ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

CME CREDIT

EDUCATIONAL OBJECTIVE: Readers will interpret hemoglobin A_{1c} values in light of the total clinical picture

Q: Is hemoglobin A_{1c} 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_{1c} 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.

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

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 A_{1c} was further accentuated with the results of the DETECT-2 project,[1] 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_{1c} in all diabetic patients, especially when it is used to monitor glucose control in the long term.[2]

doi:10.3949/ccjm.81a.13147

FACTORS THAT AFFECT THE GLYCATED HEMOGLOBIN LEVEL

Altered glycation

Although the hemoglobin A_{1c} 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.[3] It is estimated that approximately 50% of the hemoglobin A_{1c} level is determined by the plasma glucose level during the preceding 1-month period.[3]

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.[2]

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_{1c} values.

Race and ethnicity. African American, Asian, and Hispanic patients may have higher hemoglobin A_{1c} values than white people who have the same blood glucose levels. In

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.[4] However, there is no clear evidence that these differences are associated with differences in the incidence of microvascular disease.[5]

Effects due to heritable factors could vary among ethnic groups. Racial differences in hemoglobin A_{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_{1c} in nonwhites, which is not the case.[6]

Pregnancy. The mechanisms of hemoglobin A_{1c} discrepancy in pregnancy are not clear. It has been demonstrated that pregnant women may have lower hemoglobin A_{1c} levels than nonpregnant women.[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_{1c} in the last trimester of pregnancy (increase, decrease, or no change). Iron deficiency has been presumed to cause the increase of hemoglobin A_{1c} in the last trimester.[10]

Moreover, hemoglobin A_{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_{1c} values. Interestingly, iron deficiency by itself has been observed to cause elevation of hemoglobin A_{1c} through unclear mechanisms[11]; however, iron replacement may lead to reticulocytosis. Alternatively, asplenic patients may have deceptively higher hemoglobin A_{1c} values because of the increased life span of their red blood cells.[12]

Hemoglobinopathy. Hemoglobin F may cause overestimation of hemoglobin A_{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.[13]

Comorbidities

Chronic illnesses can cause fluctuation in hemoglobin A_{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_{1c} levels.

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

Recent glucose levels affect hemoglobin A_{1c} more than earlier ones

Blood transfusions. Recent reports suggest that red blood cell transfusions reduce the hemoglobin A_{1c} concentration in diabetic patients. This effect was most pronounced in patients who received large transfusion volumes or who had a high hemoglobin A_{1c} level before the transfusion.[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_{1c}. Moreover, there is concern that hemoglobin A_{1c} values may be falsely low in these patients because of shortened erythrocyte survival. Other factors that influence hemoglobin A_{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.[15]

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

cemic control in patients with severe chronic kidney disease.[16]

Medications and supplements that affect hemoglobin

Drugs that may cause hemolysis could lower hemoglobin A_{1c} 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_{1c} level. Chronic opiate use has been reported to increase hemoglobin A_{1c} levels through mechanisms yet unclear.

Aspirin, vitamin C, and vitamin E have been postulated to interfere with hemoglobin A_{1c} 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_{1c} 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 A_{1c} measurement. These glycemic excursions may be important, as data suggest that this variability may independently worsen microvascular complications in diabetic patients.[18]

Younger red blood cells have less hemoglobin A_{1c}

ALTERNATIVES TO MEASURING THE GLYCATED HEMOGLOBIN

When hemoglobin A_{1c} 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 A_{1c} 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_{1c}). There is evidence that using continuous glucose monitoring periodically can improve glycemic control, lower hemoglobin A_{1c} 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 A_{1c} 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_{1c} 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

microvascular complications as the hemoglobin A_{1c} is.[22]

BE ALERT TO FACTORS THAT AFFECT GLYCATED HEMOGLOBIN

Hemoglobin A_{1c} reflects exposure of red blood cells to glucose. Multiple factors—pathologic, physiologic, and environmental—can influence the glycation process, red blood cell turnover, and the hemoglobin structure in ways that can decrease the reliability of the hemoglobin A_{1c} measurement.

Clinicians should be vigilant for the various clinical situations in which hemoglobin A_{1c} 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

1. **Colaguiri 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.
2. **Bonora E, Tuomilehto J**. The pros and cons of diagnosing diabetes with A1C. Diabetes Care 2011; 34(suppl 2):S184–S190.
3. **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.
4. **Herman WH, Dungan KM, Wolffenbuttel 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.
5. **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.
6. **Tahara Y, Shima K**. The response of GHb to stepwise plasma glucose change over time in diabetic patients. Diabetes Care 1993; 16:1313–1314.
7. **Radder JK, van Roosmalen J**. HbA1c in healthy, pregnant women. Neth J Med 2005; 63:256–259.
8. **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.
9. **Nielsen LR, Ekbom P, Damm P, et al**. HbA1c levels are significantly lower in early and late pregnancy. Diabetes Care 2004; 27:1200-1201.
10. **Makris K, Spanou L**. Is there a relationship between mean blood glucose and glycated hemoglobin? J Diabetes Sci Technol 2011; 5:1572–1583.
11. **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.
12. **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.
13. **National Glycohemoglobin Standardization Program**. HbA1c assay interferences. www.ngsp.org/interf.asp. Accessed December 27, 2013.
14. **Spencer DH, Grossman BJ, Scott MG**. Red cell transfusion decreases hemoglobin A1c in patients with diabetes. Clin Chem 2011; 57:344–346.
15. **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.
16. **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.
17. **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.
18. **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.
19. **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.
20. **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.
21. **Koga M, Kasayama S**. Clinical impact of glycated albumin as another glycemic control marker. Endocr J 2010; 57:751–762.
22. **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*