CLINICAL PRACTICE

# Diagnosis of Diabetes

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*This* Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A 42-year-old asymptomatic man with hypertension presents for his annual physical examination. His medications include atenolol combined with chlorthalidone (at doses of 50 mg and 25 mg, respectively, per day). Both parents had type 2 diabetes mellitus later in life. He does not smoke cigarettes. His body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) is 32.3, and his blood pressure is 130/80 mm Hg. Would you screen the patient for diabetes, and if so, how?**

## THE CLINICAL PROBLEM

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Type 2 diabetes is a complex disease that is typically diagnosed in midlife and is characterized by progressive defects in insulin secretion and action. In the context of increased caloric intake and decreased activity levels in Westernized societies, the prevalence of type 2 diabetes continues to climb. According to the Centers for Disease Control and Prevention, 25.8 million persons in the United States (or 8.3% of the population) have the disease, which is diagnosed in approximately 2 million persons each year.[1] Diabetes is usually silent in its initial stages, and irreversible complications may develop before treatment is begun.[2] Data from randomized trials indicate that early and aggressive antihyperglycemic therapy significantly reduces the risk of long-term microvascular complications.[2,3] Although the effects of tight glucose control on macrovascular disease are less clear,[4] the diagnosis of diabetes in a patient provides the opportunity to apply evidence-based strategies for reducing cardiovascular risk, such as the management of blood pressure and lipid levels.

Type 2 diabetes is preceded by a lengthy asymptomatic stage, termed prediabetes, which is characterized by mild hyperglycemia, insulin resistance, and early decrements in insulin secretory capacity. Data from randomized trials show that progression to diabetes from this at-risk stage can be reduced through lifestyle modification.[5,6] The identification of persons with prediabetes, who are now estimated to number 79 million in the United States,[1] allows for the introduction of interventions to reduce risk.

*An audio version of this article is available at NEJM.org*

## STRATEGIES AND EVIDENCE

### SCREENING FOR DIABETES

The American Diabetes Association (ADA)[7] and the Veterans Health Administration (VHA)[8] recommend diabetes screening beginning at 45 years of age; the ADA advises earlier screening in patients with risk factors (Table 1). In contrast, routine screening is not recommended by the U.S. Preventive Services Task Force (USPSTF),[9] given the absence of rigorous data to show that screening and early treatment improve outcomes; this group recommends screening only in asymptomatic adults with a sustained blood pressure greater than 135/80 mm Hg — mainly because of lower blood-pressure targets once the diagnosis of diabetes is established.

KEY CLINICAL POINTS

**DIAGNOSIS OF DIABETES**

- Early screening and diagnosis allow for the identification of at-risk persons (so that preventive measures, primarily lifestyle changes, may be undertaken) and those with early disease (so that treatment can be initiated).
- The diagnostic cutoff point for diabetes is a fasting plasma glucose level of 126 mg per deciliter (7.0 mmol per liter) or more or a glycated hemoglobin level of 6.5% or more; the diagnosis requires confirmation by the same or the other test.
- A fasting glucose level of 100 to 125 mg per deciliter (5.6 to 6.9 mmol per liter) is consistent with prediabetes; the range of glycated hemoglobin levels that are diagnostic of prediabetes is controversial, but the American Diabetes Association recommends a range of 5.7 to 6.4%.
- Hemoglobinopathies and conditions of altered red-cell turnover can give spurious results for glycated hemoglobin; racial and ethnic differences in glycated hemoglobin levels have been reported for given ambient glucose levels.
- Testing of glycated hemoglobin or fasting plasma glucose appears to identify different groups of patients with diabetes and prediabetes, yet both tests identify patients at similar risk for adverse sequelae.

## DIAGNOSIS OF DIABETES

### *Glucose Levels*

Before 1997, the diagnosis of diabetes was defined by the ADA and the World Health Organization (WHO) as a fasting plasma glucose level of 140 mg per deciliter (7.8 mmol per liter) or more or a 2-hour plasma glucose level of 200 mg per deciliter (11.1 mmol per liter) or more during an oral glucose-tolerance test (OGTT) conducted with a standard loading dose of 75 g. This definition was based on earlier recommendations from the National Diabetes Data Group.[10] These values were originally chosen on the basis of the risk of future symptoms of uncontrolled hyperglycemia. In 1997, with recommendations from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus,[11] the ADA and the WHO[12] lowered the diagnostic threshold to a fasting plasma glucose level of 126 mg per deciliter (7.0 mmol per liter) — the level at which a unique microvascular complication of diabetes, retinopathy, becomes detectable. The OGTT identifies more patients as having diabetes than the fasting plasma glucose test, but the former test has drawbacks, including greater expense and complexity and lower reproducibility. Thus, the fasting plasma glucose test has been the preferred test in the United States. The diagnosis is confirmed by repeat testing on a separate day. In symptomatic patients, a random plasma glucose level of 200 mg per deciliter or more also establishes the diagnosis and does not require confirmation.

The only recognized at-risk category for diabetes before 1997 was impaired glucose tolerance, as identified on the basis of a 2-hour plasma glucose level of 140 to 199 mg per deciliter (7.8 to 11.0 mmol per liter) during an OGTT. With the revised 1997 criteria, a corresponding state was identified on the basis of the fasting plasma glucose level: impaired fasting glucose. Although the original criterion for this diagnosis was a fasting glucose level of 110 to 125 mg per deciliter (6.1 to 6.9 mmol per liter),[11] this criterion was later lowered by the ADA (but not by the WHO) to 100 to 125 mg per deciliter (5.6 to 6.9 mmol per liter) to increase sensitivity (with an acceptable drop in specificity) for persons with an increased diabetes risk.[13]

Longitudinal investigations have shown that persons categorized as being "impaired" by any of these definitions have approximately a 5 to 10% annualized risk of diabetes, a risk that is greater by a factor of approximately 5 to 10 than that among persons with normal glucose tolerance or normal fasting glucose. Risks appear to be similar among persons with isolated impaired fasting glucose (i.e., without impaired glucose tolerance) and isolated impaired glucose tolerance (without impaired fasting glucose).[14] However, the proportion of patients with impaired glucose tolerance tends to be greater than that with impaired fasting glucose in most populations. Persons with both impaired fasting glucose and impaired glucose tolerance have a higher risk of diabetes (approximately 10 to 15% per year) than those with only one abnormality. Whereas both prediabetic states are associated with increased total and cardiovascular mortality, impaired glucose

**Table 1. American Diabetes Association Recommendations for the Screening of Asymptomatic Persons for Diabetes.***

| |
|---|
| Screen beginning at 45 yr of age, at least every 3 yr |
| Screen at any age and more frequently if the body-mass index is 25 or more and if the person has at least one additional risk factor: |
| Family history of diabetes (first-degree relative) |
| High-risk race (e.g., black, Native American, Asian, and Pacific Islander) or ethnic group (Hispanic) |
| Glycated hemoglobin level of 5.7% or more or impaired fasting glucose or impaired glucose tolerance on previous testing |
| History of gestational diabetes or delivery of a baby weighing more than 9 lb (4.1 kg) |
| The polycystic ovary syndrome |
| Hypertension (blood pressure ≥140/90 mm Hg; or therapy for hypertension) |
| HDL cholesterol level of less than 35 mg per deciliter (0.91 mmol per liter), triglyceride level of more than 250 mg per deciliter (2.8 mmol per liter), or both |
| History of cardiovascular disease |
| Physical inactivity |
| Other clinical conditions associated with insulin resistance (e.g., severe obesity and acanthosis nigricans) |

* Data are adapted from the American Diabetes Association.[7] HDL denotes high-density lipoprotein.

tolerance tends to be a better predictor than impaired fasting glucose.[14]

*Glycated Hemoglobin*

Glycated hemoglobin has long been used in the management of established diabetes as a biomarker of long-term glycemic control. Levels of this end product of nonenzymatic glycation of the most prevalent protein in blood correlate well (though not perfectly) with average ambient blood glucose levels during the previous 2 to 3 months. Until recently, the lack of international standardization made glycated hemoglobin testing a suboptimal choice for diabetes screening. However, the glycated hemoglobin test is now globally standardized, so clinical laboratory results are comparable to those reported in the Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study, two trials that validated the direct relationship between glycated hemoglobin levels and clinical outcomes in patients with type 1 and 2 diabetes, respectively.[15] In response, in 2009, the International Expert Committee (IEC) recommended the use of this test for the diagnosis of diabetes, with a threshold level of 6.5%.[16] This recommendation was based on the observation that the 6.5% threshold was as accurate in indicating a risk of retinopathy as were cutoff points for fasting plasma glucose and 2-hour plasma glucose, combined with the recognized advantages of glycated hemoglobin testing (Table 2), particularly the fact that fasting is not required. The measurement of glycated hemoglobin for diabetes diagnosis was subsequently adopted as an optional test by the ADA (in 2010)[18] and the WHO (in 2011).[19]

On the basis of data showing an increased risk of diabetes among persons with increased glycated hemoglobin levels that were still below the cutoff point for diabetes, the ADA also defined a prediabetic glycated hemoglobin range of 5.7 to 6.4%, which was an expansion of the original recommendation by the IEC that levels of 6.0% to 6.4% be considered high risk.[16,18] In contrast to the risk of retinopathy, which abruptly increases at a well-defined glycated hemoglobin level, the risk of diabetes increases along a glycemic continuum. As with fasting plasma glucose and 2-hour plasma glucose, the lower bound for such a range in glycated hemoglobin values must balance adequate sensitivity (to include persons who would benefit from prevention strategies) with specificity (to avoid the inclusion of persons at relatively low absolute risk, for whom intervention may not be cost-effective). The selected range described a group of persons with at least five times the risk of diabetes developing over a period of 5 to 10 years (and an annualized incidence of at least 5% per year) as compared with those with a glycated hemoglobin level of less than 5%. Logically, the risk increases further as a glycated hemoglobin level of 6.5% is approached, with a comparative relative

**Table 2. Advantages and Disadvantages of Screening Tests for Diabetes.***

| Testing Method | Advantages | Disadvantages |
|---|---|---|
| Fasting plasma glucose | Extensive experience, widespread availability, low cost | Fasting required, reflects glycemia solely at moment of sampling, substantial biologic variability, potential influence of acute illness, sample instability in vial, lack of global standardization |
| Oral glucose-tolerance test | Most sensitive test, earliest marker of glucose dysregulation | Fasting required, substantial biologic variability, poor reproducibility from day to day, lack of association of results with complications over time, sample instability in vial, more time required, inconvenience, higher cost, lack of global standardization of plasma glucose measurements |
| Glycated hemoglobin | Fasting not required, low biologic variability, marker of long-term glycemia, stable during acute illness, sample stability in vial, global standardization, close association of results with complications | Lack of reliability in patients with hemoglobinopathies (e.g., sickle cell disease and thalassemia, usually with reduced levels), unreliability in certain anemias with high red-cell turnover (e.g., hemolytic anemia, usually with reduced levels) or low red-cell turnover (e.g., iron deficiency, usually with increased levels), lack of reliability after recent transfusion (in the previous 2 to 3 mo), falsely low results in advanced (stage 4 or 5) renal disease, racial and ethnic differences (e.g., slightly higher in blacks), possibility of a glycation gap (differential glycation in response to the same ambient glucose exposure between persons), higher cost, lack of global availability |

* Data are adapted from Sacks.[17]

risk in excess of a factor of 10 (and an annualized incidence of 5 to 10% per year).[20] The risk of diabetes at any given glycated hemoglobin level increases with the presence of other risk factors (e.g., obesity and a family history of diabetes).

Despite some advantages, the use of glycated hemoglobin testing has its limitations.[17] Depending on the assay, spuriously low values may occur in patients with certain hemoglobinopathies (e.g., sickle cell disease and thalassemia) or who have increased red-cell turnover (e.g., hemolytic anemia and spherocytosis)[21] or stage 4 or 5 chronic kidney disease, especially if the patient is receiving erythropoietin.[22] In contrast, falsely high glycated hemoglobin levels have been reported in association with iron deficiency and other states of decreased red-cell turnover.[23] Some investigators have reported a "glycation gap," or different glycated hemoglobin levels in patients with the same mean ambient blood glucose levels.[24] This phenomenon may result from genetically determined altered access of glucose to the intracellular compartment (where hemoglobin resides), although this hypothesis is controversial.[25] Inconsistencies in the correlations between glycated hemoglobin and other measures of ambient glycemia have also been reported in different ethnic and racial groups, findings that suggest genetic influences on hemoglobin glycation. For example, blacks appear to have slightly higher glycated hemoglobin levels (an absolute increase of 0.2 to 0.3 percentage points) than whites.[26] It is unclear whether this observation reflects differences in rates of postprandial hyperglycemia or in glycation rates.[27] These potential pitfalls must be recognized when glycated hemoglobin testing is used for diagnosis, especially for prediabetes, since the cutoff points for this state are already somewhat arbitrary.

In most studies, glycated hemoglobin testing identifies fewer patients with diabetes than does testing for fasting plasma glucose or 2-hour plasma glucose.[28-31] These measures may also identify distinct patients as having diabetes — groups that overlap only partially. For example, in a population-based study of U.S. adults without known diabetes, the proportions of patients with an abnormal fasting plasma glucose level (≥126 mg per deciliter) and a nondiabetic glycated hemoglobin level (<6.5%), a nondiabetic fasting plasma glucose level (<126 mg per deciliter) and an abnormal glycated hemoglobin level (≥6.5%), or both abnormalities were 1.8%, 0.5%, and 1.8%, respectively.[28] Moreover, in a prospective cohort study of older U.S. adults, roughly one third of cases of newly identified diabetes were detected by fasting plasma glucose testing only, one third by glycated hemoglobin testing only, and the remainder by both tests.[26] Furthermore, persons identified as having diabetes by glycated hemoglobin levels only were more likely to be black than those identified with the use of glucose levels.[26,28,29] Clearly, a move to increase the use of

glycated hemoglobin testing for screening would affect the epidemiology of diabetes.[32,33] Similar patterns have been reported for the diagnosis of prediabetes with glycated hemoglobin versus fasting plasma glucose.[29,32,33] Although these findings have led some observers to question the use of glycated hemoglobin for diagnostic purposes,[34,35] these questions are counterbalanced by the absence of an absolute standard measurement for the diagnosis of diabetes and the observation that all methods in use correlate equally well with retinopathy risk.[36]

*Combined Screening*

An alternative but more costly option, which has been proposed by several investigators,[37-40] is to measure both glycated hemoglobin and fasting plasma glucose, either simultaneously or in sequence, a strategy that might be considered for patients at highest risk. (In practice, fasting plasma glucose may have been checked as part of a routine blood chemical profile in patients who are being screened with glycated hemoglobin testing.) Given the different yields of these two measures, this approach is likely to capture substantially more patients than the use of either test in isolation.

When the results of two tests are available but discordant, a reasonable and cautious approach is to let the abnormal test result (if repeated and confirmed) guide categorization, as recommended by the ADA.[18] In this context, the nondiagnostic result usually is close to the abnormal range. However, if results are more widely discrepant (e.g., a fasting plasma glucose level of 123 mg per deciliter [6.8 mmol per liter] but a glycated hemoglobin level of 5.1%), repeat testing is indicated. In some cases, transient aberrations in glucose levels (as with acute illness) or abnormally low or high glycation rates may underlie such incongruities. An OGTT might be helpful in certain cases.

## DIABETES PREVENTION

The identification of any prediabetic state warrants education of the patient regarding diabetes risk as well as lifestyle measures that may be undertaken to mitigate this risk. Two large clinical trials have shown the effectiveness of intensive lifestyle interventions in high-risk patients (overweight or obese with impaired glucose tolerance), with a relative risk reduction of 58% in the diagnosis of diabetes during a 3-year period.[5,6] The specific intervention in the largest study, the Diabetes Prevention Program (DPP), involved regular aerobic exercise (at least 30 minutes on most days of the week) and a calorie-restricted diet to promote the loss of 7% of body weight.[5] Metformin was also tested in the DPP; the relative risk reduction with this drug (31%) was approximately half that with lifestyle intervention, and the drug appeared to be particularly effective in patients under the age of 60 years, with a BMI over 35 and with a fasting plasma glucose level over 110 mg per deciliter.[5,41] Other glucose-lowering or antiobesity agents (i.e., acarbose, rosiglitazone, pioglitazone, and orlistat) have also been shown in randomized trials to reduce the risk of diabetes.[42] All drugs have important side effects to consider, and none are approved by the Food and Drug Administration (FDA) for this indication.

## AREAS OF UNCERTAINTY

Although it appears logical to screen high-risk patients for dysglycemia, data are lacking to show that diabetes screening (outside of pregnancy) improves more than biochemical outcomes. The choice of a preferred screening test (fasting plasma glucose or glycated hemoglobin) remains arguable. In the United States, the OGTT has largely been abandoned outside of screening for gestational diabetes, owing to its complexity and low reproducibility.

It is unclear whether the risk of complications of diabetes differs according to whether the disease was diagnosed by means of fasting plasma glucose testing only or glycated hemoglobin testing only. Preliminary data from a large, community-based prospective cohort study suggest that the glycated hemoglobin level, which integrates fasting and postprandial glucose levels over a longer period, might be a better predictor of certain complications — especially cardiovascular disease.[43] It is also not known whether the risk of diabetes differs between patients identified as having prediabetes by means of glycated hemoglobin testing and those identified by means of fasting plasma glucose testing. Such risks probably vary according to which test is used ultimately to make the diagnosis. Ongoing research is assessing the value of risk scores that incorporate not only glycemic measures but also other biomarkers and risk factors to estimate diabetes risk.[44,45]

Other ambiguities relate to treatment strategies for patients in whom prediabetes has been

**Table 3. Major Diagnostic Criteria for Diabetes and Prediabetic or At-Risk States.***

| Measure | American Diabetes Association | | World Health Organization | |
|---|---|---|---|---|
| | Diabetes | Prediabetes | Diabetes | Impaired Glucose Regulation |
| Fasting plasma glucose | ≥126 mg/dl | 100–125 mg/dl (IFG) | ≥126 mg/dl | 110–125 mg/dl (IFG) |
| 2-Hr plasma glucose (during an OGTT with a loading dose of 75 g) | ≥200 mg/dl | 140–199 mg/dl (IGT) | ≥200 mg/dl | 140–199 mg/dl (IGT) |
| Casual (or random) plasma glucose (in a patient with classic hyperglycemic symptoms) | ≥200 mg/dl | | ≥200 mg/dl | |
| Glycated hemoglobin | ≥6.5% | 5.7–6.4% | ≥6.5% | |

* Data are adapted from the American Diabetes Association,[7,18] Alberti and Zimmet,[12] and the World Health Organization.[19] All listed plasma glucose levels are based on venous sampling. All tests (except for casual plasma glucose in a symptomatic patient) should be repeated and confirmed on a separate day. (The American Diabetes Association allows for glycated hemoglobin testing to be paired with fasting plasma glucose testing on the same day. If the values for both tests are in the diabetic range, the diagnosis is confirmed.) To convert the values for glucose to millimoles per liter, multiply by 0.05551. IFG denotes impaired fasting glucose, IGT impaired glucose tolerance, and OGTT oral glucose-tolerance test.

diagnosed. Do lifestyle or pharmacologic interventions in these patients truly prevent diabetes or simply delay its onset? Given the cumulative vascular risk associated with diabetes and the potential legacy effect of glycemic control (long-term benefit from early metabolic stability), even a modest delay of a few years in the onset of diabetes may be a worthwhile goal. However, diabetes-prevention trials to date[7,8] have focused on glycemic end points and were not powered to assess diabetes-related complications. Recent data suggest that generic metformin therapy may be particularly cost-effective in this context,[46] but the long-term benefits and risks of this or other medications (or bariatric surgery) are uncertain. There are also uncertain consequences of designating a risk factor (e.g., high fasting plasma glucose) as a disease state.

## GUIDELINES

ADA[7,18] recommendations for diabetes screening are summarized in Table 1; the ADA diagnostic criteria are listed in Table 3, along with those of the WHO.[19] As mentioned, the USPSTF recommends screening only in adults with hypertension (blood pressure, >135/80 mm Hg).[9] The American Association of Clinical Endocrinologists (AACE),[47] the VHA,[8] and the WHO use the ADA criteria for diabetes; the AACE advises confirmation with fasting plasma glucose testing when the diagnosis is made on the basis of glycated hemoglobin testing. For the identification of prediabetes, the ADA is the sole group to fully endorse glycated hemoglobin testing, with a cutoff range of 5.7 to 6.4%[7,18] and no recommended confirmatory testing. The AACE allows for the use of glycated hemoglobin testing to screen for prediabetes but stipulates the need for follow-up testing of fasting plasma glucose for those with values of 5.5 to 6.4%.[47]

## CONCLUSIONS AND RECOMMENDATIONS

The identification of patients with diabetes or prediabetes by screening allows for earlier intervention, with potential reductions in future complication rates, although randomized trials are lacking to definitively show benefit. The patient described in the vignette has risk factors (obesity, hypertension, and a family history of diabetes) and should be screened. Whether fasting plasma glucose or glycated hemoglobin is measured remains debatable; each test has advantages and disadvantages (Table 2). Given that the yield of testing is higher when both tests are performed, I typically assess both simultaneously — although most guidelines suggest the use of a single test initially. If the patient has positive results on both tests, the diagnosis is confirmed. If only one test is positive, I would repeat it on a separate day. If diabetes is confirmed, treatment should be initiated on the basis of current guidelines (see Fig. 1 for a proposed screening algorithm).[48,49]

If prediabetes is identified, a repeat test is not necessary. Lifestyle changes (diet and exercise) should be encouraged; a greater intensity of inter-

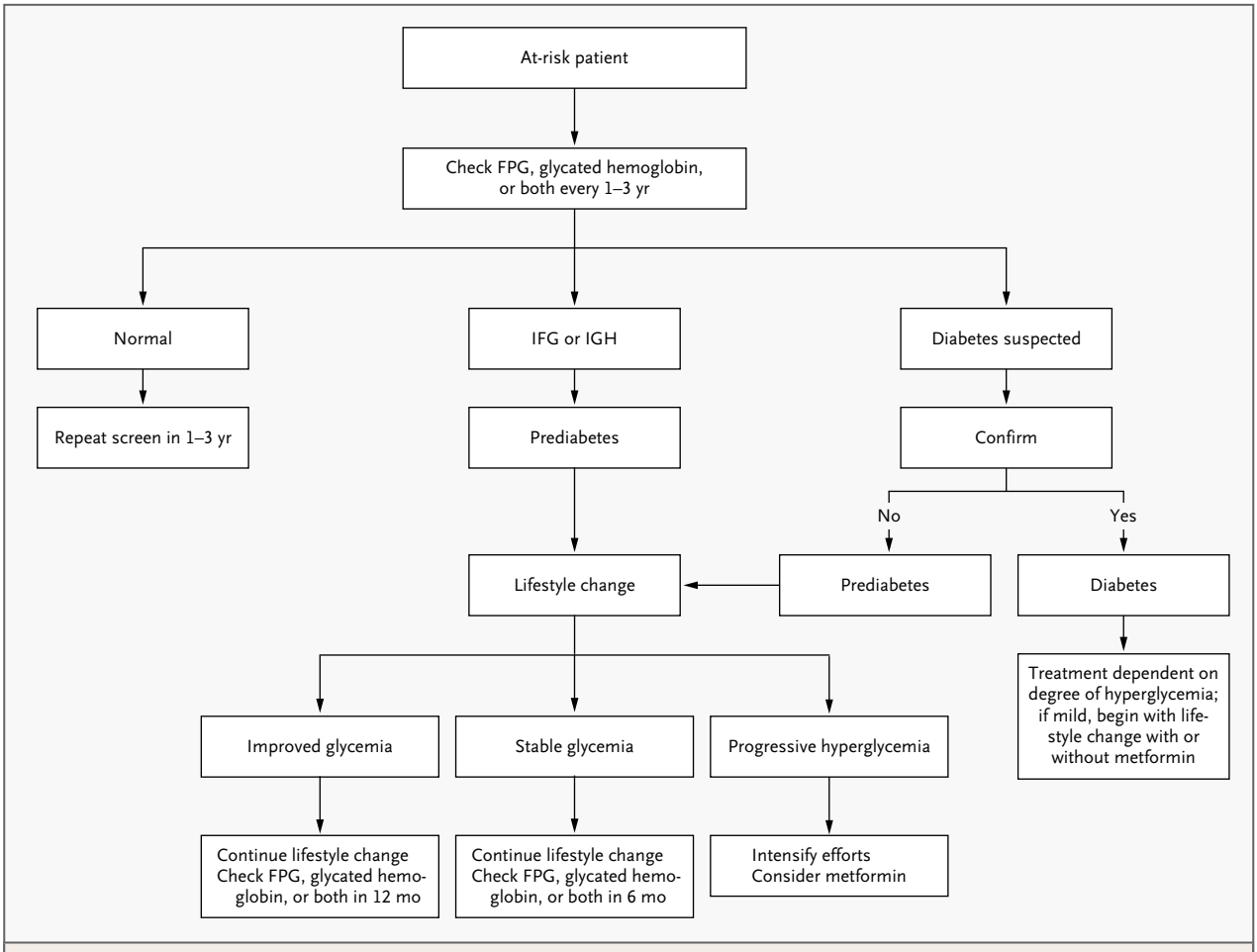


**Figure 1. Suggested Approach to Screening Patients at Risk for Diabetes.**

Impaired fasting glucose (IFG) is defined as a fasting plasma glucose (FPG) level of 100 to 125 mg per deciliter (5.6 to 6.9 mmol per liter). Increased glycated hemoglobin (IGH) is defined as a glycated hemoglobin level of 5.7 to 6.4%. The diagnosis of diabetes is confirmed with a repeat test on a separate day or by the alternative test (i.e., glycated hemoglobin instead of FPG or vice versa) on the same day or a separate day. If the result of the repeat test is in the prediabetic range, the patient should be counseled or treated for prediabetes. If the result of the repeat test is entirely normal (which is unlikely), rescreening in 6 months should be considered. Therapeutic lifestyle change is defined as a hypocaloric diet, weight reduction, and increased physical activity.

vention may be warranted in patients with higher glucose or glycated hemoglobin levels and with additional risk factors, since such findings predict more rapid progression to diabetes. I might consider metformin if progressive increases in glycemic measures were observed during follow-up, although the FDA has not approved metformin for this indication. Attention should also be paid to other cardiovascular risk factors. I might change the patient's antihypertensive therapy to an angiotensin-converting–enzyme inhibitor, given the associations between the use of a beta-blocker or thiazide and an increased risk of diabetes in some studies.[50] Periodic visits (every 6 to 12 months) are warranted to assess and encourage adherence to lifestyle recommendations and to follow glycemic status.

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