How Do We Diagnose Diabetes and Measure Blood Glucose Control?

View 1 (Diagnosing)
A Clinical Basis for the Diagnosis of Diabetes

In Brief

In 1979, criteria for the diagnosis of diabetes were selected based on levels of glycemia on the oral glucose tolerance test (OGTT) that were associated with the subsequent development of retinopathy. Since then, five long-term studies have demonstrated that when HbA1c levels are maintained below 7% (normal 6%), development of retinopathy and microalbuminuria is practically nil. Approximately 60% of people with fasting plasma glucose (FPG) concentrations of 126–139 mg/dl and 70% of those with 2-h values on the OGTT of 200–239 mg/dl have normal HbA1c levels, with another third having values between 6 and 7%. This article offers an alternative approach to diagnosis using both FPG and HbA1c values.

Except for a few populations in which the prevalence of diabetes is very high and therefore the distribution of blood glucose concentrations is bimodal,1,2 a unimodal distribution is the norm.3,4 Thus, there is no clear-cut demarcation between normal and abnormal blood glucose concentrations.

Before 1979, there were at least six sets of criteria upon which to base the diagnosis of diabetes. This led to an untenable situation in which the prevalence of diabetes in populations differed and diabetes could be either absent or present in an individual depending on which set of criteria was used.5

In 1979, the National Diabetes Data Group (NDDG) adopted a set of criteria for the diagnosis of diabetes and impaired glucose tolerance (IGT),6 which were slightly modified a year later by the World Health Organization7 (Table 1). An oral glucose tolerance test (OGTT) was administered to 1,277 individuals who were followed for 3–8 years for the subsequent development of diabetic retinopathy. The rationale was that this specific complication of diabetes would identify those subjects whose blood glucose values were high enough to reliably make the diagnosis of diabetes. The criteria in Table 1 were based on the glucose concentrations of only 77 individuals who did subsequently develop this complication.6

Several years ago, the American Diabetes Association (ADA) convened an Expert Committee to reexamine the diagnosis and classification of diabetes in light of new information acquired since the NDDG report.9 One of the goals of the committee was to make the fasting plasma glucose (FPG) and the 2-h blood glucose concentrations on the OGTT criteria equivalent for the diagnosis of diabetes, i.e., if one of these criteria were met, the other would likely be as well. This is not the situation with the

<table>
<thead>
<tr>
<th>Table 1. Previous World Health Organization Criteria for the Diagnosis of (IGT) and Diabetes</th>
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<tr>
<td><strong>FPG</strong></td>
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<tr>
<td>&lt;140 mg/dl</td>
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<tr>
<td>140–199 mg/dl</td>
</tr>
</tbody>
</table>

*2-h plasma glucose concentration following 75 g of oral glucose
two criteria in Table 1. Although ~95% of individuals with an FPG concentration ≥140 mg/dl had a 2-h value on the OGTT ≥200 mg/dl, only one-fourth to one-half of people with 2-h values ≥200 mg/dl had FPG levels ≥140 mg/dl.

The committee also made several other recommendations. Because of its poor reproducibility and limited use in clinical practice, the OGTT was not recommended to be used routinely to diagnose diabetes. (Personally, I agree with that position.)

Table 2. Expert Committee criteria for the diagnosis of diabetes

<table>
<thead>
<tr>
<th>Criteria</th>
<th>No. of Subjects (%)</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl.</td>
<td>Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.</td>
<td>≤6.1 6.2–7.0 ≥7.1</td>
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<tr>
<td>2. FPG ≥126 mg/dl. Fasting is defined as no caloric intake for at least 8 h.</td>
<td>or</td>
<td></td>
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<tr>
<td>3. 2-h plasma glucose ≥200 mg/dl during an OGTT. 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. In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.</td>
<td>or</td>
<td></td>
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The committee decided to retain the 2-h criterion of ≥200 mg/dl because of the many epidemiological studies that used it to define diabetes. Changing it, the committee noted, “would be very disruptive.” The FPG concentration that yields an equivalent prevalence of diabetes diagnosed by a 2-h value on the OGTT of ≥200 mg/dl is 126 mg/dl.

The criteria the committee did recommend for the diagnosis of diabetes are shown in Table 2. They also defined a normal FPG concentration as <110 mg/dl and individuals with FPG concentrations of 110–125 mg/dl as having impaired fasting glucose (IFG).

HbA1c Versus OGTT

If one accepts the logic that the level of glycemia chosen to define diabetes should be one that is associated with the specific complication of diabetic retinopathy (and I do), HbA1c levels are a better measure of glycemia than values on the OGTT for two reasons. First, they reflect months of prevailing glucose concentrations rather than one instance of time. Second, there have been five studies in several thousand diabetic patients carried out over 6–9 years relating the average HbA1c level to the development and progression of the microvascular complications of diabetes.

Table 3. Distribution (%) of HbA1c Levels

<table>
<thead>
<tr>
<th>Glucose (mg/dl)</th>
<th>N H A N E S III</th>
<th>M R G Data Set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Subjects (%)</td>
<td>HbA1c (%)</td>
</tr>
<tr>
<td>Fasting</td>
<td>≤6.1</td>
<td>6.2–7.0</td>
</tr>
<tr>
<td>&lt;110</td>
<td>2,284 (84)</td>
<td>97.3</td>
</tr>
<tr>
<td>110–125</td>
<td>373 (11)</td>
<td>86.7</td>
</tr>
<tr>
<td>126–139</td>
<td>77 (2)</td>
<td>60.9</td>
</tr>
<tr>
<td>≥140</td>
<td>102 (3)</td>
<td>18.6</td>
</tr>
<tr>
<td>2-h OGTT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;140</td>
<td>2,021 (76.2)</td>
<td>97.2</td>
</tr>
<tr>
<td>140–199</td>
<td>554 (17.1)</td>
<td>91.4</td>
</tr>
<tr>
<td>200–239</td>
<td>111 (2.80)</td>
<td>69.4</td>
</tr>
<tr>
<td>≥240</td>
<td>150 (3.9)</td>
<td>40.9</td>
</tr>
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aBased on U.S. population after weighting the surveyed population, which oversampled minorities.

bUpper limit of normal = 6.1%.
cPercent of M R G population.
dUpper limit of normal = 6.3%.
and 20% already have retinopathy. In my view, this argument does not hold. These people remain undiagnosed because they are not evaluated, not because the FPG concentration for diagnosis is too high.

Similarly, the ADA committee included macrovascular disease in its contention that earlier diagnosis and appropriate treatment would decrease the subsequent complications of diabetes. This reasoning is also suspect because the increased risk for coronary artery disease extends all the way down to the highest quartile of normal FPG concentrations. (After this article was submitted, a new study was published of the 4-year incidence of the age-adjusted rate of ischemic heart disease in 4,662 men aged 45–79 years. It revealed a marked increase in the relative risk of those with HbA1c levels ≥5.0% compared with individuals with lesser values, confirming the earlier studies that utilized glucose concentrations.)

Furthermore, improved glycemic control (unfortunately) has little effect on the morbidity and mortality from cardiovascular disease in people with diabetes. A number of other risk factors need addressing, but their prevalences are similar in those with IFG (FPG concentrations of 110–125 mg/dl) and those in the new cohort of diabetes (FPG concentrations of 126–139 mg/dl). Thus, from a macrovascular perspective, there is no advantage in distinguishing between the two groups and labeling people in the latter group as having diabetes.

Not only are HbA1c levels so tightly linked to diabetic retinopathy, nephropathy, and neuropathy, but recent reports have also demonstrated that blocking the production of advanced glycosylation end products beyond the formation of HbA1c (and therefore independent of hyperglycemia) markedly retards the development of these complications.

Given the importance of excessive glycation of proteins in the pathogenesis of the diabetic microvascular and neuropathic complications and the principle that the level of glycaemia associated with these complications is appropriate for the diagnosis of diabetes, an alternative approach to diagnosis, which takes into account these clinical outcomes, is suggested in Figure 1. This diagnostic algorithm uses measurements of FPG concentrations followed by HbA1c levels in people whose FPG values are neither normal (<110 mg/dl) nor meet the older criterion for the diagnosis of diabetes (≥140 mg/dl). The HbA1c level determines whether an individual with an FPG concentration of 110–139 mg/dl has diabetes or a milder degree of hyperglycemia. An HbA1c level 1 percentage point or more above the ULN for the assay used, if confirmed, makes the diagnosis of diabetes. A lower value makes the diagnosis of IFG, which is a high-risk category for the future development of both diabetes and cardiovascular disease and warrants close follow-up and aggressive treatment of the risk factors for each.

It has been argued that HbA1c assays are not yet standardized enough to be used in the diagnosis of diabetes. However, using an assay

![Figure 1. An approach to the diagnosis of diabetes based on clinical outcomes.](image-url)
meeting the recent standards of the National Glycohemoglobin Program to analyze the NHANES III data. Rohlfing and colleagues concluded that HbA1c levels are both sensitive and specific for detecting diabetes. If the approach outlined in Figure 1 is followed, diabetes will be diagnosed in those at clear risk for developing the microvascular and neurovascular complications. Individuals with milder degrees of hyperglycemia (who are currently not at risk for these complications) will also be identified so that appropriate measures can be instituted to reduce their chances of developing diabetes or cardiovascular disease.

References

Acknowledgments

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