

BRIEF REPORTS

Delay in Diagnosis of Diabetes Mellitus Due to Inaccurate Use of Hemoglobin A_{1C} Levels

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Testing of hemoglobin A_{1C} (HbA_{1C}) levels has become widespread in the management of patients with diabetes mellitus. Since the 1980s, it has proven to be an invaluable tool correlating with a patient's average blood glucose levels as well as with their disease morbidity. Clinicians often base treatment decisions and make adjustments depending on a patient's HbA_{1C} level. As useful as the HbA_{1C} is, it does have notable limitations. A number of conditions can lead to a falsely elevated or a falsely low HbA_{1C} level. When one of these conditions is present, it is important to recognize the inaccuracy of the HbA_{1C} test to prevent a delay or error in the diagnosis or care of patients with diabetes mellitus. It is also important to be aware of alternative methods of monitoring a patient's diabetes such as a fructosamine assay or home and office blood glucose measurements. Presented is the case of a patient with diabetes mellitus and hereditary spherocytosis, a condition that interfered with her HbA_{1C} value and resulted in a delay in her care. (J Am Board Fam Med 2007;20:93–6.)

Diabetes mellitus afflicts more than 18 million people in the United States at an annual cost of \$92 billion in direct medical expenses and approximately \$40 billion in indirect expenses.¹ In patients with diabetes mellitus and hereditary spherocytosis (or any condition that results in a shortened erythrocyte life span), difficulties can arise with interpretation of hemoglobin A_{1C} (HbA_{1C}) results. Presented is a patient with hereditary spherocytosis who, partly because of a falsely reassuring HbA_{1C}, was not diagnosed with diabetes mellitus despite meeting diagnostic criteria for several years.

Case Presentation

Mrs. J, a 43-year-old woman, presented to the family medicine clinic for her annual wellness ex-

amination. She had no active complaints and was feeling fine. Her past medical history was significant for gestational diabetes, hyperlipidemia, fatty liver, hereditary spherocytosis, and borderline diabetes. She reported a 30 pack-year smoking history, and her medications included folic acid, a daily multivitamin, and fenofibrate. At the time of evaluation, her physical examination was unremarkable. Review of her laboratory data showed a fasting glucose of 187 mg/dL, a hemoglobin of 10.6 g/dL, a hematocrit of 0.273, a total bilirubin of 2.4 mg/dL, and a HbA_{1C} of 0.048. The remainder of the results from her laboratory examinations was not clinically significant. Further review of her medical record revealed that her low hemoglobin and hematocrit as well as her elevated bilirubin were stable and consistent with her diagnosis of hereditary spherocytosis. Of particular note, her fasting glucose was well over the diagnostic cutoff for diabetes mellitus (Table 1). Further review of her chart showed that Mrs. J had multiple fasting glucose values in the diabetic range dating back to 4 years before her current evaluation but was never diagnosed with diabetes mellitus. Over the last 2 years, her fasting glucose had ranged from 170 to 192 mg/dL (Table 2). Her HbA_{1C} over this same period was consistently less than 0.05. Given her persistently elevated fasting glucose levels, Mrs. J was diagnosed with diabetes mellitus despite her

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Table 1. Diabetes Mellitus Diagnostic Criteria⁵

Fasting plasma glucose of ≥ 126 mg/dL
OR
Classic symptoms of diabetes (polyuria, polydipsia, and weight loss) plus random plasma glucose of ≥ 200 mg/dL
OR
Two-hour plasma glucose of ≥ 200 mg/dL during an oral glucose tolerance test using WHO parameters, using a 75-g glucose load

normal HbA_{1C} levels and was subsequently started on appropriate medical therapy.

Discussion

Hemoglobin, the protein molecule that transports oxygen throughout the body, resides predominantly in the red blood cell. When the red blood cell dies, the hemoglobin protein is released, broken down, and eventually excreted as bilirubin. The lifespan of the hemoglobin molecule is inherently related to the lifespan of the erythrocyte in which it resides. Under normal circumstances, this is approximately 120 days. During these 120 days, the hemoglobin molecule will be exposed to ambient glucose present in the circulation. Glycosylation or linkage of this circulating glucose to the hemoglobin molecule happens to approximately 5% of the adult hemoglobin (HbA) molecules. The glycosylation of HbA increases linearly over the lifespan of the red cell.² In the mid to late 1950s, it was noted that glycosylated HbA could be separated into at least 3 minor components designated HbA_{1a}, HbA_{1b}, and HbA_{1c}, the last of which is the most abundant.³ By measuring the amount of HbA_{1c} present in the circulation and taking advantage of the knowledge of the linear increase of the glyco-

Table 3. HbA_{1c} Correlation with Blood Glucose Readings²

HbA _{1c}	Blood Glucose (mg/dL)
0.060	120
0.070	150
0.080	180
0.090	210
0.010	240
0.011	270
0.012	300
0.013	330
0.014	360

sylation process over time, it became possible to obtain an estimate of a patient's average glucose level over the approximate 120-day lifespan of the hemoglobin protein found in the red blood cells (Table 3). By the early 1980s, HbA_{1c} testing was widely available, and in subsequent years has proven to be invaluable in the management of patients with diabetes.

As useful as HbA_{1c} testing has become in the management of patients with diabetes, it does have notable limitations. A number of factors may confound the interpretation of the test result. Any condition that shortens the red cell lifespan, such as hereditary spherocytosis, hemolysis, sickle cell anemia, thalassemias, acute blood loss, or chronic blood loss will shorten the time of exposure of the hemoglobin protein to circulating glucose and decrease the glycosylation process. The HbA_{1c} measured under these circumstances would be falsely low and inaccurate.² Conversely, any condition which lengthens the red cell lifespan or slows red cell turnover and prolongs the time of exposure of

Table 2. Historical Values from Laboratory Examinations for Mrs. J

Date	Fasting Plasma Glucose (mg/dL)	Hemoglobin A _{1c}	Hemoglobin (g/dL)	Hematocrit
Feb 1999	119	0.45		
Aug 1999	82	0.38	9.6	0.275
Dec 2000		0.41	12.4	0.351
Apr 2001	137	0.41	11.8	0.343
Mar 2002	136	0.46	10.9	0.296
Apr 2003	192	0.50	10.3	0.296
Apr 2004	170	0.44	11.4	0.330
Mar 2005	187	0.48	10.6	0.297

the hemoglobin protein to circulating glucose, such as iron deficiency anemia, vitamin B₁₂ deficiency anemia, or folate deficiency anemia, would increase the glycosylation process and lead to a falsely high and inaccurate HbA_{1C} level.⁴ With the possibility of both falsely low and falsely high HbA_{1C} levels, clinicians must interpret the test cautiously taking into account other pertinent data.

Although a high, low, or normal HbA_{1C} can be an extremely useful piece of information when used in the appropriate context, it is not currently recognized as a diagnostic test for patients with diabetes. During their 1997 report, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recognized the value of the HbA_{1C} test in the management of diabetes but recommended against its use as a diagnostic test.⁵ This recommendation was supported in 2003 by an Expert Committee update.⁶

In cases such as Mrs. J's, in which her red cells have a shortened lifespan because of her hereditary spherocytosis making the HbA_{1C} test unreliable, a fructosamine analysis can be useful. This test measures the glycosylation of serum proteins such as albumin rather than hemoglobin. Like HbA_{1C}, this test can be used to estimate the average blood glucose over time.⁷ However, because of the shorter lifespan of serum proteins, fructosamine analysis correlates only with the average blood glucose over the previous 2 to 3 weeks.⁸ Thus, a fructosamine analysis would need to be performed monthly to acquire the same information obtained with quarterly HbA_{1C} levels. There are also other disadvantages to using the fructosamine assay. Fructosamine values can vary with such changes in the synthesis or clearance of serum proteins as occurs with acute illness or liver disease. In addition, elevated uric acid levels, elevated bilirubin levels, or the presence of heparin may alter the results.^{2,8} The assay should not be performed if the serum albumin level is ≤ 3.0 mg/dL, because there is ongoing debate on whether to correct the results for serum protein or albumin levels. Finally, unlike the HbA_{1C} test, the fructosamine analysis has not been as extensively used or studied and consequently has not been proven to correlate with diabetic complications.⁸ Although certainly not a perfect test, when used and interpreted appropriately, the fructosamine assay can be an important instrument in clinical situations where the HbA_{1C} is unreliable.

In addition to HbA_{1C} and fructosamine assays, monitoring daily home and office blood glucose levels of patients with diabetes is another appropriate management strategy. The benefit of blood glucose monitoring is that it gives a point of care result and allows for more timely changes in therapy. The levels of a patient's blood glucose monitoring can be used alone or in conjunction with HbA_{1C} and fructosamine assays to optimize the control of a patient's diabetes. Blood glucose monitoring does require a motivated and compliant patient and additional supplies, which may be construed by some as a barrier.

Although Mrs. J's fasting glucose levels had clearly met diagnostic criteria for diabetes mellitus for quite some time, her HbA_{1C} levels were never elevated because of the decreased number and shortened lifespan of her erythrocytes (Tables 1 and 2). It is likely that the falsely reassuring HbA_{1C} values contributed to the delay in diagnosis of diabetes mellitus in this case. This should serve to remind clinicians to interpret each test result in context with the other available data. A literature review revealed another similar case reported in 2003 by Liew and Cheah⁹ involving an acutely ill hospitalized patient with hereditary spherocytosis who was diagnosed with diabetes mellitus as a result of significantly elevated glucose levels meeting diagnostic criteria for diabetes mellitus despite the normal HbA_{1C} level.

Summary

Clear criteria exist for the diagnosis of diabetes mellitus (Table 1). In Mrs. J's case, a coexisting disorder, hereditary spherocytosis, interfered with the accuracy of a test used to manage and monitor her other disorder, diabetes. This case illustrates the inherent inaccuracy of the HbA_{1C} assay in the setting of hemolytic disorders such as hereditary spherocytosis or any condition that alters the life span of the red blood cell. Clinicians should remember the importance of established diagnostic criteria for the diagnosis of diabetes mellitus and the need for the use of alternative methods, such as a fructosamine assay or blood glucose monitoring, when appropriate, to achieve long-term therapeutic success.

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