

## Q: Is hemoglobin A<sub>1c</sub> an accurate measure of glycemic control in all diabetic patients?

**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

**A:** No. Hemoglobin A<sub>1c</sub> 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  $\geq$  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 A<sub>1c</sub> was further accentuated with the results of the DETECT-2 project,<sup>1</sup> 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 A<sub>1c</sub> in all diabetic patients, especially when it is used to monitor glucose control in the long term.<sup>2</sup>

### ■ FACTORS THAT AFFECT THE GLYCATED HEMOGLOBIN LEVEL

#### Altered glycation

Although the hemoglobin A<sub>1c</sub> 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.<sup>3</sup> It is estimated that approximately 50% of the hemoglobin A<sub>1c</sub> level is determined by the plasma glucose level during the preceding 1-month period.<sup>3</sup>

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 glycaters"), 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.<sup>2</sup>

#### 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 A<sub>1c</sub> values.

**Race and ethnicity.** African American, Asian, and Hispanic patients may have higher hemoglobin A<sub>1c</sub> values than white people who have the same blood glucose levels. In

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

one study of racial and ethnic differences in mean plasma glucose, levels were higher by 0.37% in African American patients, 0.27% in Hispanics, and 0.33% in Asians than in white patients, and the differences were statistically significant.<sup>4</sup> However, there is no clear evidence that these differences are associated with differences in the incidence of microvascular disease.<sup>5</sup>

Effects due to heritable factors could vary among ethnic groups. Racial differences in hemoglobin A<sub>1c</sub> 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<sub>1c</sub> in nonwhites, which is not the case.<sup>6</sup>

**Pregnancy.** The mechanisms of hemoglobin A<sub>1c</sub> discrepancy in pregnancy are not clear. It has been demonstrated that pregnant women may have lower hemoglobin A<sub>1c</sub> levels than nonpregnant women.<sup>7-9</sup> 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<sub>1c</sub> in the last trimester of pregnancy (increase, decrease, or no change). Iron deficiency has been presumed to cause the increase of hemoglobin A<sub>1c</sub> in the last trimester.<sup>10</sup>

Moreover, hemoglobin A<sub>1c</sub> 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 glycosylated hemoglobin levels. The formation of reticulocytes whose hemoglobin lacks glycosylation may lead to falsely low hemoglobin A<sub>1c</sub> values. Interestingly, iron deficiency by itself has been observed to cause elevation of hemoglobin A<sub>1c</sub> through unclear mechanisms<sup>11</sup>; however, iron replacement may lead

to reticulocytosis. Alternatively, asplenic patients may have deceptively higher hemoglobin A<sub>1c</sub> values because of the increased life span of their red blood cells.<sup>12</sup>

**Hemoglobinopathy.** Hemoglobin F may cause overestimation of hemoglobin A<sub>1c</sub> 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 glycosylated hemoglobin.<sup>13</sup>

### Comorbidities

**Chronic illnesses** can cause fluctuation in hemoglobin A<sub>1c</sub> 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<sub>1c</sub> levels.

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

**Blood transfusions.** Recent reports suggest that red blood cell transfusions reduce the hemoglobin A<sub>1c</sub> concentration in diabetic patients. This effect was most pronounced in patients who received large transfusion volumes or who had a high hemoglobin A<sub>1c</sub> level before the transfusion.<sup>14</sup>

**Renal failure.** Patients with renal failure have higher levels of carbamylated hemoglobin, which is reported to interfere with measurement and interpretation of hemoglobin A<sub>1c</sub>. Moreover, there is concern that hemoglobin A<sub>1c</sub> values may be falsely low in these patients because of shortened erythrocyte survival. Other factors that influence hemoglobin A<sub>1c</sub> 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.<sup>15</sup>

It has been suggested that glycosylated albumin may be a better marker for assessing gly-

**Recent glucose levels affect hemoglobin A<sub>1c</sub> more than earlier ones**

emic control in patients with severe chronic kidney disease.<sup>16</sup>

### Medications and supplements that affect hemoglobin

Drugs that may cause hemolysis could lower hemoglobin A<sub>1c</sub> 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 A<sub>1c</sub> level. Chronic opiate use has been reported to increase hemoglobin A<sub>1c</sub> levels through mechanisms yet unclear.

Aspirin, vitamin C, and vitamin E have been postulated to interfere with hemoglobin A<sub>1c</sub> 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 A<sub>1c</sub> levels.<sup>17</sup> 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 A<sub>1c</sub> measurement. These glycemic excursions may be important, as data suggest that this variability may independently worsen microvascular complications in diabetic patients.<sup>18</sup>

### ALTERNATIVES TO MEASURING THE GLYCATED HEMOGLOBIN

When hemoglobin A<sub>1c</sub> levels are suspected to be inaccurate, other tests of the adequacy of glycemic control can be used.<sup>19</sup>

**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 A<sub>1c</sub> 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 A<sub>1c</sub>). There is evidence that using continuous glucose monitoring periodically can improve glycemic control, lower hemoglobin A<sub>1c</sub> levels, and lead to fewer hypoglycemic events.<sup>20</sup> As discussed earlier, patients who have labile glycemic excursions and higher risk of microvascular complications can still have “normal” hemoglobin A<sub>1c</sub> 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 A<sub>1c</sub> in patients who have postprandial hypoglycemia.<sup>21</sup>

Interestingly, recent cross-sectional analyses suggest that fructosamines and glycated albumin are at least as strongly associated with

Younger red blood cells have less hemoglobin A<sub>1c</sub>.

microvascular complications as the hemoglobin A<sub>1c</sub> is.<sup>22</sup>

### ■ BE ALERT TO FACTORS THAT AFFECT GLYCATED HEMOGLOBIN

Hemoglobin A<sub>1c</sub> 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 A<sub>1c</sub> measurement.

Clinicians should be vigilant for the various clinical situations in which hemoglobin A<sub>1c</sub> 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

- Colagui 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; 34:145–150.
- Bonora E, Tuomilehto J. The pros and cons of diagnosing diabetes with A1C. *Diabetes Care* 2011; 34(suppl 2):S184–S190.
- Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. *Diabetes Care* 2002; 25:275–278.
- Herman WH, Dungan KM, Wolfenbutter BH, et al. Racial and ethnic differences in mean plasma glucose, hemoglobin A1c, and 1,5-anhydroglucitol in over 2000 patients with type 2 diabetes. *J Clin Endocrinol Metab* 2009; 94:1689–1694.
- 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.
- Tahara Y, Shima K. The response of GHb to stepwise plasma glucose change over time in diabetic patients. *Diabetes Care* 1993; 16:1313–1314.
- Radder JK, van Roosmalen J. HbA1c in healthy, pregnant women. *Neth J Med* 2005; 63:256–259.
- Mosca A, Paleari R, Dalfra MG, et al. Reference intervals for hemoglobin A1c in pregnant women: data from an Italian multicenter study. *Clin Chem* 2006; 52:1138–1143.
- Nielsen LR, Ekblom P, Damm P, et al. HbA1c levels are significantly lower in early and late pregnancy. *Diabetes Care* 2004; 27:1200–1201.
- Makris K, Spanou L. Is there a relationship between mean blood glucose and glycated hemoglobin? *J Diabetes Sci Technol* 2011; 5:1572–1583.
- Tarim O, Kucukerdogan A, Gunay U, Eralp O, Ercan I. Effects of iron deficiency anemia on hemoglobin A1c in type 1 diabetes mellitus. *Pediatr Int* 1999; 41:357–362.
- Panzer S, Kronik G, Lechner K, Bettelheim P, Neumann E, Dudczak R. Glycosylated hemoglobins (GHb): an index of red cell survival. *Blood* 1982; 59:1348–1350.
- National Glycohemoglobin Standardization Program. HbA1c assay interferences. [www.ngsp.org/interf.asp](http://www.ngsp.org/interf.asp). Accessed December 27, 2013.
- Spencer DH, Grossman BJ, Scott MG. Red cell transfusion decreases hemoglobin A1c in patients with diabetes. *Clin Chem* 2011; 57:344–346.
- Little RR, Rohlfing CL, Tennill AL, et al. Measurement of Hba(1C) in patients with chronic renal failure. *Clin Chim Acta* 2013; 418:73–76.
- Vos FE, Schollum JB, Walker RJ. Glycated albumin is the preferred marker for assessing glycaemic control in advanced chronic kidney disease. *NDT Plus* 2011; 4:368–375.
- Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. *Diabetologia* 2007; 50:2553–2561.
- Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 2006; 295:1681–1687.
- Radin MS. Pitfalls in hemoglobin A1c measurement: when results may be misleading. *J Gen Intern Med* 2013; Sep 4 [epub ahead of print]. <http://link.springer.com/article/10.1007%2Fs11606-013-2595-x/fulltext.html>. Accessed January 29, 2014.
- Leinung M, Nardacci E, Patel N, Bettadahalli S, Paika K, Thompson S. Benefits of short-term professional continuous glucose monitoring in clinical practice. *Diabetes Technol Ther* 2013; 15:744–747.
- Koga M, Kasayama S. Clinical impact of glycated albumin as another glycemic control marker. *Endocr J* 2010; 57:751–762.
- Selvin E, Francis LM, Ballantyne CM, et al. Nontraditional markers of glycemia: associations with microvascular conditions. *Diabetes Care* 2011; 34:960–967.

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](mailto:fateh.b@gmail.com)