Glycemic Control and Hemoglobinopathy: When A1C May Not Be Reliable

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Editor’s note: The articles published in this department present patient cases using an evidence-based practice framework presented with “PICO” components: population, intervention, comparison, and outcome; a description of the search strategy employed for the integrative review; a summary of the results and critical appraisal of the search; and an evaluation of the scientific and medical evidence base for recommendations.

Background and Clinical Problem
The American Diabetes Association (ADA) recommends hemoglobin A1c (A1C) as the standard laboratory assessment of glycemic control and efficacy of treatment for patients with type 1 or type 2 diabetes.1 Large prospective research trials in patients with type 12 and type 2 diabetes3 have demonstrated that A1C levels are directly related to risk of diabetes complications, such as retinopathy, neuropathy, and nephropathy. However, in some clinical situations, laboratory assessment using the A1C test may provide unreliable information. When an A1C result is inconsistent with a patient’s clinical situation, conditions that affect red blood cell lifespan and hemoglobinopathies must be considered as possible causes1,4 because normative values for A1C are based on individuals with a normal hematological profile.

Hemoglobinopathy
Hemoglobin type is inherited. Hemoglobin A (HbA), normal adult hemoglobin, is the most common type. More than 700 forms of hemoglobinopathy or abnormal hemoglobin variants have been reported; sickle cell (HbS) is the most frequently occurring hemoglobin variant in the United States population.5 In sickle cell trait (HbAS), a person inherits a normal HbA gene from one parent and an HbS gene from the other.6 Although its prevalence is highest among African Americans (6–9%),5,7 HbAS may also occur in those of Hispanic, Greek, Italian, and other ethnic groups. In one population, those of non–African-American ethnicity accounted for 11% of people identified as having HbAS.8 It is estimated that more than 2 million people in the United States have HbAS.9 Because of its prevalence and wide ethnic variation, testing for sickle cell and other selected hemoglobinopathies is routinely performed as part of newborn screening programs in the United States.

Hemoglobinopathy and interference with A1C assessment
A1C represents the main fraction of hemoglobin bound to glucose (glycohemoglobin) and is normally present at low levels in red blood cells.10 In patients with diabetes having normal hemoglobin, A1C values strongly correlate with blood glucose level. Because the A1C test is based on normal hemoglobin, hemoglobinopathies can affect the reliability of the test10 in three ways: 1) altering the normal process of glycation of HbA to A1C, 2) causing an abnormal peak on chromatography, making estimation of A1C unreliable, and 3) making the red blood cell more prone to hemolysis, thereby decreasing the time for glycosylation to occur and producing a falsely low A1C result.11 Therefore, although HbAS is not a disease, when a person with HbAS also has diabetes, the hemoglobin variant interferes with A1C measurement.12

Several laboratory methods are available for A1C measurement; boronate affinity or affinity-binding chromatography, cation-exchange chromatography, electrophoresis, and immunoassay are the most commonly used.3 Depending on which laboratory method is used, the A1C value of a person with HbAS may be either falsely high or falsely low.

Each laboratory method for A1C determination is based on the physical, chemical, or antibody-recognized properties of the normal (HbA) hemoglobin molecule.3 Individuals with HbAS have approximately half normal (HbA) and half sickle cell (HbS) hemoglobin, with each type contributing to the contents of any one red blood cell.13 Because A1C is based on normal hemoglobin, qualitative (such as HbAS) or quantitative differences in hemoglobin can affect A1C values.10 Further, it has been suggested that the abnormal hemoglobin found in those with HbAS may also make red blood cells more vulnerable to hemolysis, thereby decreasing red blood cell lifespan and the time available for glycosylation to occur.14

Case Study
S.D. is an 11-year-old African-American girl newly diagnosed with type 1 diabetes. She returns today for her first outpatient follow-up visit since hospitalization for diabetic ketoacidosis 2 weeks ago. She comes accompanied by her maternal aunt, who has legal custody of S.D. At the time of hospitalization, S.D. was also diagnosed with Hashimo-
to’s thyroiditis and started on treatment with 100 µg/day thyroxine. She was discharged from the hospital on a two-injection-per-day regimen of short- and intermediate-acting insulins (0.79 units/kg/day). She has regained 12 lb since hospital discharge.

S.D. appears to be adjusting to her new diagnosis. She wears a medic alert bracelet and states that she is independently drawing up and administering her own injections and is responsible for remembering to take her thyroxine dose. Review of her blood glucose diary shows low blood glucose readings before breakfast and before dinner. She reports experiencing shakiness when her blood glucose is < 80 mg/dl. She and her aunt claim good medication adherence. S.D. is happy that the “lump in her neck” is getting smaller. Nocturnal enuresis, present before her diagnosis, has resolved.

S.D. is alert, interactive, and cooperative throughout the interview and physical examination. On anthropometric measurement, her height is 60.2 inches (75th percentile for age), weight is 106.3 lb (between the 75th and 90th percentiles for age), and her BMI is 20.7 kg/m² (between the 75th and 85th percentiles for age). All vital signs are within normal limits for age (heart rate 80 bpm, respiratory rate 18, blood pressure 112/70 mmHg). Pertinent physical examination findings include thyroid enlargement of 4 cm in each lobe without nodules, injection sites in good condition, and sexual exam (Tanner 2 breast and pubic hair) that indicates early puberty. Review of S.D.’s laboratory records at time of diagnosis shows that A1C was not measured by the laboratory because of an “abnormal hemoglobin peak.”

Clinical Question
In patients with diabetes, do hemoglobinopathies affect the clinical reliability of A1C measurement, and, if so, what alternate method of assessment should be used?

PICO Format
The patient population to be examined is individuals with either type 1 or type 2 diabetes and hemoglobinopathy. The intervention to be investigated is glycemic control assessment. A comparison will be made between A1C and alternate methods of assessment. The outcome of interest is clinical reliability.

Search Strategy
The author conducted a review of the literature using the Ovid Medline database of articles published between January 1950 and June 2007 and the search terms “diabetes,” “hemoglobinopathy,” “sickle cell trait,” “hemoglobin A1c,” and “fructosamine” to examine the evidence for best practice regarding assessment of glycemic control for patients with diabetes who have HbAS.

Results and Critical Appraisal
Description of studies
Articles were retrieved through the Columbia University Medical Center Health Sciences Library. Articles published in a language other than English were excluded from full review. The search was expanded to include reference lists of articles identified during the initial search, resulting in a total of 12 articles for review. Five of the articles were case reports or observations, two were literature reviews, one was a cross-sectional prospective study, two compared A1C results using different laboratory methods, and two compared an alternate method of glycemic control assessment to A1C.

Hemoglobinopathy in patients with diabetes
Hemoglobinopathy may be suspected during clinical management when there are observed discrepancies between A1C and patient symptoms or reported blood glucose values, particularly when the A1C result is lower than blood glucose values suggest. Often, the hemoglobin variant may be “silent” and therefore unknown to the patient. In a prospective series of 30 adults with type 1, type 2, or gestational diabetes and known discrepancies between reported home blood glucose monitoring and A1C results, Gunton and McElDuff found that 7 (20.3%) had some type of hemoglobinopathy identified by electrophoresis with occurrence similar in Caucasian (23.5%) and non-Caucasian (23.1%) subjects. Of the 7 subjects identified as having a hemoglobinopathy, 5 (71.4%) were women with gestational diabetes.

Variation by laboratory method
Two studies compared the effects of hemoglobinopathies on A1C assessment. Weykamp et al. compared the A1C results of a large sample of specimens of several hemoglobin variants in 102 laboratories using 16 methods of A1C assessment. The researchers reported differences in results between laboratory methods used. Of interest, in the case of HbAS, A1C results ranged from low, within the reference range, or “not measured” (similar to the case reported here). Roberts et al. compared A1C results of blood samples collected from individuals with Hba, HbAS, and hemoglobin C trait assessed by immunoassay and high-performance liquid chromatography methods and found differences in results, particularly for samples containing hemoglobin C trait. These findings highlight the fact that laboratory method may affect measurement of A1C in those with hemoglobinopathy and may lead to mismanagement of patients because of inaccurate results.

Assessment of glycemic control using fructosamine
Reports have suggested that in cases when A1C does not correlate with an individual’s level of diabetes control, an alternate method of assessment that is not affected by abnormal hemoglobin variants be chosen. Fructosamine is a measurement of the average blood glucose concentration during the past 2–3 weeks. Because fructosamine is dependent on serum protein glycation, results are unaffected by presence of a hemoglobinopathy. In a group of non diabetic subjects, fructosamine levels of subjects with hemoglobinopathy (sickle cell disease, HbA, and glucose-6-phosphate dehydrogenase deficiency) were compared to those of normal control subjects. There were no sta-
tistically significant differences in concentration of plasma fructosamine, total proteins, or plasma albumin levels, suggesting that fructosamine level is not affected by these hemoglobin variants.22 Mendlovic et al.19 reviewed the results of seven studies examining the correlation between A1C and fructosamine in patients with diabetes. In all but one study, fructosamine demonstrated moderate to strong correlation with A1C results and was recommended for use in cases of patients with hemoglobinopathy. Based on these findings, Mendlovic et al. concluded that although A1C is the preferred assessment of glycemic control in most patients with diabetes, in cases where a patient has a known hemoglobinopathy, fructosamine will provide more reliable information.19

Summary and Evidence Grading System for Clinical Practice Recommendations
Based on the ADA's evidence grading system for clinical practice recommendations, in which A is clear evidence from randomized control trials, B is supportive evidence from well-conducted cohort studies, C is from poorly controlled studies, and E is expert consensus or clinical experience, the following is an overall level of evidence for the studies in this review. Of the 12 articles reviewed, 111,3,10,14-20,22,23 met the criteria for C level of evidence; only 111 was multi-site and clearly reported all study procedures, thus providing a higher level (B) of evidence.

There is some evidence to support the contention that A1C may not be as reliable in patients with diabetes who have a hemoglobinopathy such as HbAS compared with patients without hemoglobinopathies. However, there is insufficient evidence to make definitive recommendations. Therefore, an alternate method of assessing glycemic control in these patients can be fructosamine and evaluation of blood glucose monitoring results. Although positive correlations between fructosamine and A1C have been reported in the majority 15-29 of studies reviewed by Mendlovic et al.19 one10 did not identify this relationship. Further, the relationship between fructosamine levels and diabetes complications has not been evaluated in randomized, controlled trials. The same is true for evaluation using blood glucose monitoring. Currently, evidence to support the use of a particular method is lacking. Therefore, further studies investigating the reliability of fructosamine are required.

Case Study Revisited
At her follow-up visit, S.D.’s Hashimoto’s thyroiditis is under treatment with good initial response to therapy. Nocturnal enuresis that was present at the time of diagnosis has resolved. Remaining issues of concern are 1) frequent hypoglycemia with identified pattern of occurrence, 2) the possibility that S.D. is taking on too much responsibility for her diabetes management, and 3) the abnormal hemoglobin peak reported by the laboratory during hospitalization, which may preclude ongoing assessment of S.D.’s glycemic control using A1C testing.

Clinical Question Revisited
S.D. and her aunt are instructed to reduce the morning and evening NPH insulin by 2 units. The importance of adult supervision of diabetes tasks during adolescence is stressed. A hemoglobin electrophoresis test is ordered to determine the cause of the abnormal hemoglobin peak. Laboratory results confirm that S.D. has HbAS. The team discusses the hemoglobin electrophoresis results with S.D.’s aunt, stressing the importance of blood glucose monitoring using a blood glucose meter with adequate memory, and initiates a plan to download and review blood glucose measurements with the family during each scheduled diabetes outpatient visit. Further, S.D.’s school nurse is provided with computer software and cable to enable regular downloading of blood glucose measurements performed during the school day. As an added measure of assessment, the team decides to initiate quarterly monitoring of glycemic control using fructosamine.

Implication for Practice
Since publication of the Diabetes Control and Complications Trial (DCCT) results in 1993, routine assessment of A1C has become a standard of care for patients with diabetes. Accurate assessment of glycemic control is essential to ongoing management of diabetes and titration of therapy. This assessment should include review of home blood glucose monitoring, either by downloading of blood glucose meters or review of logbook records combined with A1C laboratory assessment. Inconsistencies between home monitoring and laboratory evaluation should not be dismissed, particularly if the A1C result is lower than what is expected clinically. This is important to ensure that erroneous interpretation of A1C results does not occur.

Clinically silent hemoglobinopathies may affect A1C results more often than currently recognized, particularly in African Americans with type 2 diabetes because of the high prevalence of both the disease 31 and HbAS in this population. If hemoglobinopathy is suspected, hemoglobin electrophoresis should be performed for confirmation and identification of the hemoglobin variant.

Because of some evidence that questions the reliability of A1C in patients with hemoglobinopathies, ongoing glycemic control should be evaluated using an alternate method of laboratory evaluation, such as fructosamine and careful evaluation of blood glucose monitoring results. However, it is important to recognize that each of these methods has inherent limitations. The relationship between fructosamine results and diabetes complications has not been evaluated in randomized, controlled trials such as the DCCT or U.K. Prospective Diabetes Study.4 Further, the time period of glycemic assessment using fructosamine is quite small. A number of factors, including blood sampling technique and improper meter calibration, may potentially affect reliability of blood glucose meter readings.18 Questionable reliability of blood glucose records, particularly
the underreporting of high blood glucose values,\textsuperscript{32} suggests that downloading of blood glucose meters provides more complete and valid blood glucose monitoring data compared to self-reporting using logbooks. A recent study\textsuperscript{33} compared laboratory-determined venous blood glucose values with simultaneous readings from two modern glucose meters and found high accuracy of meter values. Therefore, both methods are recommended. At present, there is no conclusive evidence to support the substitution of fructosamine alone or with blood glucose monitoring for A1C.

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