Non-Hispanic Black Individuals Have Higher Glucose-Adjusted HbA_{1c} Levels and Risk for Severe Hypoglycemia: Evidence From the Diabetes Control and Complications Trial

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Recognition of racial disparities that affect diabetes management is important for improving care and subsequent outcomes among high-risk patients. Recent data from our group (1) and others using continuous glucose monitoring suggest that Non-Hispanic Black (NHB) patients have higher HbA_{1c} levels at any given level of mean blood glucose (MBG) compared with Non-Hispanic White (NHW) patients. We hypothesized that the occurrence of racial disparity in HbA_{1c} adjusted for MBG between NHB and NHW patients would be generalizable and evident in participant data from the landmark Diabetes Control and Complications Trial (DCCT). As this disparity would have been unrecognized at the time of the DCCT, NHB participants potentially would have been at greater risk for severe hypoglycemia when HbA_{1c} was a principal guide of therapy.

We analyzed publicly available data from the DCCT for 1983–1993. Details of study design, recruitment, and protocol for documentation of recalled severe hypoglycemia have been previously published (2). We paired HbA_{1c} determined by the DCCT high-performance liquid chromatography method with concurrently obtained MBG derived from each patient's quarterly glucose profile set. MBG was the average of the glucose profile sets and represented as the median of profile set averages over the same quarter of each study visit.

Modeling of racial difference in the relationship between HbA_{1c} and MBG was evaluated using mixed effects general linear modeling. The risk of severe hypoglycemia was evaluated using Poisson regression modeling. Both models consider the correlation across multiple assessments as well as differences in MBG, age, gender, diabetes duration, visit year and quarter, patient BMI, study group (intensive vs. standard care), and stratum (primary vs. secondary prevention). It also evaluated the need for interactive effects by race and higher-order effects of independent variables, especially in MBG assessments.

Of 1,441 participants in the DCCT, 1,391 were NHW individuals and 29 were NHB individuals. Participants were followed for a median of 17 visits over 5 years. Figure 1*A* depicts the relationship of predicted HbA_{1c} versus MBG by race over the course of the DCCT. The interaction of MBG and race was highly significant, with NHB participants having higher HbA_{1c} than NHW participants at any given level of MBG ($P = 0.013$). The HbA_{1c} difference was greatest at lower MBG levels. The difference in HbA_{1c} between NHB and NHW participants by MBG adjusted for covariables was 0.51 at MBG 150 mg/dL ($P = 0.03$) and 0.39 at MBG 450 mg/dL ($P = 0.09$).

Among NHW patients, there were 2,454 episodes of severe hypoglycemia, with 690 patients having at least one episode, compared with 68 episodes for 15 NHB individuals. The occurrence of severe hypoglycemia versus HbA_{1c} by race is depicted in Fig. 1*B*. The relative risk (RR) of severe hypoglycemia was 92% greater (RR 1.92, 95% CI 1.11–3.32, $P = 0.02$) in NHB patients and was most pronounced at lower HbA_{1c} levels.

This new analysis of DCCT data indicates that use of HbA_{1c} overestimated MBG among NHB patients and was associated with higher risk of severe hypoglycemia among the NHB enrollees. Although the number of NHB participants in the DCCT was relatively small compared with the number of NHW participants, the large number of multiyear observations for each participant made statistical detection of these differences possible. It is likely that unrecognized, glucose-independent racial disparity in HbA_{1c} has led to more aggressive insulin dosing and greater occurrence of hypoglycemia in NHB participants, especially those participants in the intensive arm of the study, where management was based on treatment to a specific HbA_{1c} target. Since the DCCT, many reports have suggested that

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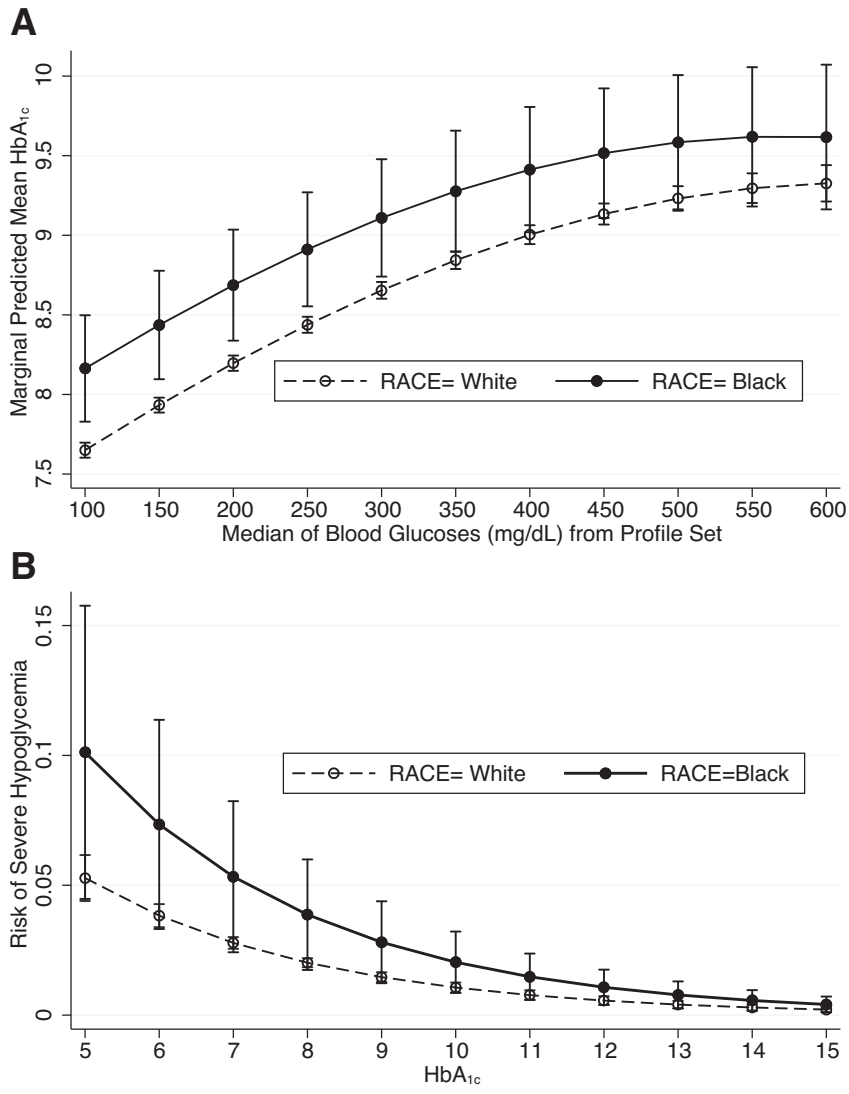

Figure 1—Predicted mean HbA_{1c} and risk of severe hypoglycemia by race for DCCT participants. *A*: Predicted mean HbA_{1c} versus median MBG by race for DCCT participants. Data are shown with 95% CI. HbA_{1c} overestimated MBG for NHB patients compared with NHW patients at the same level of MBG ($P = 0.001$). *B*: Predicted risk of severe hypoglycemia versus HbA_{1c} by race for DCCT participants adjusted for median blood glucose, age, sex, diabetes duration, BMI, study group, and study stratum. The 95% CI are shown. NHB patients had higher risk for severe hypoglycemia with decreasing HbA_{1c}. The RR of severe hypoglycemia was 92% greater (RR 1.92, 95% CI 1.11–3.32, $P = 0.02$) in NHB patients compared with NHW patients.

NHB patients are at greater risk for episodes of severe hypoglycemia during treatment. This may be due to lack of recognition that HbA_{1c} treatment targets are derived from predominantly NHW populations and may overestimate actual MBG levels for NHB patients (3,4).

In addition, HbA_{1c} appears to be a better predictor of microvascular complications even after adjustment for the influence of MBG (5). If so, racial difference in adjusted HbA_{1c} may be indicative of factors besides MBG, putting NHB patients at greater likelihood for development and progression of complications.

In conclusion, DCCT data indicate that HbA_{1c} overestimates MBG in NHB patients when referenced to an NHW population. This unrecognized difference may be associated with greater occurrence of hypoglycemia for NHB patients. Changes in insulin dosing based on an individual patient's glucose pattern rather than HbA_{1c} target may reduce the risk of severe hypoglycemia, especially in NHB patients. Further study will be needed to determine if higher glucose-adjusted HbA_{1c} levels are a predictor of increased risk for complications in NHB patients.

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