POSITION STATEMENT

Use of Glycated Hemoglobin (A1C) in the Diagnosis of Type 2 Diabetes Mellitus in Adults

Ronald M. Goldenberg[1] MD FRCPC FACE, Alice Y.Y. Cheng[2] MD FRCPC, Zubin Punthakee[3] MD FRCPC, Maureen Clement[4] MD CCFP

[1]North York General Hospital and LMC Endocrinology Centres, Toronto, Ontario
[2]Division of Endocrinology & Metabolism, St. Michael's Hospital and Credit Valley Hospital and Department of Medicine, University of Toronto, Toronto, Ontario
[3]Department of Medicine and Department of Pediatrics, McMaster University, Hamilton, Ontario
[4]University of British Columbia, Vancouver and Diabetes Education Centre, Vernon Jubilee Hospital, Vernon, British Columbia

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 macrovas-cular 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	
Altered hemoglobin			Fetal hemoglobin Hemoglobinopathies Methemoglobin Genetic determinants
Glycation	Alcoholism Chronic renal failure Decreased erythrocyte pH	Ingestion of aspirin, vitamin C or vitamin E Hemoglobinopathies Increased erythrocyte pH	

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 glycemia (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 criteria 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)

FPG ≥7.0 mmol/L
Fasting = no caloric intake for at least 8 hours
or
Casual PG ≥11.1 mmol/L + symptoms of diabetes
Casual = any time of the day, without regard to the interval since the last meal
Classic symptoms of diabetes = polyuria, polydipsia and unexplained weight loss
or
2hPG in a 75-g OGTT ≥11.1 mmol/L
or
A1C ≥6.5%
Using a standardized, validated assay, in the absence of conditions that affect the accuracy of the A1C

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 symptomatic hyperglycemia, especially with ketonuria or ketonemia), confirmatory testing should not delay initiation of treatment to avoid rapid deterioration.

2hPG = 2-hour plasma glucose
FPG = fasting plasma glucose
OGTT = oral glucose tolerance test
PG = plasma glucose

REFERENCES

1. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care.* 2009;32:1327-1334.

2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2011;34(suppl 1):S62-S69.

3. American Association of Clinical Endocrinologists Board of Directors, American College of Endocrinologists Board of Trustees. American Association of Clinical Endocrinologists/American College of Endocrinology statement on the use of hemoglobin A1c for the diagnosis of diabetes. *Endocr Pract.* 2010;16:155-156.

4. WHO Consultation. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. WHO website. http://www.who.int/entity/diabetes/publications/report-hba1c_2011.pdf. Accessed June 14, 2011.

5. McCance DR, Hanson RL, Charles MA, et al. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ.* 1994;308:1323-1328.

6. Engelgau MM, Thompson TJ, Herman WH, et al. Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes. Diagnostic criteria and performance revisited. *Diabetes Care.* 1997;20:785–791.

7. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care.* 1997;20:1183–1197.

8. The DETECT-2 Collaboration Writing Group. Glycemic thresholds for diabetes specific retinopathy. *Diabetes Care.* 2011;34:145-150.

9. Sarwar N, Aspelund T, Eiriksdottir G, et al. Markers of dysglycaemia and risk of coronary heart disease in people without diabetes: Reykjavik Prospective Study and systematic review. *PLoS Medicine.* 2010;7:e1000278. doi:10.1371/journal.pmed.1000278.

10. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med.* 2010;362:800-811.

11. Gallagher EJ, Bloomgarden ZT, Roith D. Review of hemoglobin A1c in the management of diabetes. *J Diabetes.* 2009;1:9-17.

12. Herman WH, Ma Y, Uwaifo G, et al. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. *Diabetes Care.* 2007;30:2453-2457.

13. Ziemer DC, Kolm P, Weintraub WS, et al. Glucose-independent, black-white differences in hemoglobin A1c levels. *Ann Intern Med.* 2010;152:770-777.

14. Davidson MB, Schriger DL. Effect of age and race/ethnicity on HbA1c levels in people without known diabetes mellitus: Implications for the diagnosis of diabetes. *Diab Res Clin Pract.* 2010;87:415-421.

15. Pani L, Korenda L, Meigs JB, et al. Effect of aging on A1C levels in persons without diabetes: evidence from the Framingham Offspring Study and NHANES 2001-2004. *Diabetes Care.* 2008;31:1991-1996.

16. Lin TT, Pin FJ, Tan E, et al. HbA1c may not be a sensitive determinant of diabetic status in the elderly. *Diabetes Res Clin Pract.* 2011; doi:10.1016/j.diabres.2011.01.003.

17. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes.* 2008;32(suppl 1):S1-S201.