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FAQs in Diabetes

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4
CHAPTER

Screening and Diagnosis

Question What are the criteria for the diagnosis of diabetes?

The fasting plasma glucose (FPG) or the 2-hour value in 75 g oral glucose tolerance test (OGTT) have been the criteria for diagnosing diabetes for decades. The American Diabetes Association (ADA), International Diabetes Federation, and European Association for the Study of Diabetes later recommended the use of the glycosylated hemoglobin (HbA1c) in diagnosing diabetes, which was adopted by the ADA in 2009.

A random plasma glucose (PG) level of more than 200 mg/dL (11.1 mmol/L) along with classic signs and symptoms of diabetes (polydipsia, polyuria, weight loss, etc.) is satisfactory for the diagnosis of diabetes. However, in the absence of classic signs and symptoms, a 75 g OGTT should be performed with subsequent application of diagnostic criteria (Box. 1).

BOX 1: Criteria for diagnosing diabetes

- Glycosylated hemoglobin ≥6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program certified and standardized to the Diabetes Control and Complications Trial assay*

OR

- Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours*

OR

- 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, 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, criteria 1–3 should be confirmed by repeat testing.

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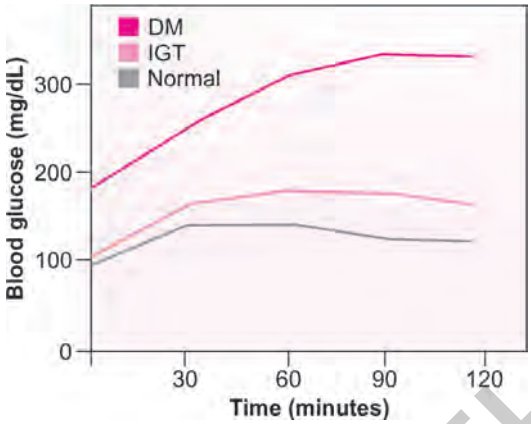

DM, diabetes mellitus; IGT, impaired glucose tolerance.

FIGURE 1: A 75 g oral glucose tolerance test for diagnosis of diabetes

In OGTT, after an overnight fast, a fasting blood sample is taken and 75 g of glucose is given by mouth, often in the form of glucose drink, and a subsequent blood sample is taken at 2 hours (Fig. 1).

Question What is the importance of HbA1c in the diagnosis of diabetes?

The International Expert Committee recommends that the diagnosis of diabetes be made, if HbA1c is more than or equal to 6.5% and should be confirmed with a repeat test. FPG, 2-hour post glucose load PG, and OGTT are recommended for the diagnosis of diabetes, only if HbA1c testing is not possible due to unavailability of the assay, patient factors that preclude its interpretation, and during pregnancy. Although HbA1c has several advantages, when used as the sole diagnostic criterion for diagnosis of diabetes, it may not be completely reliable (Table 1). Hence, HbA1c should be used in combination with PG determinations for the diagnosis of diabetes.

A diagnostic cutoff point of HbA1c more than or equal to 6.5% tends to miss out a substantial number of people with type 2 diabetes mellitus (T2DM), including some with fasting hyperglycemia, and fails to identify most individuals with impaired glucose tolerance (IGT). Therefore, a combination of HbA1c and PG measurements for the diagnosis of diabetes is indeed beneficial and reduces the risk of systematic bias inherent in HbA1c testing alone.

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TABLE 1: Use of HbA1c ≥6.5% as the cutoff in the diagnosis of diabetes

Advantages	Disadvantages
• Does not require a fasting blood sample, avoids the preanalytical instability of glucose measurements • HbA1c reflects glycemia over several weeks • Lower biological variability of HbA1c as compared to FPG or 2-hour post glucose load • Absence of significant retinopathy among individuals with HbA1c <6.5%	• Spurious results can be seen in ○ Anemia ○ Hemoglobinopathies ○ Renal failure ○ Different ethnic groups • Diagnosis by HbA1c will identify a different population to that diagnosed by FPG • Distribution of HbA1c values varies in different ethnic groups • HbA1c increases with age

FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; PG; plasma glucose.

Question What tests are recommended for screening of diabetes?

The FPG, also a component of diagnostic testing, is considered the preferred test for screening of diabetes. Fasting is defined as no consumption of food or beverage other than water for at least 8 hours before testing. Although the FPG test and the 75 g OGTT are both reliable tests for diabetes, the FPG test is preferred in clinical settings because it is convenient to perform, less expensive, and more acceptable to patients.

A FPG less than 126 mg/dL (7.0 mmol/L) along with a high suspicion for diabetes is an indication for an OGTT. A 2-hour post glucose load value in the OGTT more than or equal to 200 mg/dL (11.1 mmol/L) is a positive test for diabetes and should be confirmed on an alternate day.

Any nondiabetic individual with a FPG more than or equal to 100 mg/dL (5.6 mmol/L) but less than 126 mg/dL (7.0 mmol/L) should be considered to have impaired fasting glucose (IFG), and those with 2-hour post glucose load value in the OGTT more than or equal to 140 mg/dL (7.8 mmol/L) but less than 200 mg/dL (11.1 mmol/L) are defined as having IGT. Both IFG and IGT are risk factors for future diabetes. Normoglycemia is defined as PG levels less than 100 mg/dL (5.6 mmol/L) in the FPG test and a 2-hour post glucose load value less than 140 mg/dL (7.8 mmol/L) in the OGTT. It should be noted that the World Health Organization and a number of other diabetes organizations define the cutoff for IFG at 110 mg/dL (6.1 mmol/L).

Casual PG testing or PG measurement irrespective of the time of last meal may also be performed. A casual PG level more than or equal to 200 mg/dL (11.1 mmol/L) with symptoms of diabetes is considered diagnostic of diabetes. However, a confirmatory FPG test or OGTT should be conducted on a different day, if the clinical condition of the patient permits.

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Plasma glucose measurement is performed on the venous samples with enzymatic assay techniques, and the above-mentioned values are based on the use of such methods. Capillary blood glucose testing using a reflectance blood glucose meter has also been used but because of the imprecision of this method, it is better used for self-monitoring rather than as a screening tool.

Question What is the role of glycosylated hemoglobin in the screening of diabetes?

Although, HbA1c is commonly used in the diagnosis of diabetes, it is also useful in identifying individuals at risk of developing diabetes. In 2009, the International Expert Committee noted that individuals with HbA1c levels above the laboratory "normal" range but below the diagnostic cutoff point for diabetes (6.0 to <6.5%) are at very high risk of developing diabetes. Undeniably, the incidence of diabetes in individuals with HbA1c levels in this range has been found to be more than 10 times those with lower levels. However, the above range fails to identify a substantial number of patients who have IFG and/or IGT. Indeed, various prospective studies have reported that individuals with HbA1c in the range of 5.5–6.0% have a 5-year cumulative incidence of diabetes that ranges from 12 to 25%.

The data from the National Health and Nutrition Examination Survey indicated that the HbA1c value that most accurately identified individuals with IFG or IGT was between 5.5 and 6.0%. Moreover, evidence from the Diabetes Prevention Program (DPP), wherein the mean HbA1c was 5.9% (standard deviation 0.5%), indicated that preventive interventions were effective in individuals with HbA1c levels both below and above 5.9%. From the above data, it has been suggested that the most appropriate HbA1c level above which to initiate preventive interventions is likely to be somewhere in the range of 5.5–6%.

As was the case with FPG and 2-hour post glucose load PG, defining a lower limit of an intermediate category of HbA1c is somewhat arbitrary, as the risk of diabetes with any measure or surrogate of glycemia is a continuum, extending well into the normal ranges. Several analysts suggested that an HbA1c of 5.7% is associated with similar diabetes risk to the high-risk participants in the DPP. Hence, it is reasonable to consider an HbA1c range of 5.7–6.4% as identifying individuals with high risk for future diabetes, to whom the term prediabetes may be applied (Fig. 2).

Question What is the importance of screening in diabetes mellitus?

The goal of any screening program is to identify asymptomatic individuals who are likely to have the disease. Separate diagnostic tests using standard

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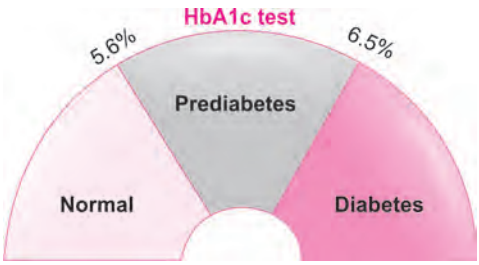

HbA1c, glycosylated hemoglobin.

FIGURE 2: Screening criteria using glycosylated hemoglobin

criteria are required after positive screening tests to establish a definitive diagnosis.

Generally, screening in asymptomatic populations is appropriate when the following conditions are met:

1. The disease represents an important health problem posing a significant burden on the population
2. The natural history of the disease is understood
3. There is a recognizable preclinical (asymptomatic) stage during which the disease can be diagnosed
4. Tests are available that can detect the preclinical stage of the disease, and the tests are acceptable and reliable
5. Treatment after early detection yields benefits superior to those obtained when treatment is delayed
6. The costs of case finding and treatment are reasonable and are balanced in relation to health expenditures as a whole, and facilities and resources are available to treat newly diagnosed cases, and
7. Screening will be a systematic ongoing process and not merely an isolated one-time effort.

Points 1–4 can easily be identified with a disease like diabetes. However, points 5–7 cannot be met completely as no randomized clinical trials document the effectiveness of screening programs in decreasing mortality and morbidity from diabetes. Moreover, there is a controversy regarding the cost-effectiveness of screening and whether screening as currently carried out is a systematic and ongoing process.

Additionally, it is also recognized that treating diabetes diagnosed through standard clinical practice definitely reduces diabetic microvascular complications, however, it has not been established that additional years of treatment that might be received by individuals diagnosed through screening would result in clinically meaning improvements in diabetes-related outcomes. A large clinical trial is underway to find out whether appropriate therapeutic interventions in patients with IGT or IFG detected through a screening program will reduce the incidence of T2DM.

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Question What is prediabetes?

"Prediabetes" is the term used for individuals with IFG and/or IGT,indicating the relatively high risk for the future development of diabetes. IFG and IGT should not be viewed as clinical entities on their own, but rather risk factors for diabetes and cardiovascular disease. IFG and IGT are associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low high density lipoprotein (HDL) cholesterol, and hypertension. Box 2 summarizes the categories of prediabetes.

Question Who all are at risk of diabetes?

- Family history of diabetes (i.e., parents or siblings with diabetes)
- Overweight (Body mass index ≥25 kg/m^2)
- Habitual physical inactivity
- Race/ethnicity (e.g., African-Americans, Hispanic-Americans, Native Americans, Asian-Americans, and Pacific Islanders)
- Previously identified IFG or IGT
- Hypertension (≥140/90 mmHg in adults)
- HDL cholesterol less than or equal to 35 mg/dL (0.90 mmol/L) and/or a triglyceride level more than or equal to 250 mg/dL (2.82 mmol/L)
- History of gestational diabetes mellitus (GDM) or delivery of a baby weighing more than 4.08 kg
- Polycystic ovary syndrome.

Question What are the recommendations for evaluation of high-risk individuals?

As discussed in detail later, because of low cost effectiveness of community screening for diabetes, the decision to test for diabetes should ultimately be based on clinical judgment and patient preference.

- Evaluation for T2DM should be performed in a health care set up. Patients should be screened at 3-year interval beginning at the age of 45 years;

BOX 2: Categories of prediabetes*

Fasting plasma glucose >100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L)—Impaired fasting glucose

OR

2-hour post glucose load plasma glucose in the 75 g oral glucose tolerance test >140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L)—Impaired glucose tolerance

OR

Glycosylated hemoglobin >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.

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testing should be considered at an earlier age or be carried out more frequently, if diabetes risk factors are present

- Any individual presenting with symptoms of marked hyperglycemia, including polyuria, polydipsia, weight loss (sometimes with polyphagia), and blurred vision, should have diagnostic testing for diabetes, as should those with potential complications of diabetes or with any other clinical presentation in which diabetes is included in the differential diagnosis. Such diagnostic testing, however, does not constitute screening
- Consistent with screening recommendations for adults, testing to detect T2DM and prediabetes should be considered in children and adolescents who are overweight and who have two or more additional risk factors for diabetes .Testing should be done every 3 years starting at the age of 10 years or at the onset of puberty, if it occurs at a younger age
- Testing for type 1 diabetes mellitus (T1DM) has been dealt elsewhere in the chapter
- Testing should also be done in the presence of any of the risk factors present.

Question What is community screening?

Although risk factors that predispose the individuals to development of diabetes are clearly defined, the cost effectiveness of a community screening program in reducing the morbidity and mortality associated with diabetes in presumably healthy individuals has not been established.

Screening outside a health care set up, i.e., community screening may also be less effective because of the failure of people with a positive screening test to seek and obtain appropriate follow-up testing and care or, conversely, to ensure appropriate repeat testing for individuals who screen negative. Community screening may also be poorly targeted, i.e., it may fail to reach the groups most at risk and inappropriately test those at low risk or even those already diagnosed.

Community screening, however, may be helpful in improving public awareness of the nature of the disease and its complications. Therefore, other less costly approaches may be more appropriate, particularly because the potential risks are poorly defined. Hence, on the basis of insufficient scientific evidence, community screening for diabetes, even in high-risk populations, is not recommended.

Question When to screen patients for type 1 diabetes mellitus?

Type 1 diabetic patients often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and some cases are diagnosed with life threatening ketoacidosis. Although there is evidence to suggest that early

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diagnosis may limit acute complications and extend long-term endogenous insulin production, there is currently a lack of consensus on accepted screening programs. One can, however, consider referring relatives of those with T1DM for antibody testing for risk assessment in the setting of a clinical research study.

Widespread clinical testing of asymptomatic low-risk individuals is not currently recommended. Higher-risk individuals may be screened, but only in the context of a clinical research setting. Individuals who screen positive should be counseled about the risk of developing diabetes, diabetes symptoms, and the prevention of diabetic ketoacidosis. Numerous clinical studies are being conducted to test various methods of preventing T1DM in those with evidence of autoimmunity (www.clinicaltrials.gov).

Question What are the recommendations for screening type 2 diabetes mellitus in children?

The last decade has witnessed a dramatic increase in the incidence of T2DM in the adolescents. Consistent with the adult recommendations, children and youth at increased risk for the presence or the development of T2DM should be tested within a health care set up. Recent research does not establish the validity of HbA1c in the pediatric population, especially in ethnic minorities, and suggest OGTT or FPG as more suitable diagnostic tests.

The American Diabetes Association, however, recognizes the limited data supporting HbA1c for diagnosing diabetes in children and adolescents. Apart from rare situations, such as cystic fibrosis and hemoglobinopathies, ADA continues to recommend HbA1c in this population. The modified recommendations of the ADA consensus statement "T2DM in children and adolescents" are listed below.

- Testing should be done at the age of 10 years or at the onset of puberty, if puberty occurs at a younger age
- Testing should be done at an interval of 3 years
- Testing to detect T2DM and prediabetes should be considered in children and adolescents (18 years or younger) who are overweight and who have two or more additional risk factors for diabetes
- Family history of T2DM 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.

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Question How to screen women for gestational diabetes mellitus?

For many decades, GDM was defined as any degree of glucose intolerance with onset or first recognition during pregnancy. This glucose intolerance was irrespective of whether or not the condition persisted after pregnancy, and not excluding the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. Although this definition provided a simple and uniform approach for detection and classification of GDM, its limitations were recognized for many years. Due to the increasing prevalence of diabetes, more women with T2DM in the child bearing age are being diagnosed along with an increase in the number of pregnant women with undiagnosed T2DM. Hence, it is rational practice to screen women with risk factors for T2DM at their initial prenatal visit, using standard diagnostic criteria. Women with diabetes in the first trimester should receive a diagnosis of overt diabetes, not GDM.

Screening and diagnosis of gestational diabetes mellitus

Screening for GDM can be done by two methods:

"One-step" (The International Association of the Diabetes and Pregnancy Study Groups consensus)

Perform a 75 g OGTT, with PG measurement fasting and at 1 and 2 hours, 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 hours.

The diagnosis of GDM is made when any of the following PG values are exceeded:

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

"Two-step" (The National Institutes of Health consensus)

Perform a 50 g glucose load test (nonfasting), with PG measurement at 1 hour (Step 1) at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

If the PG level measured 1 hour after the load is ≥140 mg/dL (7.8 mmol/L), proceed to100 g OGTT (Step 2). The 100 g OGTT should be performed when the patient is fasting. The American College of Obstetricians and Gynecologists recommends a lower threshold of 135 mg/dL(7.5 mmol/L) in high-risk ethnic minorities with higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).

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TABLE 2: Diagnosis of gestational diabetes mellitus

	Carpenter-Coustan criteria	National diabetes data group criteria
Fasting	95 mg/dL (5.3 mmol/L)	105 mg/dL (5.8 mmol/L)
1 hour	180 mg/dL (10.0 mmol/L)	190 mg/dL (10.6 mmol/L)
2 hours	155 mg/dL (8.6 mmol/L)	165 mg/dL (9.2 mmol/L)
3 hours	140 mg/dL (7.8 mmol/L)	145 mg/dL (8.0 mmol/L)

The diagnosis of GDM is made when at least two of the following four PG levels (measure fasting, 1, 2, and 3 hours after the OGTT) are met or exceed (Table 2):

Following are the recommendations given by ADA for screening of GDM:

- Screen for undiagnosed T2DM at the first prenatal visit in those with risk factors, using standard diagnostic criteria
- Screen for GDM at 24–28 weeks of gestation in pregnant women not previously known to have diabetes
- Screen women with GDM for persistent diabetes at 6–12 weeks postpartum, using the OGTT and nonpregnancy diagnostic criteria
- Women with a history of GDM should have lifelong screening for the development of diabetes or prediabetes at least every 3 years
- Women with a history of GDM, found to have prediabetes, should receive lifestyle interventions or metformin to prevent diabetes
- Further research is needed to establish a uniform approach for diagnosing GDM.

Question What are the risks associated with gestational diabetes mellitus?

Since glucose crosses the placenta freely from the maternal to the fetal compartment, untreated maternal hyperglycemia exposes the fetus to higher glucose concentrations. This in turn stimulates the production of insulin from the fetal pancreas. Fetal macrosomia then occurs, either because of the excessive fat deposition or as a direct growth-stimulating effect of insulin. A strong correlation had been observed between mean maternal PG levels and fetal blood insulin levels for neonatal birth weight.

Fetal macrosomia increases the risk of birth trauma and delivery by cesarean section. Apart from this, a variety of comorbid conditions are seen at a higher frequency in women with GDM; these include hypertensive disorders during pregnancy including pre-eclampsia and eclampsia. GDM can also result in long-term health risks to both the mother and baby (Table 3). The link between GDM and postpartum diabetes in the mother has long been recognized.

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TABLE 3: Maternal and fetal/neonatal risk associated with gestational diabetes mellitus

Maternal	Fetal	Neonatal	Childhood and beyond
Trauma during birth due to fetal macrosomia	Macrosomia	Hypoglycemia	Weight gain, obesity
Increased chances of cesarean delivery	Birth trauma	Hyperbilirubinemia	T2DM
Risk of developing T2DM in the future	Cardio-myopathy	Respiratory distress syndrome	Metabolic abnormalities
Associated comorbidities i.e., hypertension	Stillbirth	Polycythemia and dyselectrolytemias, such as hypocalcemia and hypomagnesemia	–

T2DM; type 2 diabetes mellitus

Question Should women with gestational diabetes mellitus be followed postpartum?

Women with GDM should definitely be followed postpartum as some of them may represent pre-existing undiagnosed T2DM. Women with a history of GDM should be screened for diabetes 6–12 weeks postpartum, using nonpregnant OGTT criteria. Use of HbA1c in the diagnosis of persistent diabetes is not recommended at the postpartum visit because of the treatment of hyperglycemia given during pregnancy.

As women with a history of GDM are at an increased risk of diabetes subsequently and should be followed up with subsequent screening for the development of diabetes or prediabetes.

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