Inaccurate Glycosylated Hemoglobin A1C Measurements in Human Immunodeficiency Virus–Positive Patients with Diabetes Mellitus

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Persistent differences in blood glucose and serum glycosylated hemoglobin (HbA1C) measurements were observed in 4 human immunodeficiency virus–positive patients with diabetes mellitus, all of whom were taking drugs associated with hemolysis, which interferes with the reliability of HbA1C levels. Determination of fructosamine levels was a more accurate alternative for measuring average glycemic control in these patients.

With the improved duration of survival for HIV-positive patients, the prevalence of diabetes mellitus among HIV-infected individuals will most likely increase. The incidence of new-onset diabetes is 1%–7% among HIV-infected patients, and several of the antiretroviral medications used to treat HIV infection are associated with significant insulin resistance [1]. In HIV-negative diabetic patients, control of hyperglycemia dramatically reduces microvascular complications associated with diabetes. Measurement of glycosylated hemoglobin (HbA1C) levels is widely used in clinical practice and is a well-validated method for determining average glycemic control over the course of ~120 days. The American Association of Diabetes recommends checking HbA1C levels ⩾2 times per year for patients with stable glycemic control and more frequently for patients with inadequate control [2]. Fructosamine levels measure glycated serum proteins and provide an additional method for determining average glycemic control [3]. A fructosamine level indicates average glycemic control over a 2–3-week period.

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Although no specific society-sponsored guidelines exist for the monitoring of diabetes control in HIV-infected patients, some recommend checking HbA1C levels [4]. We report 4 cases of a persistent discordance between patients' blood glucose levels and their HbA1C levels. In each of these cases, HbA1C levels were consistently normal or within an acceptable range for >9 months. However, randomly measured blood glucose levels, home blood glucose monitoring, and fructosamine levels all indicated poor glycemic control.

Case reports. Patient 1 was a 42-year-old HIV-positive man who had diabetes mellitus diagnosed after he presented with fatigue, polydipsia, polyuria, and multiple randomly measured glucose levels of >200 mg/dL. HIV infection had been diagnosed 9 years earlier, and the patient's current HIV therapy consisted of lopinavir-ritonavir, efavirenz, and abacavir. While receiving this regimen, he achieved a CD4 cell count of >100 cells/μL and a virus load of <1000 copies/mL. He was taking dapsone for *Pneumocystis carinii* pneumonia (PCP) prophylaxis, and his diabetes was treated with insulin.

Self-reported home fingerstick glucose levels varied from 100 to 400 mg/dL. Random glucose measurements checked at clinic visits were routinely >200 mg/dL, and the levels were >400 mg/dL on 4 occasions. During this period, the patient required hospital admission for severe hyperglycemia and was treated with intravenous insulin. However, during the same period of time (September 2001 to June 2002), his average HbA1C level was 6.1%, indicating excellent glucose control (figure 1). Clinical suspicion prompted us to make serial measurements of fructosamine levels, which were consistently abnormal, ranging from 356 to 694 μmol/L (normal level, <285 μmol/L).

Patient 2 was a 40-year-old man who had HIV infection diagnosed 10 years previously and who had developed diabetes mellitus 7 years before presentation. His diabetes was initially treated with an oral sulfonylurea. His glucose control worsened after he started an HIV treatment regimen consisting of ritonavir, saquinavir, stavudine, and lamivudine. Although this regimen resulted in a nondetectable virus load, his CD4 cell count remained <200 cells/μL, and he continued receiving dapsone for PCP prophylaxis. To avoid possible metabolic side effects, his HIV therapy was switched to an HIV regimen consisting of efavirenz, stavudine, and lamivudine, and his diabetes management was intensified by the addition of metformin and insulin. Self-reported blood glucose measurements ranged from 150 to 300 mg/dL, and his random serum glucose levels, which were measured during visits to the clinic, were 140–520 mg/dL (mean, 255 mg/dL; figure 1). However, his HbA1C levels,

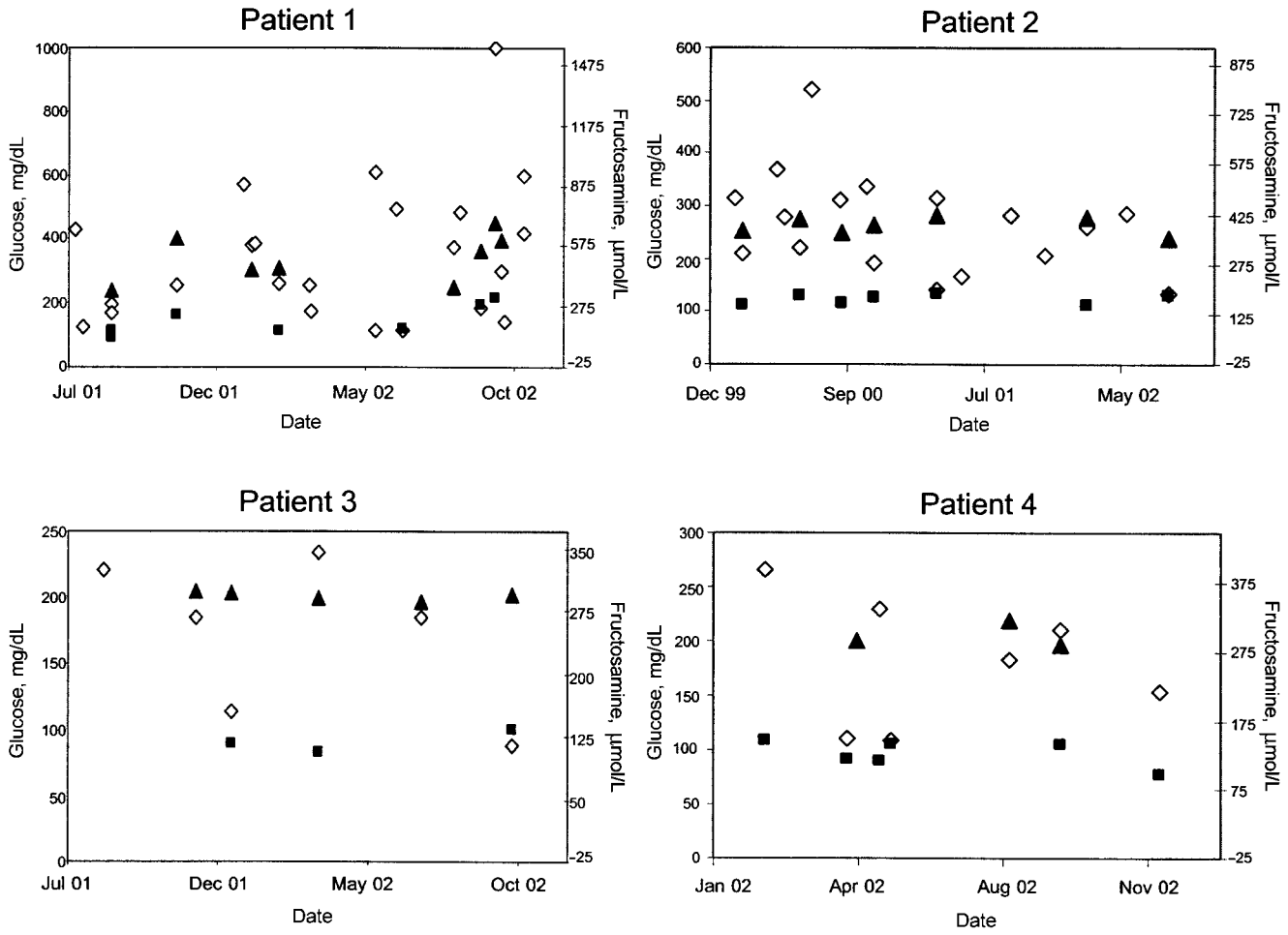

Figure 1. Serum glucose (◇), fructosamine (▲), and predicted glucose (determined on the basis of glycosylated hemoglobin levels [HbA1C]; ■) levels for 4 HIV-positive patients with diabetes. The actual HbA1c measurements are not displayed in this figure.

all of which were <6.4%, indicated excellent glycemic control. Because of this inconsistency, fructosamine levels were analyzed, and all measured levels were found to be abnormal, ranging from 372 to 421 μmol/L.

Patient 3 was a 50-year-old man who had been HIV positive for 9 years and who developed hyperglycemia while receiving an HIV regimen consisting of nevirapine, nelfinavir, and stavudine. His CD4 cell count was 725 cells/μL, and he had a nondetectable virus load; thus, he was not receiving PCP prophylaxis. Three HbA1c measurements were made during a 10-month period, all of which were within the normal range and corresponded to a computed average blood glucose level of 91 mg/dL. Three concurrent measurements of fructosamine levels were all abnormal, and his random serum glucose measurements in the clinic averaged 155 mg/dL (figure 1). During the same period, he had started receiving interferon and ribavirin therapy for coinfection with hepatitis C virus.

Patient 4 was a 48-year-old man who had been HIV positive for 15 years and who had diabetes mellitus diagnosed soon after he started receiving an HIV regimen containing a protease inhibitor. A sulfonylurea initially controlled his blood sugar levels, as determined on the basis of his random serum glucose measurements and his home fingerstick glucose readings. Because of HIV treatment failure, his antiviral medications were changed to saquinavir, ritonavir, didanosine, and zidovudine on the basis of results of resistance testing. He began receiving trimethoprim-sulfamethoxazole (TMP-SMX) for PCP prophylaxis. His HIV load decreased to 242 copies/mL, and his CD4 cell count increased to 320 cells/μL. Both self-reported glycemic measurements and the random serum glucose measurements also increased. However, his HbA1c levels were consistently normal and corresponded to a calculated average blood glucose level of 96 mg/dL (figure 1). Fructosamine levels during the same 9-month period were all abnormal and ranged from 286 to 320 μmol/L.

Discussion. In all 4 cases, the measurements of HbA1c levels were consistently discordant with other measures of glycemic control. In these cases, reliance on the HbA1c level would

have given a false indication of excellent glycemic control. In patients 1 and 2, reliance on HbA1c levels would have been completely misleading and could have had a negative impact on patient care. The HbA1c discordances in patients 3 and 4 were not as dramatic, perhaps because the degree of hyperglycemia was not as pronounced.

Because HbA1c measurements represent an average of serum glucose concentrations measured over the course of ~120 days, the patients could have had both very high and very low glucose levels within that period of time and still have had an estimated average glucose level, as measured by the HbA1c value, within normal limits. However, other measurements of glycemic control, all of which were abnormally high, argue against this possibility.

The glycosylation of hemoglobin proceeds throughout the lifespan of an erythrocyte. Thus, factors that shorten the lifespan of erythrocytes also lower HbA1c levels [5]. During hemolysis, a state of shortened survival for circulating erythrocytes, the number of glycosylated hemoglobin molecules in circulation is reduced. In addition, the number of immature and less-glycosylated erythrocytes increases to relative abundance. Medications that cause even subtle hemolysis without anemia may interfere with the accuracy of HbA1C measurements [6]. All 4 of the patients in this series were taking a medication reported to cause varying degrees of hemolysis. Two of the 4 patients were receiving dapsone [7], 1 patient was receiving ribavirin [8], and the last patient was an African American man receiving TMP-SMX [9].

The process of "HbA1c interference" in diabetic patients with hemolysis is not widely appreciated and, to our knowledge, has only been reported for 3 patients receiving dapsone and 1 receiving sulfasalazine [6, 10, 11]. Ribavirin- and TMP-SMX–associated cases have not been reported elsewhere. The patients reported previous evidence of hemolysis (either an abnormal haptoglobin level or elevated lactate dehydrogenase [LDH] levels), although the degree of hemolysis was insufficient to cause anemia [6, 10, 11]. Similarly, in our series, LDH levels were abnormal for patients 1 (284 U/L), 2 (350 U/L), and 4 (263 U/L) (normal range, 90–210 U/L), suggesting a hemolytic process. The LDH level was not checked for patient 3. In addition, patients 1–3 had evidence of polychromasia noted on peripheral blood smears, signifying increased RBC production. Patients 1 and 2 also had abnormally high reticulocyte counts. Three of 4 patients had persistently normal hemoglobin levels.

The association of hemolysis with both dapsone and ribavirin is strong, and almost all patients receiving these drugs experience some degree of hemolysis [8, 12, 13]. Because TMP-SMX is not as strongly associated with hemolysis, an alternative explanation is that patient 4 could have had an undiagnosed hemoglobinopathy. This would also shorten the lifespan of his erythrocytes, interfering with the accuracy of HbA1c measurements.

HbA1c monitoring is the reference standard test for monitoring long-term glycemic control in HIV-negative patients. In the absence of hemolysis, HbA1c data should be reliable for HIV-positive patients. However, a significant number of HIV-positive patients take medications capable of affecting the lifespan of erythrocytes, potentially causing "HBA1c interference." In addition, a hemolytic process not severe enough to induce anemia can still dramatically alter the HbA1C level.

Fructosamine levels measure the glycosylation of serum proteins and are not dependent on hemoglobin glycosylation. The test is widely available and comparable in cost to that used to measure HbA1c levels, and the results of the 2 tests are highly correlated ($r = 0.8$) [4]. However, because fructosamine levels measure the glycosylation of serum albumin, the test is less reliable in patients with abnormally low albumin levels. Also, fructosamine levels measure glycosylation over a much shorter time period than do HbA1c levels; thus, they must be monitored every 2–3 weeks when they are used instead of serial HbA1c measurements.

Determination of fructosamine levels is recommended for monitoring glucose control in patients with hemoglobinopathies, because these patients are also subject to misleading HbA1c measurements [14]. We recommend checking fructosamine levels in HIV-positive patients with diabetes mellitus who are taking drugs associated with hemolysis and when there are discrepancies between home- or clinic-obtained blood glucose values and HbA1c levels.

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References

1. Dube MP. Disorders of glucose metabolism in patients infected with human immunodeficiency virus. Clin Infect Dis **2000**; 31:1467–75.
2. American Diabetes Association. Tests of glycemia in diabetes—position statement. Diabetes Care **2003**; 26:S106–8.
3. Armbruster DA. Fructosamine: structure, analysis, and clinical usefulness. Clin Chem **1987**; 33:2153–63.
4. Bartlett JG, Gallant JE. Laboratory results. In: Medical management of HIV infection. Baltimore: Johns Hopkins University Press, **2001**:30.
5. Sacks DB, Bruns DE, Goldstein DE, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem **2002**; 48:436–72.
6. Kesson CM, Whitelaw JW, Ireland JT. Drug-induced haemolysis and fast haemoglobin A_1 in diabetes mellitus. Br Med J **1979**; 2:1037–8.
7. Paniker U, Levine N. Dapsone and sulfapyridine. Dermatol Clin **2001**; 19:79–86.
8. Van Vlierberg H, Delanghe JR, De Vos M, et al. Factors influencing ribavirin-induced hemolysis. J Hepatol **2001**; 34:911–6.

9. Reinke CM, Thomas JK, Graves AH. Apparent hemolysis in an AIDS patient receiving trimethoprim/sulfamethoxazole: case report and literature review. J Pharm Technol **1996**; 11:256–62.
10. Bertholon M, Mayers A, Francina A, Thivolet CH. Interference of dapsone in HbA1c monitoring of a type i diabetic patient with necrobiosis lipoidica. Diabetes Care **1994**; 17:1364.
11. Tack CJJ, Wetzels JFM. Decreased HbA1c levels due to sulfonamide-induced hemolysis in two IDDM patients. Diabetes Care **1996**; 19: 775–6.
12. Di Bisceglie AM, Bacon BR, Kleiner DE, et al. Increase in hepatic iron stores following prolonged therapy with ribavirin in patients with chronic hepatitis C. J Hepatol **1994**; 21:1109–12.
13. Fiel MI, Schiano TD, Guido M, et al. Increased hepatic iron deposition resulting from treatment of chronic hepatitis C with ribavirin. Am J Clin Pathol **2000**; 113:35–9.
14. Schnedl WJ, Liebminger A, Roller RE, et al. Hemoglobin variants and determination of glycated hemoglobin (HBA1c). Diabetes Metab Res Rev **2001**; 17:94–8.