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The implications of using Hemoglobin A1C for diagnosing Diabetes Mellitus

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Abstract

Until 2010 the diagnosis of diabetes mellitus was based solely on glucose concentration, but American Diabetes Association (ADA) recommendations now include a new criterion: hemoglobin A1C ≥6.5%. Because this change may have significant implications for diabetes diagnosis, we conducted a comprehensive literature review including peer-reviewed articles not referenced in the ADA report.

We conclude that A1C and plasma glucose tests are frequently discordant for diagnosing diabetes. A1C ≥6.5% identifies fewer individuals as having diabetes than glucose-based criteria. Convenience of A1C test might increase the number of patients diagnosed, but this is unproven. Diagnostic cut-points for both glucose and A1C are based on consensus judgments regarding optimal sensitivity and specificity for the complications of hyperglycemia. A1C may not accurately reflect levels of glycemia in some situations, but in comparison with glucose measurements, it has greater analytic stability and less temporal variability. When choosing a diagnostic test for diabetes, the limitations of each choice must be understood. Clinical judgment and consideration of patient preference are required to appropriately select among the diagnostic alternatives.

Keywords

Diabetes mellitus; Diagnosis; Hemoglobin A1C; Glycohemoglobin; Fasting plasma glucose; Oral glucose tolerance test; Diabetes complications; American Diabetes Association

INTRODUCTION

In January, 2010 the American Diabetes Association (ADA) published revised criteria for the diagnosis of diabetes mellitus1. In addition to older criteria, which include fasting plasma glucose concentration (FPG) and the oral glucose tolerance test (OGTT), hemoglobin A1C (‘A1C’) ≥6.5% can now be used to diagnose the disease (Table 1).

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The new diagnostic criteria are based on recommendations of an International Expert Committee2. The committee concluded that improvement of assays through the National Glycohemoglobin Standardization Program3 (NGSP) has made the A1C accurate and reliable enough to use for the diagnosis of diabetes. In addition, A1C is routinely used to assess individuals with diabetes, allowing clinicians to use the same test for diagnosis and follow-up. The A1C correlates well with both mean glucose concentration4 and the complications of diabetes5,6. It is also more convenient than glucose testing as it does not require fasting or timed samples, and unlike blood glucose it is not affected by recent changes in diet or activity.

The new recommendations acknowledge that a diagnostic threshold (or "cut-point") for the A1C of ≥6.5% classifies one-third fewer individuals as having diabetes than does FPG ≥126 mg/dl1, but the expert committee contends that the greater ease with which the A1C test can be performed will enhance the likelihood of identifying more individuals with diabetes. As discussed below, however, recent studies suggest that A1C criteria will result in fewer people being diagnosed with diabetes7.

The ADA recommendations state that if a diagnostic test needs to be repeated, it is preferable to repeat the same test as there is greater likelihood of agreement with the initial test1. However, if two different tests have been performed and the results are discordant for the diagnosis of diabetes, the test that yielded the positive result should be repeated. In contrast to previous recommendations that specify FPG as the preferred test, the new criteria leave the selection of the diagnostic test to the physician1.

Here we examine the rationale behind recommending the A1C for diabetes diagnosis by reviewing the literature cited by the International Expert Committee2 and the new ADA guidelines1. We also performed an independent exhaustive review of all literature on this topic published during the past five years by searching the Pubmed database. Particular attention was paid to well designed population based studies that evaluated the performance of A1C criteria compared to plasma glucose-based criteria, the relationship between the A1C and glucose concentrations, and the correlation of these parameters with diabetes complications.

EVOLUTION OF DIAGNOSTIC CRITERIA FOR DIABETES

The first widely accepted laboratory standard for diagnosing diabetes was proposed by the World Health Organization (WHO) in 19658. It stated that the disease was present if a venous whole-blood glucose concentration was ≥130 mg/dl (plasma glucose ≥150 mg/dl) 2 hours after a 50 or 100 gram oral glucose challenge.

In 1979, the National Diabetes Data Group proposed new diagnostic criteria9. These were based on the midpoints of bimodal curves observed in certain populations tested for FPG and for 2-h PG using a 75 gram glucose challenge. The criteria were also based on population data demonstrating risk of progression to overt hyperglycemia. The chosen cut-points were FPG ≥140 mg/dl and 2-h PG ≥200 mg/dl. An intermediate group was classified as having "impaired glucose tolerance" (IGT) if 2-h PG was 140 to 200 mg/dl. The WHO adopted these criteria in 198010.

In 1997, the ADA recommended that the FPG threshold for diagnosis be lowered to 126 mg/dl from 140 mg/dl because the former tended to correlate better with a 2-h PG ≥200 mg/dl11. The new FPG cut-point was also chosen because several studies had reported a linear increase in the prevalence of diabetic retinopathy above these levels12,13. The FPG was recommended as the preferred test because of limited clinical use of the relatively cumbersome OGTT and the likelihood that more individuals would be diagnosed with the

FPG. Alternatively, diabetes could be diagnosed if typical symptoms were present in association with a random plasma glucose concentratio ≥200 mg/dl. A category of "impaired fasting glucose" (IFG) was added when the FPG was 110 to 125 mg/dl.

The 1999 WHO criteria concurred with the 1997 ADA criteria, but recommended that an OGTT be considered if the FPG was 110 to 125 mg/dl14. A 2003 ADA recommendation lowered the threshold for diagnosing IFG to 100 mg/dl15.

RATIONALE FOR USING A1C FOR DIAGNOSIS WITH A CUT-POINT OF 6.5%

Correlation with Microvascular Complications

A1C is accepted as the best single measure of average glucose concentration16,17, and it is used routinely to guide adjustments to therapy. A1C has been shown to correlate with likelihood of diabetic retinopathy18–20, and in some studies this correlation was found to be stronger than that for fasting glucose19. In large clinical trials of both type 1 and type 2 diabetes, A1C also correlates with the probability of developing other microvascular complications21,22.

Technical Considerations

With the adoption of the NGSP protocols the measurement of A1C is currently well standardized in many, but not all countries. In contrast, plasma glucose concentration remains difficult to assay with consistent accuracy23. A1C has greater analytical stability (consistency with repetitive sample testing) and less day-to-day variability than either the FPG or 2-h PG24,25. For any given individual, the A1C exhibits little short-term biologic variability; its coefficient of variation (CV) is 3.6%, compared to FPG (CV of 5.7%) and 2-h PG (CV of 16.6%)26. A recent study concluded that 12% of patients can be misclassified with respect to diabetes diagnosis due to laboratory instrument error in measuring glucose27.

The Cut-point Conundrum

Using the A1C for diabetes diagnosis seems logical given its reliability as a measure of chronic glycemia levels and its correlation, in overtly hyperglycemic individuals, with the eventual appearance of the microvascular complications. Choosing a single, optimal threshold A1C for making the diagnosis of diabetes, however, has proven more difficult than establishing correlations with glycemia and disease progression.

The expert committee recommended a cut-point of 6.5% based on evidence that, in diverse populations, "moderate" retinopathy seemed to increase above this level20. This recommendation was based on an unpublished analysis of data derived from the DETECT-2 study28 and cited as a personal communication by one of the committee members, Stephen Colagiuri1. Another article by Borch-Johnsen and Colaguiri discussing the DETECT-2 study states:

> "In a recent analysis of the DETECT-2 collaboration there was a glucose and A1C range below which diabetes specific moderate or advanced retinopathy was rare and above which it clearly increased with increasing levels of glycemia. However, currently available statistical and mathematical models were not able to identify a clear cut-point. In the absence of a clear, objective cut-point, all past and present cut-points for diabetes represent a combination of the best available evidence and a round-table consensus among experts."29

This statement clearly summarizes the dilemma posed by attempting to choose a cut-point for diabetes based on retinopathy. The expert committee report2 also cites older studies that examined the relationship of retinopathy to FPG, 2-h PG, and A1C12,13. These studies reported lower inflection points above which the prevalence of retinopathy began to rise; increasing retinopathy was observed at an A1C of 6% in the National Health and Nutrition Examination Survey (NHANES) III, 6.2% in the Pima Indian Study and 6.3% in a study done in the Egyptian population30.

In an analysis of 1,066 individuals studied as part of the 2005–2006 NHANES cohort, however, the inflection point for increased prevalence of retinopathy occurred at an A1C ≥5.5%31. A Japanese study also suggested that an A1C of 5.3% to 5.5% was the optimal cut-point for diabetes diagnosis based on retinopathy32.

On the other hand, a recent South Asian study examining the relationship between retinopathy, glucose concentration, and A1C actually called into question the concept of a threshold effect20. The authors report a continuous linear relationship between A1C and all microvascular complications in their study population. These include any, mild and moderate retinopathy; micro- or macroalbuminuria; chronic kidney disease; and peripheral neuropathy. The authors also report that mild to moderate retinopathy was rare below an A1C of 6.6% to 7%. They concluded that an A1C of 6.6% may represent an optimal cut-point for diagnosing diabetes based on the risk of mild to moderate retinopathy but not other microvascular complications20.

Another review of three population-based cross-sectional studies of the relationship between retinopathy and FPG concluded that there is “inconsistent evidence” for a uniform glycemia threshold for prevalent and incident retinopathy. The analyses also suggested the existence of a continuous relationship between glucose levels and retinopathy, including moderate retinopathy33. One of these studies, the Multi-Ethnic Study of Atherosclerosis (MESA)34, also examined the relationship between A1C and retinopathy and found a continuous, non-inflected relationship between these two parameters with no threshold effect33.

The discrepancies among studies that do and do not show a threshold effect for retinopathy can be explained by several factors. Older studies relied on direct ophthalmoscopy or single field retinal photographs, whereas newer studies use cameras that take multiple field photos; the latter may be more efficient at detecting early stage retinopathy17. It may also be that some ethnic groups have a higher prevalence of retinopathy at relatively lower glycemia levels. Intercurrent hypertension may also contribute to retinopathy. In an Australian study, it was found that “non-diabetic” individuals with retinopathy at baseline had a higher risk of being diagnosed with diabetes 5 years later, which suggests that retinopathy can start at glucose concentrations below the threshold for diabetes diagnosis19. This association of retinopathy with “pre-diabetes” was also observed in the Diabetes Prevention Program35 and in the 2005–2006 NHANES study; both found that 8% of individuals with FPG levels below the diagnostic threshold for diabetes had retinopathy36.

In addition to issues pertaining to the correlation of A1C with retinopathy, there are noteworthy issues when correlating A1C with glycemia in “non-diabetic” populations. The Dutch New Hoorn Study found that A1C correlated well with FPG and 2-h PG in individuals with diabetes diagnosed by pre-2010 criteria (r^2=0.71 and 0.79, respectively). In contrast, the correlation of A1C with FPG and 2-h PG in the general population was much lower (r^2=0.46 and 0.33, respectively)37. The authors concluded that the A1C is affected by other processes including aging, genetic traits, differences in red-cell lifespan and erythrocyte environments, especially for individuals without diabetes.

WHO GETS THE DIAGNOSIS OF DIABETES: A1C ≥ 6.5% COMPARED TO FPG ≥126 AND 2-H PG ≥200?

The ADA report on the new diagnostic criteria states that, based on data from the NHANES, the A1C cut-point of ≥6.5% will identify one-third fewer individuals than a FPG cut-point of ≥126 mg/dl1. Other studies confirm this viewpoint. A report comparing the 1999 WHO criteria (2-h PG) and the 2003 ADA criterion of FPG ≥126 mg/dl with an A1C of ≥6.5% found that A1C categorized the fewest individuals as having diabetes38. A1C identified 5.2% of individuals in this study as diabetic, compared to FPG (7.1%) and the 2-h PG (15.4%)38. Another analysis of 6,890 adults from the NHANES 1999–2006 survey identified 3.6% of individuals as having diabetes based on FPG ≥126 mg/dl and 2.3% as having diabetes based on A1C ≥6.5%39. Among individuals classified as having diabetes based on their FPG, 50% had an A1C <6.5%. Importantly, individuals diagnosed with diabetes using the A1C criteria, may not fulfill more traditionally defined glycemia-based criteria. For instance, of those with a diagnosis of diabetes based on A1C criteria, 22% had a FPG <126 mg/dl39. In a cohort of older adults with a mean age of 69±11 years, 85% of individuals with A1C ≥6.5% would have been classified non-diabetic by ADA OGTT criteria; concordance for type 2 diabetes diagnosis made by A1C criteria and pre-2010 ADA criteria was low40. Most recently, a comparison of A1C and OGTT for diabetes diagnosis in 4,706 individuals drawn from the Screening for Impaired Glucose Tolerance (SIGT) and two NHANES cohorts concluded that the ADA A1C criterion might miss up to 70% of cases of diabetes7.

These studies lead to two conclusions. The first is that, in comparison with older criteria, A1C ≥6.5% categorizes the smallest proportion of individuals as having diabetes. The second is that the A1C, FPG, and 2-h PG measure different aspects of glycemia. These conclusions are supported by the New Hoorn Study37, which analyzed the diagnostic properties of the A1C defined by receiver operating curve analysis, using OGTT as the diagnostic criterion. The analysis suggested that an A1C of 5.8% had a sensitivity of 72% and specificity of 91%. This compares with specificity of 24% and sensitivity of 99% for the A1C cut-point of 6.5%. On the other hand, the 6.5% cutpoint had a positive predictive value of 93%, compared with a positive predictive value of only 24% for a cut-point of 5.8%.

SPECIAL CONSIDERATIONS THAT APPLY TO THE AIC ASSAY

Multiple factors affect the accuracy of the A1C as an indicator of average glucose concentration (Table 2). Appropriate use of the A1C for diabetes diagnosis requires that clinicians be aware of these factors. For comparison, some factors that affect glucose concentration are listed in Table 3.

When using A1C as a diagnostic tool, it is important that the test be done in a laboratory that uses a method certified by the NGSP. This program allows clinical laboratories to relate their A1C assay results to those of large-scale studies. This requirement could be a problem in parts of the world where laboratories do not use the standardized test.

Another limitation of A1C testing is its greater expense compared to plasma glucose determination. The ADA is in discussions with Medicare and other payers to approve the A1C as a screening test for diabetes. Point-of-care A1C assays have not yet been validated as diagnostic tools; they are not currently recommended for the diagnosis of diabetes.

It is also known that there are racial and ethnic disparities in the A1C independent of mean blood glucose41⁻43. An analysis of 3,819 participants in the Diabetes Prevention Program35, found higher A1C levels among U.S. minority groups with impaired glucose

tolerance44. In the SIGT study noted above, A1C-based diagnosis had more false positives in African Americans and more false negatives in whites when compared with the results of OGTT testing7. More data are needed on A1C in ethnic groups worldwide.

The International Federation of Clinical Chemistry has established a working group to achieve global standardization of the A1C assay. The IFCC has developed a new, more specific reference method for measuring A1C that measures only glycation of the n-terminal valine of the hemoglobin beta chain45. A collaborative effort by the ADA and other international organizations including the IFCC is working to provide a framework for future global standardization of the A1C 46.

Because the A1C, FPG, and 2-h PG measure different aspects of glucose metabolism, a person could be diagnosed as having diabetes with one test and not with another. Previously, the ADA recommended the FPG as the preferred diagnostic test, but the current criteria leave the choice of test to the clinician. Indeed, Fajans *et al*. have recently written that, “A combination of A1C and plasma glucose determinations, where necessary, is recommended for diagnosis or screening of diabetes or IGT”47. An individual’s diagnosis of diabetes could depend on which test is used and how many different tests a provider orders to pursue a suspected diagnosis.

CONCLUSIONS AND RECOMMENDATIONS

The A1C obtained from appropriately selected patients and performed in a qualified laboratory, provides an accurate measure of the individual’s mean glucose concentration. It correlates well with the probability of microvascular complications, and it offers significant technical and practical advantages over laboratory glucose measurement. There are confounding factors (Table 2) that can interfere with A1C assay accuracy, and clinicians need to be aware of these. The ADA diagnostic threshold of A1C ≥6.5% is more specific, but less sensitive than both fasting and OGTT plasma glucose tests.

The use the A1C as a screening tool may miss individuals who would have been identified as diabetic using older criteria7. Whether its widespread use will result in medically significant delays in diagnosis is not known. Studies defining the natural history of persons with an A1C >5.5% but <6.5% have yet to be performed. A recent analysis suggests that A1C in this range is a risk factor for cardiovascular disease48, but the probability and time to onset of diabetes (by whatever criterion) and of microvascular complications is unclear. We and others 47 suggest that it is both acceptable and prudent to use a combination of different diagnostic criteria (Table 1) to establish or exclude diagnosis of diabetes whenever the disorder is suspected based on presence of other risk factors.

It is also evident that the complications of hyperglycemia appear to be a continuous function of blood glucose levels, with no clear threshold effect except, possibly, in the case of moderate or severe retinopathy. Discrete binary cut-points placed along a continuous function are inevitably somewhat arbitrary and generally developed by consensus. There are many population studies comparing the performance characteristics of the A1C, FPG, and 2-h PG, but there is little evidence that any of these parameters is superior for predicting eventual complications. Caregivers must decide on which diagnostic test to use, based on the circumstances of their practice, index of suspicion for diabetes and inconvenience of obtaining fasting samples.

Because discordance among the different diagnostic tests for diabetes is most common in those with early disturbances of glucose homeostasis, institution of appropriate interventions in persons with strong family histories, an increasing trajectory of weight, or other components of “metabolic syndrome” should not be delayed by over-reliance on consensus

diagnostic criteria. In such circumstances, combination of tests47 or a tool with higher sensitivity may be more appropriate than one that offers greater convenience. For screening patients without established risk factors, suspicion that a hemoglobinopathy may be present, the willingness of the patient to fast, and perhaps even out-of-pocket patient cost may also be appropriate considerations in test selection. One also needs to be aware that a diagnosis of diabetes by whatever criterion may impact employment, insurability, or qualification for medical assistance. It is always important to integrate test data with clinical judgment.

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TABLE 1

ADA CRITERIA FOR DIAGNOSIS OF DIABETES1

1	A1C ≥ 6.5 %. This test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay*
	OR
2	FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*
	OR
3	2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. This test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 grams anhydrous glucose dissolved in water.*
	OR
4	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.

NGSP= National Glycohemoglobin Standardization Program

DCCT= Diabetes Control and Complications Trial; FPG= Fasting Plasma Glucose

TABLE 2

FACTORS THAT AFFECT A1C

- Abnormal erythrocyte lifespan
  - Hemoglobinopathies3, *e.g.*, thalassemia, hemoglobins S, C, E, D
  - Erythrocyte abnormalities, *e.g.*, spherocytosis
  - Acute blood loss; increased reticulocyte number
  - Iron deficiency may increase A1C due to increased erythrocyte survival
  - Normal variation in erythrocyte lifespan may account for difference in A1C between individuals with the same average BG
- Assay-related artifacts
  - Carbamylated hemoglobin (*e.g.*, renal failure) increases A1C
  - Acetylated hemoglobin (*e.g.*, aspirin)
  - High hemoglobin F levels increase A1C
  - Hemoglobins S, G, D, C, and E decrease A1C
- Miscellaneous
  - Vitamins E and C can reduce hemoglobin glycation
  - Hypertriglyceridemia and hyperbilirubinemia may increase A1C
  - Patients receiving anti-retroviral treatment have lower A1C
  - A1C increases with age by up to 0.4%
  - Ethnic differences, *e.g.*, A1C is higher in Afro-Caribbeans by 0.4%
  - A1C is lower in pregnancy by 0.5%
  - Chronic liver disease lowers A1C
- Fast *vs.* slow glycosylation: A1C is more closely correlated in monozygotic than in dizygotic twins

TABLE 3

FACTORS THAT AFFECT GLUCOSE CONCENTRATIONS

- Acute increase in plasma glucose concentration
  - Physiological stress
    - Acute illness
    - Major surgery
  - Drugs
    - Corticosteroids
    - Sympathomimetics
    - Isoniazid
    - Olanzapine
    - Diazoxide
    - Niacin
- Acute decrease in plasma glucose concentration
  - Physiologic Factors
    - Intense exercise
    - Prolonged fasting or starvation
    - Pregnancy
  - Acute illness
    - Sepsis
    - Acute Renal Insufficiency
    - Adrenal insufficiency
    - Hypopituitarism
  - Drugs
    - Oral hypoglycemic agents (sulfonylureas)
    - Antibiotics (ciprofloxacin, gatifloxacin)
    - Chloroquine, Quinine
    - Acetaminophen overdose
    - Salicylates
    - Alcohol
  - Spurious Hypoglycemia (Low laboratory measurement in a normoglycemic patient)
    - Prolonged storage of blood sample
    - Leukocytosis and Leukemias