 4"	145-173	174-231	232+
5' 5"	150-179	180-239	240+
5' 6"	155-185	186-246	247+
5' 7"	159-190	191-254	255+
5' 8"	164-196	197-261	262+
5' 9"	169-202	203-269	270+
5' 10"	174-208	209-277	278+
5' 11"	179-214	215-285	286+
6' 0"	184-220	221-293	294+
6' 1"	189-226	227-301	302+
6' 2"	194-232	233-310	311+
6' 3"	200-239	240-318	319+
6' 4"	205-245	246-327	328+
	(1 Point)	(2 Points)	(3 Points)
You weigh less than the amount in the left column (0 points)			

Add up
your score.



If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes (a condition that precedes type 2 diabetes in which blood glucose levels are higher than normal). Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, American Indians, and Asian Americans and Pacific Islanders.

Higher body weights increase diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weights than the rest of the general public (about 15 pounds lower).

For more information, visit us at diabetes.org or call 1-800-DIABETES (1-800-342-2383)

Adapted from Bang et al., Ann Intern Med 151:775-783, 2009.
 Original algorithm was validated without gestational diabetes as part of the model.

Lower Your Risk

The good news is that you can manage your risk for type 2 diabetes. Small steps make a big difference and can help you live a longer, healthier life. If you are at high risk, your first step is to see your doctor to see if additional testing is needed. Visit diabetes.org or call 1-800-DIABETES (1-800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.



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Figure 2.1—ADA risk test.

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 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. Patients with type 1 diabetes are also prone to other autoimmune disorders such as Hashimoto thyroiditis, Graves disease, Addison disease, celiac disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia (see Section 3 “Comprehensive Medical Evaluation and Assessment of Comorbidities”).

Idiopathic Type 1 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 β -cell 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 and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may be intermittent.

Testing for Type 1 Diabetes Risk

The incidence and prevalence of type 1 diabetes is increasing (23). Patients with type 1 diabetes often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and approximately one-third are diagnosed with life-threatening ketoacidosis (3). Several studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes may identify individuals who are at risk for developing type 1 diabetes (5). Such testing, coupled with education about diabetes symptoms and close follow-up, may enable earlier identification of type 1 diabetes onset. A 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 (24). 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 familial cases of type 1 diabetes. Indeed, the risk of type 1 diabetes increases as the number of relevant autoantibodies detected increases (25–27).

Although 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://www.diabetestrialnet.org>). Widespread clinical testing of asymptomatic low-risk individuals is not currently recommended due to lack of approved therapeutic interventions. 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

- Screening for type 2 diabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults. **B**
- Testing for type 2 diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese ($\text{BMI} \geq 25 \text{ kg/m}^2$ or $\geq 23 \text{ kg/m}^2$ in Asian Americans) and who have one or more additional risk factors for diabetes. **B**
- For all people, 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 type 2 diabetes, fasting plasma glucose, 2-h plasma glucose after 75-g oral glucose tolerance test, and A1C are equally appropriate. **B**
- In patients with diabetes, identify and treat other cardiovascular disease risk factors. **B**

- Testing for 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

Type 2 diabetes, previously referred to as “noninsulin-dependent diabetes” or “adult-onset diabetes,” accounts for 90–95% of all diabetes. This form encompasses individuals who have relative (rather than absolute) insulin deficiency and have peripheral insulin resistance. 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 overweight or obese. Excess weight itself causes some degree of insulin resistance. Patients who are not obese or overweight 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, even undiagnosed patients are at 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. In adults without traditional risk factors for type 2 diabetes and/or younger age, consider antibody testing for type 1 diabetes (i.e., GAD).

Screening and Testing for Type 2 Diabetes and Prediabetes in Asymptomatic Adults

Screening for prediabetes and type 2 diabetes through an informal assessment of risk factors (Table 2.3) or with an assessment tool, such as the ADA risk test (Fig. 2.1), is recommended to guide providers on whether performing a diagnostic test (Table 2.2) is appropriate. Prediabetes and type 2 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 9 “Cardiovascular Disease and Risk Management” and Section 10 “Microvascular Complications and Foot Care”).

Approximately one-quarter of people with diabetes in the U.S. and nearly half of Asian and Hispanic Americans with diabetes are undiagnosed (28). 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 (29). General practice patients between the ages of

40 and 69 years were screened for diabetes and randomly assigned 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 (29). The excellent care provided to patients in the routine care group and the lack of an unscreened control arm limited the authors' ability to determine whether screening and early treatment improved outcomes compared with no screening and later treatment after clinical diagnoses. Computer simulation modeling studies suggest that major benefits are likely to accrue from the early diagnosis and treatment of hyperglycemia and cardiovascular risk factors in type 2 diabetes (30); moreover, 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) (31).

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

Age

Screening recommendations for diabetes in asymptomatic adults are listed in Table 2.3. Age is a major risk factor for diabetes. Testing should begin at age 45 years for all patients. Screening should be considered in overweight or obese adults of any age with one or more risk factors for diabetes.

BMI and Ethnicity

In general, BMI ≥ 25 kg/m² is a risk factor for diabetes. Data and recommendations from the ADA position statement “BMI Cut Points to Identify At-Risk Asian Americans for Type 2 Diabetes Screening” (32,33) suggest that the BMI cut point should be lower for the Asian American population. The BMI cut points fall consistently between 23 and 24 kg/m² (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/m² 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/m² 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 of ≥ 23 kg/m² should be used to define increased risk in Asian Americans (34). The finding that half of diabetes in Asian Americans is undiagnosed suggests that testing is not occurring at lower BMI thresholds (28).

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/m² in non-Hispanic whites was equivalent to a BMI of 26 kg/m² in African Americans (35).

Medications

Certain medications, such as glucocorticoids, thiazide diuretics, and atypical antipsychotics (36), are known to increase the risk of diabetes and should be considered when deciding whether to screen.

Testing Interval

The appropriate interval between screening tests is not known (37). 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 (37).

Community Screening

Ideally, testing should be carried out within a health care setting because of the need for follow-up and treatment. Community screening 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 (38).

Screening in Dental Practices

Because periodontal disease is associated with diabetes, the utility of chair-side screening and referral to primary care as a means to improve the diagnosis of prediabetes and diabetes has been explored (39–41), with one study estimating that 30% of patients ≥ 30 years

of age seen in general dental practices had dysglycemia (41). Further research is needed to demonstrate the feasibility, effectiveness, and cost-effectiveness of screening in this setting.

Screening and 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 racial and ethnic minority populations (23). 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 (42). 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 (43). The ADA acknowledges the limited data supporting A1C for diagnosing type 2 diabetes in children and adolescents. Although A1C is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes and only A1C assays without interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend A1C for diagnosis of type 2 diabetes in this cohort (44,45). The modified recommendations of the ADA consensus report "Type 2 Diabetes in Children and Adolescents" are summarized in **Table 2.5** (46).

GESTATIONAL DIABETES MELLITUS

Recommendations

- Test for undiagnosed diabetes at the first prenatal visit in those with risk factors, using standard diagnostic criteria. **B**
- Test for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant women not previously known to have diabetes. **A**
- Test women with gestational diabetes mellitus for persistent diabetes at 4–12 weeks' postpartum, using the oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **E**
- Women with a history of gestational diabetes mellitus should

Table 2.5—Testing for type 2 diabetes or prediabetes in asymptomatic children* (46)

Criteria
<ul style="list-style-type: none"> • 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:
<ul style="list-style-type: none"> • 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.

have lifelong screening for the development of diabetes or prediabetes at least every 3 years. **B**

- Women with a history of gestational diabetes mellitus found to have prediabetes should receive intensive 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 (17), 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, with an increase in the number of pregnant women with undiagnosed type 2 diabetes (47). 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 2.3**) at their initial prenatal visit, using standard diagnostic criteria (**Table 2.2**). Women diagnosed with diabetes in the first trimester should be classified as having preexisting pregestational diabetes (type 2 diabetes or, very rarely, type 1 diabetes). GDM is diabetes that is first diagnosed in the second or third trimester of pregnancy that is not clearly either preexisting type 1 or type 2 diabetes (see Section 13 "Management of Diabetes in Pregnancy"). The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) GDM diagnostic criteria for the 75-g

OGTT were not derived from data in the first half of pregnancy, so the diagnosis of GDM in early pregnancy by either FPG or OGTT values is not evidence based (48).

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 (49), a large-scale multinational cohort study completed by more than 23,000 pregnant women, 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 2.6**) 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 (50), the ADA for the first time recommended that all pregnant women not known to have prior diabetes undergo a 75-g

Table 2.6—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 ≥ 130 mg/dL, 135 mg/dL, or 140 mg/dL* (7.2 mmol/L, 7.5 mmol/L, or 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 (59)	or	NDDG (60)
• 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 either 135 mg/dL (7.5 mmol/L) or 140 mg/dL (7.8 mmol/L). A systematic review determined that a cutoff of 130 mg/dL (7.2 mmol/L) was more sensitive but less specific than 140 mg/dL (7.8 mmol/L) (55).

OGTT at 24–28 weeks of gestation, based on a recommendation of the IADPSG (51). The IADPSG defined diagnostic cut points for GDM as the average fasting, 1-h, and 2-h plasma glucose values in the HAPO study at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean fasting, 1-h, and 2-h PG 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 a substantial impact on costs and medical infrastructure needs and had the potential to “medicalize” pregnancies previously categorized as normal. Nevertheless, the ADA recommended these changes in diagnostic criteria with the intent of optimizing gestational outcomes because these criteria were the only ones based on pregnancy outcomes rather than end points such as prediction of subsequent maternal diabetes.

The expected benefits to the offspring are inferred from intervention trials that focused on women with lower levels of hyperglycemia than identified using

older GDM diagnostic criteria. Those trials found modest benefits including reduced rates of large-for-gestational-age births and preeclampsia (52,53). It is important to note that 80–90% of women being treated for mild GDM in two randomized controlled trials could be managed with lifestyle therapy alone. The OGTT glucose cutoffs in these two trials overlapped with the thresholds recommended by the IADPSG, and in one trial (53), the 2-h PG threshold (140 mg/dL [7.8 mmol/L]) was lower than the cutoff recommended by the IADPSG (153 mg/dL [8.5 mmol/L]). No randomized controlled trials of identifying and treating GDM using the IADPSG criteria versus older criteria have been published to date. Data are also lacking on how the treatment of lower levels of hyperglycemia affects a mother’s future risk for the development of type 2 diabetes and her offspring’s risk for obesity, diabetes, and other metabolic disorders. 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 to consider diagnostic

criteria for diagnosing GDM (54). The 15-member panel had representatives from obstetrics/gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields. The panel recommended a two-step approach to screening that used a 1-h 50-g glucose load test (GLT) followed by a 3-h 100-g OGTT for those who screened positive. Commonly used cutoffs for the 1-h 50-g GLT include 130, 135, and 140 mg/dL (7.2, 7.5, and 7.8 mmol/L). The American College of Obstetricians and Gynecologists (ACOG) recommends either 135 or 140 mg/dL (45). A systematic review for the U.S. Preventive Services Task Force compared GLT cutoffs of 130 mg/dL (7.2 mmol/L) and 140 mg/dL (7.8 mmol/L) (55). The higher cutoff yielded sensitivity of 70–88% and specificity of 69–89%, while the lower cutoff was 88–99% sensitive and 66–77% specific. Data regarding a cutoff of 135 mg/dL are limited. As for other screening tests, choice of a cutoff is based upon the tradeoff between sensitivity and specificity. The use of A1C at 24–28 weeks as a screening test for GDM does not function as well as the GLT (56).

Key factors cited by the NIH panel in their decision-making process were the lack of clinical trial data demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large group of women with GDM, including medicalization of pregnancy with increased health care utilization 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 (57), and shoulder dystocia, without increasing small-for-gestational-age births. ACOG updated its guidelines in 2013 and supported the two-step approach (58). The ACOG recommends either of two sets of diagnostic thresholds for the 3-h 100-g OGTT (59,60). Each is based on different mathematical conversions of the original recommended thresholds, which used whole blood and nonenzymatic methods for glucose determination. A recent secondary analysis of data from a randomized clinical trial of identification and treatment of

mild GDM (61) demonstrated that treatment was similarly beneficial in patients meeting only the lower thresholds (59) and in those meeting only the higher thresholds (60). If the two-step approach is used, it would appear advantageous to use the lower diagnostic thresholds as shown in Step 2 in **Table 2.6**.

Future Considerations

The conflicting recommendations from expert groups underscore the fact that there are data to support each strategy. A cost-benefit estimation comparing the two strategies concluded that the one-step approach is cost-effective only if patients with GDM receive postdelivery counseling and care to prevent type 2 diabetes (62). 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., willingness to change practice based on correlation studies rather than intervention trial results, available infrastructure, and importance of cost considerations).

As the IADPSG criteria ("one-step strategy") have been adopted internationally, further evidence has emerged to support improved pregnancy outcomes with cost savings (63) and may be the preferred approach. Data comparing population-wide outcomes with one-step versus two-step approaches have been inconsistent to date (64,65). In addition, pregnancies complicated by GDM per the IADPSG criteria, but not recognized as such, have comparable outcomes to pregnancies diagnosed as GDM by the more stringent two-step criteria (66,67). There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policymakers. Longer-term outcome studies are currently under way.

MONOGENIC DIABETES SYNDROMES

Recommendations

- All children diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. **A**
- Children and adults, diagnosed in early adulthood, who have diabetes not characteristic of type 1 or type 2 diabetes that occurs in successive generations (suggestive of an autosomal dominant pattern of

inheritance) should have genetic testing for maturity-onset diabetes of the young. **A**

- In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of these mutations and how best to approach further evaluation, treatment, and genetic counseling. **E**

Monogenic defects that cause β -cell dysfunction, such as neonatal diabetes and MODY, represent a small fraction of patients with diabetes (<5%). **Table 2.7** describes the most common causes of monogenic diabetes. For a comprehensive list of causes, see *Genetic Diagnosis of Endocrine Disorders* (68).

Neonatal Diabetes

Diabetes occurring under 6 months of age is termed "neonatal" or "congenital" diabetes, and about 80–85% of cases can be found to have an underlying monogenic cause (69). Neonatal diabetes occurs much less often after 6 months of age, whereas autoimmune type 1 diabetes rarely occurs before 6 months of age. Neonatal diabetes can either be transient or permanent. Transient diabetes is most often due to overexpression of genes on chromosome 6q24, is recurrent in about half of cases, and may be treatable with medications other than insulin. Permanent neonatal diabetes is most commonly due to autosomal dominant mutations in the genes encoding the Kir6.2 subunit (*KCNJ11*) and SUR1 subunit (*ABCC8*) of the β -cell K_{ATP} channel. Correct diagnosis has critical implications because most patients with K_{ATP} -related neonatal diabetes will exhibit improved glycemic control when treated with high-dose oral sulfonylureas instead of insulin. Insulin gene (*INS*) mutations are the second most common cause of permanent neonatal diabetes, and, while treatment presently is intensive insulin management, there are important genetic considerations as most of the mutations that cause diabetes are dominantly inherited.

Maturity-Onset Diabetes of the Young MODY is frequently characterized by onset of hyperglycemia at an early age (classically before age 25 years, although diagnosis may occur at older

ages). MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action (in the absence of coexistent obesity). It is inherited in an autosomal dominant pattern with abnormalities in at least 13 genes on different chromosomes identified to date. The most commonly reported forms are GCK-MODY (MODY2), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1).

Clinically, patients with GCK-MODY exhibit mild, stable, fasting hyperglycemia and do not require antihyperglycemic therapy except sometimes during pregnancy. Patients with HNF1A- or HNF4A-MODY usually respond well to low doses of sulfonylureas, which are considered first-line therapy. Mutations or deletions in *HNF1B* are associated with renal cysts and uterine malformations (renal cysts and diabetes [RCAD] syndrome). Other extremely rare forms of MODY have been reported to involve other transcription factor genes including *PDX1* (*IPF1*) and *NEUROD1*.

Diagnosis

A diagnosis of one of the three most common forms of MODY including GCK-MODY, HNF1A-MODY, and HNF4A-MODY allows for more cost-effective therapy (no therapy for GCK-MODY; sulfonylureas as first-line therapy for HNF1A-MODY and HNF4A-MODY). Additionally, diagnosis can lead to identification of other affected family members.

A diagnosis of MODY should be considered in individuals who have atypical diabetes and multiple family members with diabetes not characteristic of type 1 or type 2 diabetes, although admittedly "atypical diabetes" is becoming increasingly difficult to precisely define in the absence of a definitive set of tests for either type of diabetes. In most cases, the presence of autoantibodies for type 1 diabetes precludes further testing for monogenic diabetes, but the presence of autoantibodies in patients with monogenic diabetes has been reported (70). Individuals in whom monogenic diabetes is suspected should be referred to a specialist for further evaluation if available, and consultation is available from several centers. Readily available commercial genetic testing following the criteria listed below now enables a cost-effective (71), often cost-saving, genetic diagnosis that is increasingly supported by health insurance. It

Table 2.7—Most common causes of monogenic diabetes (68)

	Gene	Inheritance	Clinical features
MODY			
	<i>GCK</i>	AD	GCK-MODY: stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
	<i>HNF1A</i>	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	<i>HNF4A</i>	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	<i>HNF1B</i>	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
Neonatal diabetes			
	<i>KCNJ11</i>	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	<i>INS</i>	AD	Permanent: IUGR; insulin requiring
	<i>ABCC8</i>	AD	Transient or permanent: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (<i>PLAGL1</i> , <i>HYMA1</i>)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication or maternal methylation defect; may be treatable with medications other than insulin
	<i>GATA6</i>	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	<i>EIF2AK3</i>	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	<i>FOXP3</i>	X-linked	Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes; autoimmune thyroid disease; exfoliative dermatitis; insulin requiring

AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction.

is critical to correctly diagnose one of the monogenic forms of diabetes because these patients may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal, even potentially harmful, treatment regimens and delays in diagnosing other family members (72). The information is especially critical for GCK-MODY mutations where multiple studies have shown that no complications ensue in the absence of glucose-lowering therapy (73). Genetic counseling is recommended to ensure that affected individuals understand the patterns of inheritance and the importance of a correct diagnosis.

The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:

- Diabetes diagnosed within the first 6 months of life (with occasional cases presenting later, mostly *INS* and *ABCC8* mutations) (69,74)
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies; nonobese, lacking other metabolic

features, especially with strong family history of diabetes)

- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), stable A1C between 5.6 and 7.6% (between 38 and 60 mmol/mol), especially if nonobese

CYSTIC FIBROSIS–RELATED DIABETES

Recommendations

- Annual screening for cystic fibrosis–related diabetes with oral glucose tolerance test should begin by age 10 years in all patients with cystic fibrosis not previously diagnosed with cystic fibrosis–related diabetes. **B**
- A1C as a screening test for cystic fibrosis–related diabetes is not recommended. **B**
- Patients with cystic fibrosis–related diabetes should be treated with insulin to attain individualized glycemic goals. **A**
- Beginning 5 years after the diagnosis of cystic fibrosis–related diabetes, annual monitoring for complications of diabetes is recommended. **E**

Cystic fibrosis–related diabetes (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, compared with individuals with type 1 or type 2 diabetes, is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality. Insulin insufficiency is the primary defect in CFRD. Genetically determined β -cell function and insulin resistance associated with infection and inflammation may also contribute to the development of CFRD. Milder abnormalities of glucose tolerance are even more common and occur at earlier ages than CFRD. Whether individuals with IGT should be treated with insulin replacement has not currently been determined. Although screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with abnormal glucose tolerance, no benefit has been established with respect to weight, height, BMI, or lung function. Continuous glucose monitoring may be more sensitive than OGTT to detect risk for progression to CFRD; however, evidence linking continuous glucose

monitoring results to long-term outcomes is lacking, and its use is not recommended for screening (75).

CFRD mortality has significantly decreased over time, and the gap in mortality between cystic fibrosis patients with and without diabetes has considerably narrowed (76). There are limited clinical trial data on therapy for CFRD. The largest study compared three regimens: premeal insulin aspart, repaglinide, or oral placebo in cystic fibrosis patients with diabetes or abnormal glucose tolerance. Participants all had weight loss in the year preceding treatment; however, in the insulin-treated group, this pattern was reversed, and patients gained $0.39 (\pm 0.21)$ BMI units ($P = 0.02$). The repaglinide-treated group had initial weight gain, but this was not sustained by 6 months. The placebo group continued to lose weight (77). Insulin remains the most widely used therapy for CFRD (78).

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" (79).

POSTTRANSPLANTATION DIABETES MELLITUS

Recommendations

- Patients should be screened after organ transplantation for hyperglycemia, with a formal diagnosis of posttransplantation diabetes mellitus being best made once a patient is stable on an immunosuppressive regimen and in the absence of an acute infection. **E**
- The oral glucose tolerance test is the preferred test to make a diagnosis of posttransplantation diabetes mellitus. **B**
- Immunosuppressive regimens shown to provide the best outcomes for patient and graft survival should be used, irrespective of posttransplantation diabetes mellitus risk. **E**

Several terms are used in the literature to describe the presence of diabetes following organ transplantation. "New-onset diabetes after transplantation" (NODAT) is one such designation that

describes individuals who develop new-onset diabetes following transplant. NODAT excludes patients with pretransplant diabetes that was undiagnosed as well as posttransplant hyperglycemia that resolves by the time of discharge (80). Another term, "posttransplantation diabetes mellitus" (PTDM) (80), describes the presence of diabetes in the posttransplant setting irrespective of the timing of diabetes onset.

Hyperglycemia is very common during the early posttransplant period, with ~90% of kidney allograft recipients exhibiting hyperglycemia in the first few weeks following transplant (80,81). In most cases, such stress or steroid-induced hyperglycemia resolves by the time of discharge. Risk factors for PTDM include both general diabetes risks (such as age, family history of diabetes, etc.) as well as transplant-specific factors, such as use of immunosuppressant agents. Whereas posttransplantation hyperglycemia is an important risk factor for subsequent PTDM, a formal diagnosis of PTDM is optimally made once the patient is stable on maintenance immunosuppression and in the absence of acute infection.

The OGTT is considered the gold standard test for the diagnosis of PTDM (80,82–84). However, screening patients using fasting glucose and/or A1C can identify high-risk patients requiring further assessment and may reduce the number of overall OGTTs required (85). There is currently a lack of clinical data examining the use of antidiabetes agents in the setting of PTDM to inform specific recommendations for use in this population. Although the use of immunosuppressive therapies is a major contributor to the development of PTDM, the risks of transplant rejection outweigh the risks of PTDM and the role of the diabetes care provider is to treat hyperglycemia appropriately regardless of the type of immunosuppression (80).

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