EDUCATIONAL OBJECTIVE: Readers will interpret hemoglobin A1c values in light of the total clinical picture

FATEH BAZERBACHI, MD
Department of Medicine, University of Minnesota, Minneapolis

SHABAN NAZARIAN, MD
HealthPartners Specialty Clinic, Division of Endocrinology, St. Paul, MN

ABDUL HAMID ALRAIYES, MD
Department of Pulmonary, Allergy, and Critical Care Medicine, Respiratory Institute, Cleveland Clinic

M. CHADI ALRAIES, MD
Division of Cardiology, University of Minnesota, Minneapolis

No. Hemoglobin A1c has been validated as a predictor of diabetes-related complications and is a standard measure of the adequacy of glucose control. But sometimes we need to regard its values with suspicion, especially when they are not concordant with the patient’s self-monitored blood glucose levels.

■ UNIVERSALLY USED

Measuring glycated hemoglobin has become an essential tool for detecting impaired glucose tolerance (when levels are between 5.7% and 6.5%), for diagnosing diabetes mellitus (when levels are ≥ 6.5%), and for following the adequacy of control in established disease. The results reflect glycemic control over the preceding 2 to 3 months and possibly indicate the risk of complications, particularly microvascular disease in the long term.

The significance of hemoglobin A1c was further accentuated with the results of the DETECT-2 project, which showed that the risk of diabetic retinopathy is insignificant with levels lower than 6% and rises substantially when it is greater than 6.5%.

However, because the biochemical hallmark of diabetes is hyperglycemia (and not the glycation of proteins), concerns have been raised about the universal validity of hemoglobin A1c in all diabetic patients, especially when it is used to monitor glucose control in the long term.

■ FACTORS THAT AFFECT THE GLYCATED HEMOGLOBIN LEVEL

Altered glycation
Although the hemoglobin A1c value correlates well with the mean blood glucose level over the previous months, it is affected more by the most recent glucose levels than by earlier levels, and it is especially affected by the most recent peak in blood glucose. It is estimated that approximately 50% of the hemoglobin A1c level is determined by the plasma glucose level during the preceding 1-month period.

Other factors that affect levels of glycated hemoglobin independently of the average glucose level during the previous months include genetic predisposition (some people are “rapid glycators”), labile glycation (ie, transient glycation of hemoglobin when exposed to very high concentrations of glucose), and the 2,3-diphosphoglycerate concentration and pH of the blood.

Hemoglobin factors

Age of red blood cells. Red blood cells last about 120 days, and the mean age of all red blood cells in circulation ranges from 38 to 60 days (50 on average). Turnover is dictated by a number of factors, including ethnicity, which in turn significantly affect hemoglobin A1c values.

Race and ethnicity. African American, Asian, and Hispanic patients may have higher hemoglobin A1c values than white people who have the same blood glucose levels. In

Q: Is hemoglobin A1c an accurate measure of glycemic control in all diabetic patients?

A: No. Hemoglobin A1c has been validated as a predictor of diabetes-related complications and is a standard measure of the adequacy of glucose control. But sometimes we need to regard its values with suspicion, especially when they are not concordant with the patient’s self-monitored blood glucose levels.

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

This standard test may not be as reliable as one would think

1-MINUTE CONSULT
doi:10.3949/ccjm.81a.13147

1-MINUTE CONSULT

CREDIT CME

CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 81 • NUMBER 3 MARCH 2014

146
Effects due to heritable factors could vary among ethnic groups. Racial differences in hemoglobin A\textsubscript{1c} may be ascribed to the degree of glycation, caused by multiple factors, and to socioeconomic status. Interestingly, many of the interracial differences in conditions that affect erythrocyte turnover would in theory lead to a lower hemoglobin A\textsubscript{1c} in nonwhites, which is not the case.\textsuperscript{6}

**Pregnancy.** The mechanisms of hemoglobin A\textsubscript{1c} discrepancy in pregnancy are not clear. It has been demonstrated that pregnant women may have lower hemoglobin A\textsubscript{1c} levels than nonpregnant women.\textsuperscript{7–9} Hemodilution and increased cell turnover have been postulated to account for the decrease, although a mechanism has not been described. Interestingly, conflicting data have been reported regarding hemoglobin A\textsubscript{1c} in the last trimester of pregnancy (increase, decrease, or no change). Iron deficiency has been presumed to cause the increase of hemoglobin A\textsubscript{1c} in the last trimester.\textsuperscript{10}

Moreover, hemoglobin A\textsubscript{1c} may reflect glucose levels during a shorter time because of increased turnover of red blood cells that occurs during this state. Erythropoietin and erythrocyte production are increased during normal pregnancy while hemoglobin and hematocrit continuously dilute into the third trimester. In normal pregnancy, the red blood cell life span is decreased due to “emergency hemopoiesis” in response to these elevated erythropoietin levels.

**Anemia.** Hemolytic anemia, acute bleeding, and iron-deficiency anemia all influence glycated hemoglobin levels. The formation of reticulocytes whose hemoglobin lacks glycosylation may lead to falsely low hemoglobin A\textsubscript{1c} values. Interestingly, iron deficiency by itself has been observed to cause elevation of hemoglobin A\textsubscript{1c} through unclear mechanisms\textsuperscript{11}; however, iron replacement may lead to reticulocytosis. Alternatively, asplenic patients may have deceptively higher hemoglobin A\textsubscript{1c} values because of the increased life span of their red blood cells.\textsuperscript{12}

**Hemoglobinopathy.** Hemoglobin F may cause overestimation of hemoglobin A\textsubscript{1c} levels, whereas hemoglobin S and hemoglobin C may cause underestimation. Of note, these effects are method-specific, and newer immunoassay techniques are relatively robust even in the presence of common hemoglobin variants. Clinicians should be aware of their institution’s laboratory method for measuring glycated hemoglobin.\textsuperscript{13}

**Comorbidities**

**Chronic illnesses** can cause fluctuation in hemoglobin A\textsubscript{1c} and make it unreliable. Uremia, severe hypertriglyceridemia, severe hyperbilirubinemia, chronic alcoholism, chronic salicylate use, chronic opioid use, and lead poisoning all can falsely increase hemoglobin A\textsubscript{1c} levels.

Vitamin and mineral deficiencies (eg, deficiencies of vitamin B\textsubscript{12} and iron) can reduce red blood cell turnover and therefore falsely elevate hemoglobin A\textsubscript{1c} levels. Conversely, medical replacement of these deficiencies could lead to higher red blood cell turnover and reduced hemoglobin A\textsubscript{1c} levels.

**Blood transfusions.** Recent reports suggest that red blood cell transfusions reduce the hemoglobin A\textsubscript{1c} concentration in diabetic patients. This effect was most pronounced in patients who received large transfusion volumes or who had a high hemoglobin A\textsubscript{1c} level before the transfusion.\textsuperscript{14}

**Renal failure.** Patients with renal failure have higher levels of carbamylated hemoglobin, which is reported to interfere with measurement and interpretation of hemoglobin A\textsubscript{1c}. Moreover, there is concern that hemoglobin A\textsubscript{1c} values may be falsely low in these patients because of shortened erythrocyte survival. Other factors that influence hemoglobin A\textsubscript{1c} and cause the measured levels to be misleadingly low in renal failure patients include use of recombinant human erythropoietin, the uremic environment, and blood transfusions.\textsuperscript{15}

It has been suggested that glycated albumin may be a better marker for assessing glyc-
Hemoglobin A1c

Euglycemic control in patients with severe chronic kidney disease.16

Medications and supplements that affect hemoglobin
Drugs that may cause hemolysis could lower hemoglobin A1c levels. Examples are dapsone, ribavirin, and sulfonamides. Other drugs can change the structure of hemoglobin. For example, hydroxyurea alters hemoglobin A into hemoglobin F, thus lowering the hemoglobin A1c level. Chronic opiate use has been reported to increase hemoglobin A1c levels through mechanisms yet unclear.

Aspirin, vitamin C, and vitamin E have been postulated to interfere with hemoglobin A1c measurement assays, although studies have not been consistent in demonstrating these effects.

Labile diabetes
In some patients with diabetes, blood glucose levels are labile and oscillate between states of hypoglycemia and hyperglycemia, despite optimal hemoglobin A1c levels.17 In these patients, the average blood glucose level may very well correlate appropriately with the glycated hemoglobin level, but the degree of control would not be acceptable. Fasting hyperglycemia or postprandial hyperglycemia, or both, especially in the setting of significant glycemic variability over the month before testing, may not be captured by the hemoglobin A1c measurement. These glycemic excursions may be important, as data suggest that this variability may independently worsen microvascular complications in diabetic patients.18

Alternatives to measuring the glycated hemoglobin
When hemoglobin A1c levels are suspected to be inaccurate, other tests of the adequacy of glycemic control can be used.19

Continuous glucose monitoring is the gold standard and precisely shows the degree of glycemic variability, usually over 5 days. It is often used when hypoglycemia and wide fluctuations in within-day and day-to-day glucose levels are suspected. In addition, we believe that continuous monitoring could be used to confirm the validity of hemoglobin A1c testing. In a clinical setting in which the level does not seem to match the fingerstick blood glucose readings, it can be a useful tool to assess the range and variation in glycemic control.

This method, however, is not practical in all diabetic patients, and it certainly does not have the same long-term predictive prognostic value. Yet it may still have a role in validating measures of long-term glycemic control (eg, hemoglobin A1c). There is evidence that using continuous glucose monitoring periodically can improve glycemic control, lower hemoglobin A1c levels, and lead to fewer hypoglycemic events.20 As discussed earlier, patients who have labile glycemic excursions and higher risk of microvascular complications can still have “normal” hemoglobin A1c levels; in this scenario, the use of continuous glucose monitoring can lead to lower risk and better control.

1,5-anhydroglucitol and fructosamine are circulating biomarkers that reflect short-term glucose control, ie, over 2 to 3 weeks. The higher the average blood glucose level, the lower the 1,5-anhydroglucitol level, since higher glucose levels competitively inhibit renal reabsorption of this molecule. However, its utility is limited in renal failure, liver disease, and pregnancy.

Fructosamines are nonenzymatically glycated proteins. As markers, they are reliable in renal disease but are unreliable in hypoproteinemic states such as liver disease, nephrosis, and lipemia. This group of proteins represents all of serum-stable glycated proteins; they are strongly influenced by the concentration of serum proteins, as well as by coexisting low-molecular-weight substances in the plasma.

Glycated albumin is superior to glycated hemoglobin in reflecting glycemic control, as it has a faster metabolic turnover than hemoglobin and is not affected by hemoglobinopathies. Unlike fructosamines, it is not influenced by the serum albumin concentration. Moreover, it may be superior to the hemoglobin A1c in patients who have postprandial hypoglycemia.21

Interestingly, recent cross-sectional analyses suggest that fructosamines and glycated albumin are at least as strongly associated with...
Hemoglobin A1c reflects exposure of red blood cells to glucose. Multiple factors—pathologic, physiologic, and environmental—can influence the glycation process, red blood cell turn-over, and the hemoglobin structure in ways that can decrease the reliability of the hemoglobin A1c measurement.

Clinicians should be vigilant for the various clinical situations in which hemoglobin A1c is hard to interpret, and they should be familiar with alternative tests (eg, continuous glucose monitoring, 1,5-anhydroglucitol, fructosamines) that can be used to monitor adequate glycemic control in these patients.

**REFERENCES**


**ADDRESS:** Fateh Bazerbachi, MD, Department of Medicine, University of Minnesota, 420 Delaware Street SE, MMC 284, Minneapolis, MN 55455; e-mail: fateh.b@gmail.com