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Glycated Hemoglobin in Diabetic Women with and Without HIV Infection: Data from the Women's Interagency HIV Study

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Abstract

Background—Limited data suggest that glycated hemoglobin (hemoglobin A1c; A1C) values may not reflect glycemic control accurately in HIV-infected individuals with diabetes.

Methods—We evaluated repeated measures of paired fasting glucose and A1C values in 315 HIV-infected and 109 HIV-uninfected diabetic participants in the Women's Interagency HIV Study. Generalized estimating equations used log A1C as the outcome variable, with adjustment for log fasting glucose concentration in all models.

Results—An HIV-infected woman on average had 0.9868 times as much A1C (that is, 1.32% lower; 95% confidence interval 0.9734–0.9904) as an HIV-uninfected woman with the same log fasting glucose concentration. In multivariate analysis, HIV serostatus was not associated, but white, other non-black race, and higher red blood cell mean corpuscular volume (MCV) were statistically associated with lower A1C values. Use of diabetic medication was associated with higher A1C values. In multivariate analysis restricted to HIV-infected women, white and other race, higher MCV, and HCV viremia were associated with lower A1C values whereas older age, use of diabetic

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medications and higher CD4 cell count were associated with higher A1C values. Use of combination antiretroviral therapy, protease inhibitors, zidovudine, stavudine, or abacavir was not associated with A1C values.

Conclusions—We conclude that A1C values were modestly lower in HIV-infected diabetic women relative to HIV-uninfected diabetic women after adjustment for fasting glucose concentration. The difference was abrogated by adjustment for MCV, race, and diabetic medication use. Our data suggest that in clinical practice A1C gives a **reasonably** accurate reflection of glycemic control in HIV-infected diabetic women.

Introduction

HIV-infected patients on antiretroviral therapy appear to be at increased risk for diabetes mellitus [1-3]. Measurement of glycated hemoglobin (hemoglobin A1c; A1C) is an important tool for monitoring medium term glycemic control in diabetics as non-enzymatic glycation of hemoglobin occurs continuously in proportion to ambient glucose concentration over the approximate 120 day lifespan of the red blood cell [4;5]. Furthermore, a recent international panel recommended that elevated A1C could also be used to diagnose diabetes [6]. A published case series [7] and cross-sectional sectional study[8], however, suggest that A1C values may overestimate glycemic control in HIV-infected compared to HIV-uninfected patients with diabetes. A recent prospective study of HIV-infected patients with diabetes or impaired fasting glucose had similar conclusions that A1C values may be inappropriately low for the degree of glycemia in this patient population[9]. We aimed to explore these findings by evaluating paired fasting glucose and A1C values measured longitudinally among participants in the Women's Interagency HIV Study (WIHS).

Methods

The WIHS is a prospective cohort study that has enrolled 3,772 primarily minority women with or at high risk of HIV infection at six urban sites in the United States [10;11]. At baseline and at each semi-annual follow-up visit, detailed information is collected on demographics, HIV-related risk behavior, antiretroviral therapy, anthropometric data, co-morbidities, and lifestyle and medication history. The present study includes data from 11 semi-annual study visits from visit 13 (October 2000), when WIHS first began collecting fasting blood specimens, to visit 23 (April 2006). Fasting glucose and A1C were measured at each visit. Diabetes mellitus was defined as having either: fasting plasma glucose ≥ 126 mg/dL, self-report of diabetes medication use (insulin or oral agents), or self-report of diabetes diagnosis at a given visit with subsequent confirmation at a later visit by either elevated fasting glucose (≥ 126 mg/dL) or self-reported diabetes medication use. The index visit for each diabetic woman was defined as the first study visit that the individual met criteria for diabetes.

Glucose analysis was performed on Olympus 5200, 5400 and AU600 automated instruments (Olympus America, Inc., Melville, NY) using the Olympus Hexokinase method reagents. A1C analysis was performed using standard methods on Cobas Integra 700 automated instruments (Roche Diagnostics, Indianapolis, IN) using Roche Cobas Integra monoclonal antibody-based reagents. Quantification of HIV-1 RNA in plasma was performed using the isothermal nucleic acid sequence based amplification (NASBA/Nuclisens) method (Organon Teknika Corp., Durham, NC) in laboratories participating in the NIH/NIAID, Virology Quality Assurance Laboratory proficiency testing program. The lower limit of quantification was 80 copies/ml. Hepatitis C viremia at entry into the WIHS cohort was assessed by either the COBAS Amplicor Monitor 2.0 or the COBAS Taqman assays (both from Roche Diagnostics, Branchburg, New Jersey, USA) as previously described[12].

Informed consent was obtained from all participants and human experimentation guidelines of the US Department of Health and Human Services and those of the authors' institutions were followed in the conduct of this research.

Data were analyzed descriptively using plots, histograms, means, medians, standard deviations, skewness and kurtosis to identify erroneous values, outliers and optimal transformations. Due to large skewness in the original variables, fasting glucose and A1C concentrations were natural logarithm transformed. Continuous variables are summarized in this paper by means $\pm$ standard deviations. Associations between variables of interest and log A1C as a continuous variable were assessed by bivariate and multivariate generalized estimating equations (linear regression modeling), with all models adjusting for log glucose concentration. The cluster units were repeated measures in the same person and independence covariance structure was conservatively chosen. Forward stepwise selection of covariates using a P-value of < 0.10 to enter or leave the model was used to generate multivariate models. HIV serostatus was forced into the multivariate models that included the entire study population. Regression results and 95% confidence limits are expressed as relative (percent) change in A1C concentration associated with a given change in the predictor, calculated as $100 * (\exp^{\beta} - 1)$ where β is the regression coefficient from the model with log A1C concentration as the outcome. Statistical analysis was performed using SAS version 9.1 software (SAS Institute Inc. Cary, NC, USA). Statistical significance was considered to be $p \leq 0.05$.

Results

The study population consisted of 315 HIV-infected and 109 HIV-uninfected diabetic women who had at least one paired A1C and fasting glucose measurement. The mean number of paired measurements per person included in the analysis was 3.9 for HIV-infected and 4.3 for HIV-uninfected women. Table 1 summarizes the demographic and clinical characteristics of these subjects at their index visits. Of note, the mean body mass index was lower in HIV-infected women, though obesity was prevalent in both groups. Fasting glucose at the index visit did not differ significantly between groups whereas the mean A1C value was slightly lower in the HIV-infected group ($6.4\% \pm 2.0$ versus $6.8\% \pm 2.0$; $P = 0.025$).

Table 2 summarizes the bivariate and multivariate regression analyses that included both HIV-infected and HIV-uninfected women. In bivariate models each of which adjusted for log fasting glucose ("glucose adjusted"), lower log A1C concentrations were associated with HIV seropositivity, white and other non-black race (relative to black race), higher hemoglobin concentration, and higher red blood cell mean corpuscular volume (MCV). For example, an HIV-infected diabetic woman would be expected to have an A1C value approximately 1.3% lower than an HIV-uninfected diabetic woman with the same fasting glucose value. In absolute terms, given that both women had the same fasting glucose level, an HIV-infected woman having an A1C of, say, 8.00% would be equivalent to an HIV-uninfected woman having a value of 8.11%. In contrast, body mass index $\geq 30 \text{ kg/m}^2$ and use of diabetic medication were associated with higher glucose-adjusted log A1C values. Women with a family history of diabetes had higher glucose-adjusted log A1C values compared with women without a family history, but this association did not reach statistical significance.

In multivariate glucose-adjusted analyses that included both HIV-infected and uninfected women (Table 2), white and other non-black race and higher MCV remained independently associated with lower log A1C values, while use of diabetic medication remained associated with higher log A1C values. HIV serostatus was not statistically associated with log A1C in multivariate analysis ($p = 0.62$).

In bivariate glucose-adjusted analyses limited to HIV-infected diabetic women (Table 3), white and other non-black race, higher hemoglobin concentration, higher MCV, use of combination antiretroviral therapy (cART), and specifically use of an NNRTI or zidovudine (but not a PI, abacavir, or stavudine) were statistically associated with lower glucose-adjusted log A1C values. There were trends for associations between both higher albumin concentrations and detectable HIV RNA and higher glucose-adjusted log A1C values. Use of diabetic medication was statistically associated with higher glucose-adjusted log A1C values. Body mass index ≥ 30 kg/m² also appeared to be associated with higher glucose-adjusted A1C values, but the association did not reach statistical significance. In multivariate glucose-adjusted analysis, white and other race, higher MCV, and HCV viremia were statistically associated with lower log A1C values whereas age, use of diabetic medications and higher CD4 cell count were statistically associated with higher log A1C values.

To further explore the relationships of HIV infection and MCV with A1C values among diabetic women, we constructed two models with log A1C as the outcome variable (Table 4): model 1 adjusted for log glucose and a four category variable (HIV-uninfected or HIV-infected taking lamivudine without zidovudine, zidovudine with or without lamivudine, or not taking either drug); Model 2 included the same covariates as model 1 with the addition of MCV. Zidovudine and lamivudine use was considered in these models due to the known association of zidovudine with MCV and since zidovudine is commonly used in a fixed dose combination with lamivudine. Relative to HIV-uninfected women in model 1, HIV-infected women taking zidovudine and possibly those taking lamivudine without zidovudine had statistically lower log A1C values after adjusting for log glucose concentration. After further adjustment for MCV, however, there was no longer an association between use of these antiretrovirals and log A1C values. Mean MCV levels differed significantly across each of the four HIV / antiretroviral use groups (87.4 ± 8.0 fL in HIV-uninfected, 95.0 ± 9.3 fL in HIV-infected taking lamivudine without zidovudine, 104.6 ± 12.3 fL in those taking zidovudine with or without lamivudine, or and 89.3 ± 8.6 fL in those not taking either drug; $P < 0.001$).

Discussion

We found slightly lower A1C values in HIV-infected women compared to demographically similar HIV-uninfected women after adjustment for fasting glucose values. After further adjustment, the differences by HIV serostatus of women were largely accounted for by higher MCV values in the HIV-infected group.

A number of conditions are known to alter the relationship between A1C and mean glycemia. Situations that shorten erythrocyte survival or decrease mean erythrocyte age (such as hemolysis or some hemoglobinopathies) are associated with lower A1C values since shortened survival time provides less opportunity for glycation to occur[4;5]. Pregnancy, excess Vitamins C and E, hypertriglyceridemia, hyperbilirubinemia, uremia, chronic alcoholism, chronic salicylate ingestion, and opiate addiction may also alter the relationship between A1C and glucose with some assay methods[13]. It is increasingly well appreciated that factors other than glycemia, such as race[14] and glycation differences may also influence the A1C[15]. Indeed, one analysis indicated that only one-half the variance in A1C can be attributed to the glucose profile [15]. Assay variability due to differences in methodology may be an additional factor.

Our finding that higher MCV values emerged as the single most important factor associated with a lower A1C than predicted by blood glucose is important in this context. One possible explanation is that higher MCV values are a marker of a greater proportion of younger erythrocytes that have had a shorter time to become glycated due to greater red blood cell turnover in the HIV-infected group. This interpretation is consistent with a case series of four HIV-infected subjects who had unexpectedly low A1C values relative to available glucose

values; all of these persons were on medications associated with hemolysis [7]. Furthermore, in a two part study Diop and colleagues first determined that A1C levels underestimated fasting glycemia in HIV-infected subjects and found that the higher the MCV level, the greater the difference between estimated glycemia by A1C and measured fasting glycemia [8]. The second part of this study documented subclinical hemolysis in a convenience sample of 54 (21.7%) of 249 HIV-infected subjects by low serum haptoglobin levels. Both high MCV and low haptoglobin were associated with nucleoside reverse transcriptase inhibitor (NRTI) use.

Kim and colleagues, however, conducted a prospective study of the relationship between A1C and fasting and non-fasting glucose values in 100 HIV-infected adults with diabetes or impaired fasting glucose and 200 HIV-uninfected controls matched on sex, race, and age [9]. Using mean glucose calculated from one fasting and one non-fasting sample, they found that A1C underestimated glucose in HIV-infected subjects and that the discordance was associated in multivariate analysis with MCV and NRTI use, specifically abacavir. Haptoglobin, however, was not independently associated with the glucose-A1C discordance, suggesting that hemolysis was not responsible. These findings suggest that the relationship between elevated MCV and glucose-A1C discordance seen in multiple studies, including the present one, may be mediated by (or be a marker of) a mechanism other than hemolysis.

We found that use of diabetic medication was associated with higher log A1C values for any given fasting glucose value among diabetics. One possible explanation for this observation is that certain diabetes medications, such as sulfonylureas, may have greater beneficial effects on fasting glucose than on postprandial glucose [16]. Since we only measured fasting glucose in this study, we may have overestimated the effect of medical treatment on overall glycemic control by not factoring in potentially higher postprandial glucose levels.

We also found several other notable associations with log A1C values. In this study, after adjusting for log glucose concentration, white and other non-black subjects had lower A1C levels relative to the reference group of blacks. This is consistent with recently published data from the general population indicating that African-Americans have higher A1C at a given glucose concentration relative to whites[14]. The association between HCV viremia and lower A1C that we observed among HIV-infected diabetic women, however, is novel and unexplained albeit potentially a spurious finding attributable to multiple comparisons. It was, however, not due to ribavirin-induced hemolysis as no diabetic women were treated with ribavirin during the study period.

Our study has several limitations and strengths. We were only able to examine the relationship between fasting blood sugar and A1C; we did not have data on post-prandial glucose values, which may contribute substantially to A1C. We also had no data on hemoglobinopathy, which could affect the relationship between glucose and A1C. Our study population consisted only of women, and our findings may not generalize to HIV-infected men. We were also unable to determine if low grade, subclinical hemolysis may contribute to MCV elevations in the HIV-infected women. While we only included data from visits at which women reported that they were fasting, it is possible that some women may not have been truly fasting at each visit, for example due to ingestion of medications with a caloric beverage. Lastly, for consistency with other analyses from the WIHS cohort [2], we used a definition of diabetes that included use of diabetic medications as a diagnostic criterion. It is possible that some women were prescribed diabetic medications for indications other than diabetes, such as polycystic ovary disease, impaired glucose tolerance, or abdominal fat accumulation. Strengths of this study include the relatively large sample size and the racial/ethnic diversity of the population.

In summary, we found that A1C modestly underestimated glycemic control, as assessed by concurrent fasting plasma glucose concentration, in HIV-infected women. Fasting blood

glucose was therefore a reasonable surrogate for A1C in this population. The small difference in fasting glucose-adjusted A1C observed between HIV-infected and HIV-uninfected women disappeared after adjustment for MCV, which may be increased in HIV-infected women primarily due to concurrent zidovudine use. For individual HIV-infected patients where a discrepancy exists between measured plasma glucose and A1C values, such as in the setting of MCV elevations, clinicians should consider more frequent self-monitoring of blood glucose or using other less well validated measures of glycemia such as fructosamine [17].

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Table 1Characteristics of Study Participants at Index Visit^a

Variable	HIV-Infected	HIV-Uninfected	P-value ^b
No. of women	315	109	
Age (yr)	43.7 ± 8.0	41.5 ± 8.9	0.063
Race/ethnicity			
African American	46 (14.6%)	10 (9.2%)	
Hispanic	184 (58.4%)	66 (60.6%)	
White	77 (24.4%)	33 (29.3%)	
Other	8 (2.5%)	1 (0.9%)	0.30
HIV risk group			
Injection drug use	112 (34.8%)	28 (25.7%)	
Heterosexual	123 (38.9%)	31 (28.4%)	
Blood transfusion	9 (2.6%)	5 (4.6%)	
None	69 (23.6%)	45 (41.3%)	< 0.001
Clinical AIDS at or before visit	164 (52.1%)	NA	
Body mass index (kg/m ²)	30.6 ± 8.1	35.1 ± 8.7	< 0.001
CD4 count (/mm ³), median (interquartile range)	502 (260, 661)	NA	
HIV viral load (log ₁₀ copies/mm ³)	2.86 ± 1.09	NA	
Detectable HIV viral load	143 (42.1%)	NA	
HCV RNA positive	132 (42.0%)	67 (63.2%)	0.26
Fasting glucose (mg/dL)	136 ± 71	142 ± 66	0.17
Hemoglobin A1C (%)	6.4 ± 2.0	6.8 ± 2.0	0.025
Mean corpuscular volume (fl)	97.0 ± 12.2	88.0 ± 8.0	< 0.001

^aContinuous variables are expressed as mean ± standard deviation (unless otherwise specified) and categorical values are expressed as n (%)^bChi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables

Table 2

Factors Associated with Hemoglobin A1c Values in HIV-Infected and HIV-Uninfected Diabetic Women from Bivariate and Multivariate Linear Regression of Log Hemoglobin A1c

Variable	Bivariate model ^a			Multivariate model ^b		
	Percent Change ^c	95% Confidence Interval	P-value	Percent Change ^c	95% Confidence Interval	P-value
HIV-infected	-1.32	-2.56, -0.06	0.040	-0.28	-1.36, 0.81	0.617
Age (per 10 years)	0.22	-0.39, 0.83	0.483			
Race						
Black	referent			referent		
White	-2.89	-4.16, -1.60	< 0.001	-1.80	-2.99, -0.59	0.004
Other	-2.04	-3.42, -0.70	0.003	-1.31	-2.37, -0.24	0.017
Family history of diabetes mellitus	1.08	-0.06, 2.24	0.063			
Diabetic medication	6.10	4.83, 7.38	< 0.001	5.71	4.50, 6.94	< 0.001
BMI category (kg/m ²)						
< 25	referent					
≥ 25 – 29	-0.50	-2.03, 1.05	0.523			
≥ 30	1.70	0.29, 3.12	0.018			
Hemoglobin (g/dL)	-0.37	-0.70, -0.03	0.033			
Mean corpuscular volume (per 10 fL)	-1.86	-2.30, -1.42	< 0.001	-1.61	-2.01, -1.20	< 0.001
Albumin (g/dL)	-0.89	-1.97, 0.20	0.109			
HCV RNA positive	-0.71	-1.90, 0.50	0.249			

^a Adjusted for log plasma glucose concentration

^b Final model from stepwise multiple regression model of all variables in this table (including log fasting plasma glucose and HIV serostatus, which were forced into the model)

^c Reflects the percentage change on a multiplicative scale relative to the referent group, obtained as $100(\exp\beta - 1)$ where β is the regression coefficient (or corresponding lower or upper confidence limit for this coefficient) using log-transformed hemoglobin A1c as the outcome

Table 3

Factors Associated with Hemoglobin A1c Values in HIV-Infected Diabetic Women from Bivariate and Multivariate Linear Regression of Log Hemoglobin A1c

Variable	Bivariate model ^a			Multivariate model ^b		
	Percent Change ^c	95% Confidence Interval	P-value	Percent Change ^c	95% Confidence Interval	P-value
Age (per 10 years)	0.08	-0.67, 0.83	0.840	0.72	0.05, 1.38	0.034
Race						
Black	referent			referent		
White	-2.64	-4.14, -1.12	<0.001	-1.79	-3.28, -0.28	0.020
Other	-2.24	-3.75, -0.71	0.004	-1.42	-2.61, -0.22	0.021
Family history of diabetes mellitus	0.55	-0.75, 1.87	0.15			
Diabetic medication	5.65	4.21, 7.10	<0.001	4.91	3.50, 6.34	<0.001
cART use	-1.41	-2.60, -0.20	0.023			
PI use	-0.38	-1.61, 0.87	0.548			
NNRTI use	-1.80	-3.04, -0.55	0.005			
Zidovudine use	-1.59	-2.99, -0.17	0.029			
Stavudine use	-0.96	-2.17, 0.26	0.123			
Abacavir use	-0.84	-2.25, 0.59	0.247			
BMI category (kg/m ²)						
< 25	referent					
≥ 25 – 29	-0.83	-2.42, 0.79	0.313			
≥ 30	1.44	-0.15, 3.05	0.075			
Hemoglobin (g/dL)	-0.41	-0.79, -0.02	0.038			
Mean corpuscular volume (per 10 fL)	-1.86	-2.36, -1.36	<0.001	-1.77	-2.21, -1.33	<0.001

Variable	Bivariate model ^a			Multivariate model ^b		
	Percent Change ^c	95% Confidence Interval	P- value	Percent Change ^c	95% Confidence Interval	P- value
Albumin (g/dL)	-1.18	-2.38, 0.03	0.056			
CD4 (per 100 cells/mm ³)	0.13	-0.06, 0.32	0.181	0.23	0.05, 0.40	0.011
Detectable HIV RNA	-1.06	-2.27, 0.13	0.080			
HCV RNA positive	-1.12	-2.49, 0.27	0.114	-1.44	-2.69, -0.18	0.025

^a Adjusted for log plasma glucose concentration

^b Final model from stepwise multiple regression model of all variables in this table (including log glucose, which was forced into the model)

^c Reflects the percentage change on a multiplicative scale relative to the referent group, obtained as $100(\exp\beta - 1)$ where β is the regression coefficient (or corresponding lower or upper confidence limit for this coefficient) using log-transformed hemoglobin A1c as the outcome

Abbreviations: cART, combination antiretroviral; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

Table 4

Association of HIV Status, NRTI Use, and Mean Corpuscular Volume with Percent Change in Log Hemoglobin A1c Values from Multivariate Linear Regression Models

	Model 1			Model 2 ^a		
	Percent Change ^b	95% CI	P-value	Percent Change ^b	95% CI	P-value
Log plasma glucose (mg/dL)	56.94	52.18, 61.85	<0.001	53.97	49.23, 58.85	<0.001
HIV Status/Specific antiretroviral use:						
HIV-uninfected	referent			referent		
HIV-infected not taking ZDV or 3TC	-0.34	-1.71, 1.05	0.631	-0.03	-1.35, 1.31	0.964
HIV- infected taking 3TC but not ZDV	-1.53	-3.06, 0.03	0.055	-0.07	-1.67, 1.55	0.934
HIV-infected taking ZDV with or without 3TC	-2.40	-4.01, -0.77	0.004	1.26	-0.61, 3.16	0.187
Mean corpuscular volume (per 10 fL)				-2.10	-2.70, -1.60	<0.001

^aModel 2 is identical to Model 1 except for inclusion of mean corpuscular volume as a covariate

^bReflects the percentage change on a multiplicative scale relative to the referent group, obtained as $100(\exp\beta - 1)$ where β is the regression coefficient (or corresponding lower or upper confidence limit for this coefficient) using log-transformed hemoglobin A1c as the outcome

Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; 3TC, lamivudine; ZDV, zidovudine