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Diagnosing Diabetes with Hemoglobin A1c: Current Debates and Considerations for Anemic Patients

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Over the past few decades hemoglobin A1c (HbA1c) has become a targeted measurement in the management of diabetes mellitus (DM). Its pivotal role derives from its use in reports of major outcome studies, including two major multicenter randomized control trials: the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study [1-3]. HbA1c levels can be directly related to the risk of developing microvascular complications in both type 1 and type 2 diabetes.

The use of HbA1c for the diagnosis of diabetes was suggested as early as the mid-1980s [4], but concerns regarding its availability and lack of assay standardization prevented its use for diagnostic purposes. In 2009, an international expert committee recommended that HbA1c be introduced into the diagnostic criteria for DM at a cutoff level of ≥6.5% [5]. This recommendation was adopted by the 2010 American Diabetes Association (ADA) and more recently by the 2011 World Health Organization [6,7].

The association between high glucose levels and diabetic retinopathy has been the basis for the diagnosis of diabetes. The DETECT-2 analysis pooled data on retinopathy and blood glucose levels from over 44,000 participants across five countries and found that HbA1c is as good at predicting diabetic retinopathy as either fasting or 2-hour plasma glucose and that the diagnostic threshold of ≥6.5% is appropriate [8]. The diagnostic accuracy of this proposed HbA1c cutoff for detecting diabetic retinopathy has also been tested in an independent Korean population cohort study [9]. In this study, the prevalence of retinopathy was very low until the HbA1c reached 6.5% to 6.8%. In addition, the optimal HbA1c cutoff for detecting diabetic retinopathy was 6.6% as determined by receiver-operator characteristic curve analysis. Indeed, this accuracy was similar to the ADA-proposed HbA1c threshold of 6.5%.

There is no doubt that HbA1c has advantages as a diagnostic test. HbA1c is a stable indicator of chronic hyperglycemia and offers a potentially easier, nonfasting, and therefore more acceptable test. Furthermore, there appears to be less intraindividual variation and greater preanalytical stability with HbA1c than glucose testing. Nevertheless, the role of HbA1c for diagnostic purposes is still the subject of much debate [10-12]. Some of the major arguments against its use include that HbA1c may vary with age and between ethnic groups, independent of glycemic control. For instance, blacks and younger individuals are more likely to receive a diagnosis of diabetes using HbA1c than using fasting glucose testing [13]. In addition, HbA1c is more expensive than plasma glucose testing, which may preclude its use in many low-cost settings.

Accumulating evidence for the diagnostic yield of HbA1c indicates that it will detect a different population as having diabetes than will plasma glucose testing [12]. A study in the United States comparing the diagnostic rates showed that a HbA1c of 6.5% categorized the fewest individual as having diabetes

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(5.2%) than did either the fasting plasma glucose (7.1%) or the 2-hour plasma glucose (15.4%) [14]. In a Korean population cohort converted to a DCCT-aligned assay, the sensitivity of a 6.5% cutoff for detecting diabetes by oral glucose tolerance test (OGTT) criteria was only 52.3% with a 96.8% specificity [15]. This raises concerns that overreliance on the proposed HbA1c criterion for the diagnosis of diabetes could lead to delayed diagnoses, most probably in patients with early diabetes [9].

Numerous factors related to erythrocyte lifespan could affect HbA1c levels because HbA1c itself is not a direct measure of glycemia but is instead a measure of the proportion of hemoglobin proteins that are bound by glucose. Any process that reduces the average age of erythrocytes (i.e., acute blood loss and hemolysis) will lower HbA1c, while any increase in the age of erythrocytes will increase HbA1c [12]. Accordingly, iron deficiency anemia, which reduces erythropoiesis, is generally known to increase HbA1c levels. Analysis of 10,535 adults in the National Health and Nutrition Examination Survey III who did not have a history of diabetes revealed that 13.7% of women had iron deficiency. Iron deficiency in women was associated with a 40% greater odds of a HbA1c ≥5.5% but was not associated with an increased likelihood of a HbA1c ≥6.5% [11,16].

In this regard, the article by Son et al. [17] provides clinically relevant information when interpreting HbA1c levels in patients with anemia, given that anemia is one of the most common situations that can affect erythrocyte lifespan. They enrolled 112 anemic cases and 217 age- and gender-matched nonanemic controls who were suspected of having diabetes and who underwent an OGTT and a standardized HbA1c test. Acute blood loss, hematologic malignancies, and chronic renal failure cases were excluded in this study, and no patients had rare causes of anemia such as hemolysis or hemoglobinopathy. They found, with borderline significance, that patients with anemia tended to have a higher mean HbA1c level than did patients without anemia. Interestingly, these differences were observed only in patients with prediabetes (5.9%±0.7% vs. 5.6%±0.4%; P=0.08) or diabetes (7.3%±1.5% vs. 6.9%±1.2%; P=0.06) but not in patients with normal glucose levels. The specificity of a HbA1c threshold of ≥6.5% for detecting OGTT-defined diabetes was significantly lower in the anemic group than in the nonanemic group (81.1% vs. 93.9%; P<0.05), which means that the false positive rate reached about 20% in the anemic group when using a HbA1c ≥6.5% for a diagnostic threshold. The study did not evaluate the specific cause of anemia and had limited statistical power to demonstrate the differences in HbA1c levels between the study groups. Nonetheless, the work by Son et al. [17] extends previous findings indicating that the diagnostic accuracy of HbA1c could be affected by the presence of anemia.

Based on the results from these studies, HbA1c is a convenient new measure for diagnosing diabetes. Clinicians should determine the suitability of HbA1c for diagnostic purposes in their specific setting with consideration of the various epidemiologic factors and conditions that can affect its measurement.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
3. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
4. Simon D, Coignet MC, Thibult N, Senan C, Eschwege E. Comparison of glycosylated hemoglobin and fasting plasma glucose with two-hour post-load plasma glucose in the detection of diabetes mellitus. Am J Epidemiol 1985;122:589-93.
5. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327-34.
6. Executive summary: standards of medical care in diabetes: 2010. Diabetes Care 2010;33 Suppl 1:S4-10.
7. World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Geneva: World Health Organization; 2011.
8. Colagiuri S, Lee CM, Wong TY, Balkau B, Shaw JE, Borch-Johnsen K; DETECT-2 Collaboration Writing Group. Glycemic thresholds for diabetes-specific retinopathy: implications for

diagnostic criteria for diabetes. Diabetes Care 2011;34:145-50.
9. Cho NH, Kim TH, Woo SJ, Park KH, Lim S, Cho YM, Park KS, Jang HC, Choi SH. Optimal HbA1c cutoff for detecting diabetic retinopathy. Acta Diabetol. Epub 2013 Jan 25. DOI: 10.1007/s00592-013-0452-3.
10. Malkani S, DeSilva T. Controversies on how diabetes is diagnosed. Curr Opin Endocrinol Diabetes Obes 2012;19:97-103.
11. Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care 2011;34:518-23.
12. Hare MJ, Shaw JE, Zimmet PZ. Current controversies in the use of haemoglobin A1c. J Intern Med 2012;271:227-36.
13. Carson AP, Reynolds K, Fonseca VA, Muntner P. Comparison of A1C and fasting glucose criteria to diagnose diabetes among U.S. adults. Diabetes Care 2010;33:95-7.
14. Lorenzo C, Haffner SM. Performance characteristics of the new definition of diabetes: the insulin resistance atherosclerosis study. Diabetes Care 2010;33:335-7.
15. Choi SH, Kim TH, Lim S, Park KS, Jang HC, Cho NH. Hemoglobin A1c as a diagnostic tool for diabetes screening and new-onset diabetes prediction: a 6-year community-based prospective study. Diabetes Care 2011;34:944-9.
16. Kim C, Bullard KM, Herman WH, Beckles GL. Association between iron deficiency and A1C Levels among adults without diabetes in the National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care 2010;33:780-5.
17. Son JI, Rhee SY, Woo JT, Hwang JK, Chin SO, Chon S, Oh S, Kim SW, Kim YS. Hemoglobin A1c may be an inadequate diagnostic tool for diabetes mellitus in anemic subjects. Diabetes Metab J 2013;37:343-8.