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Racial Disparity in HbA1c Persists When Fructosamine is Used as a Surrogate for Mean Blood Glucose in Youth with Type 1 Diabetes

Stuart Chalew, MD, Mahmoud Hamdan, MD

Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, Louisiana State University Health Science Center, New Orleans, LA and the Children's Hospital of New Orleans

Abstract

Introduction: Blacks have been reported to have higher HbA1c than Whites even after adjustment for differences in blood glucose levels. Potentially glucose-independent racial disparity in HbA1c is an artifact of glucose ascertainment methods. In order to test this possibility we examined the relationship of HbA1c with race after adjustment for concurrent fructosamine level as a surrogate for mean blood glucose (MBG).

Methods: Youth with T1D self-identified as either Black or White had blood drawn for HbA1c, fructosamine CBC, ferritin, and soluble transferrin receptor (sTfR) at a clinic visit. MBG was calculated as the average of self-monitored capillary glucoses over the preceding 30-days. The effect of race on HbA1c was evaluated in a general linear model adjusting for either MBG or fructosamine, along with other covariates.

Results: Fructosamine was correlated with both HbA1c ($r=0.73$, $p<0.0001$), MBG ($r=0.46$, $p<0.0001$), RDW-CV ($r=0.31$, $p=0.0045$), Fe ($r=0.27$, $p=0.017$), sTfR ($r=0.32$, $p=0.0042$). HbA1c was approximately 0.7% higher in Blacks than Whites after adjustment for fructosamine along with age, gender, RDW-CV, Fe, sTfR.

Conclusions: Blacks tend to have higher HbA1c than Whites even after statistical adjustment for fructosamine levels as a surrogate for MBG. Thus, HbA1c tends to overestimate corresponding MBG or fructosamine levels in Black patients. Racial differences should be taken into consideration when using HbA1c as a guide to diagnosis and therapy of diabetes in mixed race populations

Introduction:

The biochemical formation of HbA1c by the non-enzymatic attachment of glucose to Hb within the red blood cell is proportional to the glucose concentration (1). HbA1c is highly correlated with mean blood glucose (MBG) calculated from even a single-day glucose profile set (2, 3). Unlike costly and labor intensive procedures for collecting multiple glucose samples to calculate MBG, HbA1c can be obtained from a single sample of blood, and requires patient collaboration limited to allowing the sample to be drawn (4). Clinical assay

of HbA1c has become readily available and is nationally standardized(5). Furthermore HbA1c was found to be a predictor for the development of chronic complications in patients with diabetes(6). These advantageous features of HbA1c led it to become a widely used clinical and research metric for estimation of MBG(4). HbA1c is not only an established criterion to guide diabetes management but also is recommended as a diagnostic tool for diabetes(7).

When HbA1c measurements are obtained in clinical settings without concurrent glucoses to calculate MBG, it is generally presumed from the biochemistry of HbA1c formation and the correlation of HbA1c with MBG, that higher HbA1c between groups of patients is due to higher MBG between those groups(8). However, multiple studies where HbA1c and concurrent measures of glucose were available have provided evidence that HbA1c tends to be higher in Blacks even after adjustment for blood glucose levels(9–13). Thus, HbA1c tends to overestimate MBG for many Black patients which would compromise its usefulness as a guide to diabetes management and for diagnosis of diabetes across racial groups. The mechanism for MBG-independent higher HbA1cs in Blacks is unclear. It is not explained by differences in RBC indices(13) or iron status(14) .

Estimation of a patient's MBG level from multiple glucose samples over time is challenging. It requires considerable cooperation from each patient in order to obtain a sufficient number of glucose measures at appropriate times of the day that will yield the most comprehensive estimate of MBG(15). The patient also needs training in technique as well as specialized equipment and supplies to properly obtain each glucose sample(16). In order to estimate MBG, The Diabetes Control and Complications Trial (DCCT) periodically had patients collect a one day, 7-sample "glucose profile set" with samples to be obtained before and after breakfast, lunch, and dinner, as well as before bed. There were no overnight samples. Not all patients were able to regularly collect all 7 samples. Furthermore, it was not clear how well the average of a 7-sample set of glucoses from a single day reflect the true MBG over the preceding days and weeks(16–18).

With the advent of home glucose monitors we and others have calculated MBG from multiple capillary glucose samples collected by patients over several weeks time preceding the drawing of HbA1c sample(19–22). In prior studies, we have relied on estimates of MBG derived from stored data in patients' home glucose meters in the month before their clinic visit(22). The MBG obtained from home glucose sampling and HbA1c are highly correlated(13, 20, 22, 23). But MBG from home glucose monitoring data has limitations . Patients typically are sampling preprandially, there is variation in number and timing of samples each day between individual patients. Few patients regularly obtain glucose samples overnight in the early morning hours. Technique of obtaining the sample may vary between patients. Thus estimation of MBG from home meter data obtained over multiple days and weeks is labor intensive, costly, may be affected by equipment, patient technique and motivation, and sampling frequency(4). There may be variation in sampling frequency among patients of different race, income and age (24). Use of a single day glucose profile sets or just a single fasting or single postprandial glucose sample also have limitations when trying to carefully define the relationship between MBG and HbA1c.

Potentially differences in how glucose samples are obtained and MBG calculated might cause artifacts in the relationship between glucose and HbA1c which underlie the observed racial disparity in HbA1c. In order to confirm the presence of a biological difference in HbA1c between the races not due to MBG it would be desirable to use an alternate metric of glycemia that would be free of factors potentially interfering with sampling and which might skew estimation of MBG from a single sample or a series of directly drawn glucoses .

Fructosamine refers to circulating plasma proteins, predominantly albumin, which have been non-enzymatically glycated in the circulation. Concurrent fructosamine levels are correlated with both MBG and HbA1c. Fructosamine has been previously used as an alternative metric for assessment of glycemia (25, 26). Between-patient biological variation in HbA1c has been documented using fructosamine as surrogate for MBG(26). In this study to eliminate potential patient and environmental factors which might skew MBG estimates, we compared HbA1c from Black and White youth with type 1 diabetes (T1D) adjusting the data for concurrent fructosamine levels serving as a surrogate for MBG.

Methods:

Youth with T1D from the Children's Diabetes Center at Children's Hospital of New Orleans, LA from families who self-identified as either Black or White were recruited for a study of iron status on HbA1c. All patients had typical clinical presentation of T1D, had at least one anti-pancreatic autoantibody positive at time of diagnosis, required insulin for metabolic control of diabetes. Patients were studied at least one year post diagnosis and were biochemically euthyroid. None of the patients were on oral hypoglycemic agents. Examination of whether there was a fructosamine-independent racial difference in HbA1c was part of a preplanned analysis. The study was reviewed and approved by the Louisiana State University Health Sciences Center Institutional Review Board, New Orleans, LA (protocol #9227). Parent/guardian and patient signed informed consent or assent as appropriate.

At the time of clinic visit, blood was drawn for HbA1c, complete blood count (CBC), ferritin (Fe) and soluble transferrin receptor (sTfR). A fructosamine sample was also obtained. MBG was derived from the average of self-monitored capillary glucoses from the patient's home glucose meter, collected during the 30-days prior to the clinic visit as previously described(13, 27). Patients were in good general health at the time of clinic visit. Patients with abnormal thyroid function, macroalbuminuria, or hypoproteinemia were excluded from the study.

HbA1c was assayed by immunoassay in the Vista automated system at the Children's Hospital Clinical lab, this assay is standardized through The National Glycohemoglobin Standardization Program(5). HbA1c is reported as percent of total hemoglobin. Fructosamine levels from the same blood draw were assayed at ARUP, Salt Lake City, Utah in a Roche Cobas C analyzer utilizing a colorimetric reaction method with nitroblue tetrazolium(28, 29). Fructosamine levels were not corrected for total protein. Pre-assay, fructosamine samples were collected and stored per ARUP guidelines and assayed within one week of being drawn. Fructosamine is reported in units of $\mu\text{mol/L}$.

Red cell distribution width (RDW), RDW coefficient of variation (RDW-CV) and other CBC indices were determined on a Sysmex XN-1000™ Hematology Analyzer in the Children's Hospital of New Orleans clinical lab.

Statistical Analysis: Pearson correlation between fructosamine and the other variables were calculated (using PROC CORR of Statistical Analysis System). Unadjusted group differences in means of variables between Black and White patients were initially compared by t-test (using PROC TTEST of Statistical Analysis System). The relationship of HbA1c with MBG or fructosamine, statistically adjusted for the presence of race, gender, chronologic age, RDW-CV, ferritin (Fe), soluble transferrin receptor (sTfR) were further tested in multiple variable regression models (using PROC GLM of Statistical Analysis System). Besides MBG or fructosamine, and race, the other independent variables in the model were chosen beforehand. The ratio of the soluble transferrin receptor divided by the ferritin level was also calculated as another metric of iron status (30). Gender, chronologic age, RDW-CV were chosen as covariates in the model as they had been previously reported to be independent factors associated with HbA1c levels. As there is conflicting evidence as to whether iron status influences fructosamine levels (31) ferritin, sTfR and the their ratio were also included in the analysis. Variables which were not normally distributed were log transformed prior to entry into the model. In the regression models the difference in HbA1c between Black and White patients was tested on the least squares means adjusted for MBG or fructosamine, race, age, gender, ferritin , sTfR and RDW-CV. Results were considered to be statistically significant at $p=0.05$ level or less.

Results:

Seventy-nine patients with a complete set of data for concurrent HbA1c, fructosamine, MBG, ferritin, sTfR and CBC were evaluated. The group consisted of 35 Black, 44 White, ranging in age from 5 to 21 years, 40 female, 39 male. The gender ratio female/male for Blacks was 13/22 and for Whites 27/17 (the gender composition differed between the groups $p=0.0324$). Characteristics of the patients are presented in Table 1 by race. In univariate comparison Blacks had higher HbA1c, MBG, fructosamine, ferritin, soluble transferrin receptor and RDW-CV than Whites. Age, duration of diabetes, hemoglobin levels and sTfR/fe ratio were not different between the groups.

Pearson correlations between fructosamine with HbA1c, MBG, RDW-CV, ferritin, sTfR duration of diabetes and chronologic age are presented in Table 2. Fructosamine was correlated with both HbA1c and MBG, as well as with RDW-CV Ferritin and sTfR.

HbA1c was then analyzed as the dependent variable in a multiple variable general linear model with race, gender, age, RDW-CV, ferritin, sTfR and either MBG or fructosamine level. Race was statistically significant in both models after adjustment for the other variables, with Blacks having higher HbA1c compared to Whites (overall model $R^2=0.38$, $p<0.0001$) least squares means of HbA1c adjusted for MBG and covariates 9.8% Blacks vs 8.9% Whites, $p=0.0118$). When fructosamine was substituted in the model (overall $R^2=0.61$, $p<0.0001$) for MBG blacks again had higher HbA1c after adjustment for other variables (least squares means 9.7 % for Blacks vs 9.0 % for Whites, $p=0.0158$). MBG and

fructosamine were also significant covariates in the respective models. Figure 1a depicts the relationship between HbA1c vs MBG by race while figure 1b depicts the relationship between HbA1c vs fructosamine by race. We further evaluated fructosamine as a dependent variable and MBG, race and the other covariates as independent variables, Ismeans of fructosamine for Blacks was 466 $\mu\text{mol/L}$ which was not statistically different from that for Whites 422 $\mu\text{mol/L}$ ($p=0.2217$).

Discussion:

Prior studies from our group and others have suggested that HbA1c levels tend to be higher in Black patients compared to Whites even at similar levels of MBG and adjustment for other covariates (9–13). Recognition that a component of racial disparity in HbA1c is independent of glucose concentration has been contentious (32) in part due to potential problems in accuracy of estimating MBG from a finite number of glucose samples. To improve accuracy of MBG determinations for comparison with HbA1c investigators have turned to continuous glucose monitoring (CGM). The ADAG study reported a trend for Black patients to have higher HbA1c than Whites at the same MBG(18). More recently the Type 1 Diabetes Exchange conducted a CGM study which confirmed higher HbA1c, - independent of MBG between Black and White patients with diabetes (33). . Higher adjusted HbA1c were found in Blacks even after study data was stratified by age in patients younger than 18 years and those 18 years and older (33, 34).

The current study attempted to avoid various limitations associated with deriving MBG from various glucose sampling by techniques including CGM (35) by using fructosamine as a surrogate for MBG. Fructosamine is a group of circulating serum proteins, primarily albumin, which become non-enzymatically glycated extracellularly through the Maillard reaction(25). As fructosamine levels can be influenced by processes which alter the amount of total circulating serum proteins, some authorities recommend adjusting fructosamine levels for total serum protein levels (31, 36). Fructosamine can be assayed from a single blood sample and thus does not have problems that are associated with getting patient cooperation to obtain multiple glucose levels throughout the day in order to get the best approximation of the true MBG(25, 31). Fructosamine levels are highly correlated with MBG and HbA1c(25). Fructosamine can be used as a metric for glycemic control in situations where HbA1c measurement may be confounded by differences in red cell turnover (31). Fructosamine has also been previously used as an alternate for MBG, to assess between-patient biological variation in HbA1c not due to MBG. Cohen et al described the use of fructosamine as a surrogate for MBG to quantify MBG-independent between-patient differences in HbA1c (26). This fructosamine-based method gave similar information to an index based on calculated MBGs (37).

Using fructosamine as a surrogate for MBG, we found that Black patients had higher HbA1c than White patients at the same given level of fructosamine and adjusted for potential influence of age, gender, ferritin, sTfR and RDW-CV. This was similar to the results using MBG derived from self-monitored home capillary blood glucoses. There was no interaction of race with MBG or fructosamine. Our results also suggest that fructosamine could be a low

cost, easily obtained alternative to MBG calculated by CGM or other techniques in the evaluation of glucose-independent biological variation in HbA1c.

In contrast to findings with HbA1c, we tested but did not find a glucose-independent racial difference in fructosamine in our study population. Our finding complements data from the CARDIA study where there was no racial difference in fructosamine in adult patients with diabetes (38). However the CARDIA investigators did find higher adjusted levels of fructosamine in blacks versus whites who did not have diabetes(38). The Type 1 Diabetes Exchange Group did not find a difference between blacks (n=104) and whites (n=104) for fructosamine or glycated albumin after adjustment for MBG determined by continuous monitoring in a mixed population of children and adults (33). These findings suggest that the glucose-independent racial disparity in HbA1c is due to factors involved with glycation of Hb within the erythrocyte as fructosamine is glycated extracellularly(35).

There is conflicting evidence as to whether fructosamine is influenced by iron status(31, 39). In this population we found that ferritin and sTfR but not their ratio was higher in Blacks than Whites. Fructosamine had simple correlation with RDW-CV, ferritin, and sTfR, but not the ratio of sTfR/ferritin. We previously found that HbA1c was also correlated with RDW-CV, ferritin, and sTfR, but not the ratio of sTfR/ferritin. In a multiple variable regression model fructosamine was statistically associated with MBG and sTfR, but not race and the other covariates. It is not clear whether the correlation of fructosamine with RDW-CV, ferritin, and sTfR is due to direct influence of iron metabolism on glycation (39) or merely an associated correlation shared by HbA1c and fructosamine which are both highly correlated.

In the current study, Black youth with T1D tended to have ~ 0.7% higher HbA1c than Whites even after adjustment for concurrent fructosamine levels and other covariates. This difference is similar to our prior findings after adjustment for MBG derived from SMBG(10, 13). This is further evidence that higher HbA1c in Black patients is not simply due to higher MBG in those patients nor an artifact of technical issues related to how MBG was derived from patient glucose sampling. At present the mechanism leading to MBG-independent racial disparity in HbA1c levels is unclear. MBG-independent racial differences in HbA1c persist after adjustment for RBC indices, iron status and measures of inflammation(13, 40). Potentially, differences in RBC lifespan, intra-RBC deglycating enzymes, intra-RBC glucose metabolism(41–43) may contribute to biological variation of HbA1c at the same exposure to glucose. Differences in genetic loci between ethnic groups are under study in relation to glucose-independent differences in HbA1c (44, 45). Determination of the precise mechanism/s for HbA1c racial disparity remains a focus of ongoing inquiry. The occurrence of clinically meaningful differences in HbA1c between Blacks and Whites not due to glucose may require a reappraisal of the current approach to assessing diabetes management and diagnosis of diabetes in racially diverse populations(12, 46, 47).

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Figure 1. Relationship of HbA1c versus Mean Blood Glucose (MBG) or Fructosamine by Race in Youth with Type 1 Diabetes. Figure 1a HbA1c vs MBG. Overall Blacks have higher HbA1c than Whites ($p=0.0118$) after statistical adjustment for MBG along with RDW-CV, ferritin, sTfR, gender, and age. MBG was also significantly associated with HbA1c ($p<0.0011$). Figure 1b HbA1c vs Fructosamine. Overall Blacks have higher HbA1c than Whites ($p=0.0158$) after statistical adjustment for fructosamine along with RDW-CV, ferritin, sTfR, gender, and age. Fructosamine was also significantly associated with HbA1c ($p<0.0001$). Black patients represented filled circles and solid regression line, White patients represented by open circles and interrupted line.

Table1.

Patient Characteristics by Race Unadjusted for other variables.

<i>Variable</i>	<i>N</i>	<i>Mean</i>	<i>SD</i>	Black		White		<i>p=</i>
				<i>N</i>	<i>Mean</i>	<i>SD</i>		
Age (Yrs)	35	14.3	3.4	44	14.2	3.7		NS
Diabetes Duration (Yrs)	35	7.1	3.8	44	6.9	5.3		NS
HbA1c (%)	35	10.0	1.8	44	8.7	1.2		0.0004
Fructosamine (μmol/L)	35	468.7	103.9	44	404.4	60.4		0.0020
MBG (mg/dL)	35	252.2	61.2	44	217.4	59.7		0.013
Hemoglobin (g/dL)	35	13.8	1.2	44	13.7	0.9		NS
RDW-CV (%)	34	12.8	1.0	44	12.4	0.6		0.0194
Ferritin	35	57.5	52.3	44	36.6	22.4		0.0326
sTfR	35	4.5	1.1	44	3.9	1.4		0.0341
Ratio	35	0.1	0.1	44	0.2	0.2		NS

Table 2.

Simple Pearson Correlations of Fructosamine versus other variables. MBG=Mean Blood Glucose, Hbb=hemoglobin, RDW-CV=RBC distribution width coefficient of variation, sTfR=soluble transferrin receptor, ratio=sTfR/ferritin, Duration=duration of diabetes.

	HbA1c	MBG	Hb	RDW-CV	Ferritin	sTfR	Ratio	Age	Duration
<i>Fructosamine</i>	0.73031	0.45733	0.05062	0.31821	0.26792	0.31857	-0.06783	0.05988	0.18944
p	<.0001	<.0001	0.6577	0.0045	0.0170	0.0042	0.5525	0.6001	0.0945
	79	79	79	78	79	79	79	79	79