The Canadian Diabetes Association (CDA) reviewed the use of glycated hemoglobin (A1C) in the diagnosis of diabetes mellitus. An International Expert Committee, the American Diabetes Association, a joint statement from the American Association of Clinical Endocrinologists/American College of Endocrinology, and a World Health Organization Consultation each recommend an A1C of 6.5% or higher as a criterion for the diagnosis of diabetes (1-4).

The relationship between A1C and retinopathy is similar to that of fasting plasma glucose (FPG) or 2-hour plasma glucose (2hPG) with a threshold at around 6.5% (5-8). Although the diagnosis of diabetes is based on an A1C threshold for developing microvascular disease, A1C is also a continuous cardiovascular risk factor and a better predictor of macrovascular events than FPG or 2hPG (9,10). While many people identified as having diabetes using A1C will not be identified as having diabetes by traditional glucose criteria, and vice versa, there are several advantages to using A1C for diabetes diagnosis (4). A1C can be measured at any time of day and is more convenient than FPG or 2-hour oral glucose tolerance test (OGTT). A1C testing also avoids the problem of day-to-day variability of glucose values, as it reflects the average plasma glucose over the previous 2 to 3 months (2).

In order to use this diagnostic criterion, A1C must be measured using a validated assay standardized to the National Glycohemoglobin Standardization Program—Diabetes Control and Complication Trials reference. It is important to note that A1C may be misleading in individuals with various

| Table 1. Factors that can affect A1C (adapted from 11) |
|---|---|---|
| **Factor** | **Increased A1C** | **Decreased A1C** | **Variable change in A1C** |
| Erythropoiesis | Iron deficiency B12 deficiency Decreased erythropoiesis | Use of erythropoietin, iron or B12 Reticulocytosis Chronic liver disease | Fetal hemoglobin Hemoglobinopathies Methemoglobin Genetic determinants |
| Altered hemoglobin | Alcoholism Chronic renal failure Decreased erythrocyte pH | Ingestion of aspirin, vitamin C or vitamin E Hemoglobinopathies Increased erythrocyte pH | |
| Glycation | | | |
| Erythrocyte destruction | Increased erythrocyte lifespan: Splenectomy | Decreased erythrocyte lifespan: Chronic renal failure Hemoglobinopathies Splenomegaly Rheumatoid arthritis Antiretrovirals Ribavirin Dapsone | |
| Assays | Hyperbilirubinemia Carbamylated hemoglobin Alcoholism Large doses of aspirin Chronic opiate use | Hypertriglyceridemia | Hemoglobinopathies |
hemoglobinopathies, iron deficiency, hemolytic anemias, and severe hepatic and renal disease (2,3,11) (Table 1). In addition, studies of various ethnicities indicate that African Americans, American Indians, Hispanics and Asians have A1C values up to 0.4% higher than white patients at similar levels of glycaemia (12,13). Further research is required to determine if specific ethnic-based A1C cut-points for diabetes diagnosis are warranted. A1C values are also affected by age, rising by up to 0.1% per decade (14-16). More studies may help determine if age-adjusted A1C thresholds are required for diabetes diagnosis in the elderly.

The CDA recommends the addition of A1C as a diagnostic criterion for type 2 diabetes in adults as follows:

1. A1C can be used as a diagnostic test for diabetes using a standardized, validated assay when there are no conditions that preclude its accurate measurement.

2. A1C ≥6.5% is one of the diagnostic criteria for diabetes that should be confirmed by repeat testing on a subsequent day.

3. A1C <6.5% does not exclude diabetes that may be diagnosed using standard glucose tests (Table 2).

4. Traditional diagnosis using FPG, random glucose with symptoms, or 2hPG during an OGTT are still recommended options for diagnosing diabetes (Table 2).

5. A1C is not recommended for diagnostic purposes in children, adolescents, pregnant women or people with type 1 diabetes.

6. A1C may be misleading and therefore should not be used as a diagnostic tool in the setting of hemoglobinopathies, hemolytic anemia, thalassemias, iron deficiency, spherocytosis, and severe hepatic or renal failure.

7. A1C may be misleading in certain ethnicities and in the elderly, and therefore its utility as a diagnostic tool in these populations is unclear.

The decision as to which test to use for diabetes diagnosis (Table 2) is left to clinical judgment. In the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation, a repeat confirmatory laboratory test (FPG, casual PG, 2hPG in a 75-g OGTT, A1C) must be done in all cases on another day. It is preferable that the same test be repeated for confirmation. If results of two different tests are available, and both are above the diagnostic cut-points, the diagnosis of diabetes is confirmed. When results of more than one test are available and are discordant, the test with a result above the diagnostic cut-point should be repeated and the diagnosis made on the basis of the repeat test.

The CDA does not recommend specific A1C criteria for the diagnosis of prediabetes. While there is a continuum of risk for diabetes with A1C levels <6.5%, further research is required to determine whether A1C can be used to identify people at risk for diabetes (currently comprising people with impaired fasting glucose or impaired glucose tolerance).

### Table 2. Diagnostic criteria for diabetes (adapted from 17)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnostic Criteria</th>
</tr>
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<tbody>
<tr>
<td>Fasting</td>
<td>FPG ≥7.0 mmol/L or Casual PG ≥11.1 mmol/L + symptoms of diabetes</td>
</tr>
<tr>
<td>2hPG</td>
<td>2hPG in a 75-g OGTT ≥11.1 mmol/L or A1C ≥6.5%</td>
</tr>
</tbody>
</table>

A repeat confirmatory laboratory test (FPG, casual PG, 2hPG in a 75-g OGTT, or A1C) must be done in all cases on another day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation. It is preferable that the same test be repeated for confirmation. However, in individuals in whom type 1 diabetes is likely (younger or lean or asymptomatic hyperglycemia, especially with ketonuria or ketonemia), confirmatory testing should not delay initiation of treatment to avoid rapid deterioration.

#### REFERENCES