Impact of Race on the Incidence of Hypoglycemia in Hospitalized Older Adults With Type 2 Diabetes

Adline Ghazi, MD, Lawrence R. Landerman, PhD, Lillian F. Lien, MD, and Cathleen S. Colon-Emeric, MD, MHS

Hypoglycemia is a potentially serious adverse drug event in hospitalized patients with diabetes that has been associated with worse hospital outcomes, including increased mortality.[1–4] The risk of hypoglycemia also increases with age, especially among patients treated with insulin and those with recent hospitalizations.[2,5–8] Associations between African-American race and increased risk of hypoglycemia have been reported in studies in the outpatient setting,[5,6] as well as during hospitalization.[2]

In these studies, the association between race and hypoglycemia was incidentally noted when analyzing the basic demographics of the patients. However, no study to our knowledge has attempted to explore the clinical factors that could potentially explain this association. Consequently, the objectives of this study were *1*) to determine the impact of race on the incidence of hypoglycemic events in hospitalized older adults with type 2 diabetes and *2*) to find out which clinical factors explain the differential risk.

Research Design and Methods

Setting and population

Using an automated research tool that searches electronic clinical data, we identified all adults with type 2 diabetes ≥ 65 years of age who were admitted to medical or surgical wards at Duke University Hospital in Durham, N.C., between 1 January 2006 and 29 December 2009. Subjects were excluded if their admission was *1*) for an admission diagnosis of hypoglycemia, *2*) for palliative care, or *3*) to an intensive care unit, step-down unit, recovery room, or oncology ward. After implementing these exclusion criteria, we identified 650 participants. All study procedures were approved by the Institutional Review Board at Duke University Medical Center.

Data collection

Electronic medical records, including patients' admission history and physical examination, pharmacy orders, laboratory results, and discharge summary, were abstracted to obtain data on baseline demographics, comorbidities, medications on admission, laboratory results on admission, place of residence before admission, and treating hospital service. Medication administration records were not available for review. However, pharmacy orders were reviewed to identify all hypoglycemic agents ordered within 24 hours of the first hypoglycemic event (if present) or in the first 24 hours of admission (if no hypoglycemic events occurred).

IN BRIEF

Hypoglycemia is a serious adverse event leading to bad outcomes in hospitalized patients. The risk of hypoglycemia has been previously associated with the African-American race. This retrospective study of hospitalized older adults aimed to identify clinical factors that could explain this association. The home diabetes regimen partially explains the increased risk of hypoglycemia during hospitalization for older African-American men with diabetes.

Hypoglycemia definition

Hypoglycemia was defined according to the American Diabetes Association[9] as a blood serum glucose or capillary glucose < 70 mg/dl. If multiple hypoglycemic events occurred in a single patient during his or her hospitalization, the first was considered the index event.

Statistical analysis

To determine the impact of clinical factors on time until a hypoglycemic event, we used Cox regression models. The analysis proceeded in four models:

1. We estimated the effects of race on hypoglycemic events controlling for age and sex.
2. We determined the degree to which racial differences are the result of comorbidities and home diabetes therapies by adding these covariates to the model.
3. We determined whether racial differences are the result of hospital diabetes therapies by adding these covariates to the model.
4. We tested for the presence of nonproportionality, a pattern in which the effect of a predictor on the hazard rate changes over the observation period.

At each stage in the model-building process, we retained age, race, sex, and any other previous-stage variable with a P value < 0.05, controlling for other predictors. Other demographic characteristics and treatment location were not significant in univariate testing and were not included in the models.

We report descriptive statistics on the variables used in these analyses and their bivariate associations with a hypoglycemic episode.

Study Results

In this study of 650 patients with type 2 diabetes, 342 patients (52.6%) were white, and 308 (47.4%) were African American (Table 1). The incidence of one or more hypoglycemic events during hospitalization (blood glucose < 70 mg/dl) was 28.61% for the entire cohort and 32.79% among African-American patients. Before adjusting for other factors, hypoglycemia occurred significantly more often in the patients with the following risk factors ($P < 0.05$): age ≥ 75 years, African-American race, higher admission white blood cell count, lower admission glomerular filtration

Table 1. Baseline Characteristics and the Incidence of Hypoglycemia

	All Patients (n = 650)	Patients Having One or More Hypoglycemic Episode (n = 186)	Patients Having No Hypoglycemic Episodes (n = 464)	P
Patient Characteristics (n [%])				
Age ≥ 75 years	321 (49.4)	111 (60.0)	210 (45.2)	< 0.01
Female	362 (55.7)	98 (53.0)	264 (56.8)	0.39
White	342 (52.6)	84 (45.4)	275 (59.1)	< 0.01
African American	308 (47.4)	101 (54.6)	190 (40.9)	< 0.01
Comorbidities and Location (n [%])				
Hypertension	606 (93.2)	174 (94.1)	432 (92.9)	0.60
Congestive heart failure	198 (30.5)	65 (35.1)	133 (28.6)	0.10
Coronary artery disease	341 (52.5)	91 (49.2)	250 (53.8)	0.29
Dementia	90 (13.9)	36 (19.5)	54 (11.6)	< 0.01
Cerebrovascular accident	174 (26.8)	54 (29.2)	120 (25.8)	0.38
Chronic obstructive pulmonary disease	85 (23.1)	27 (14.6)	58 (12.5)	0.47
Peripheral vascular disease	141 (21.7)	51 (27.6)	90 (19.4)	0.02
End-stage renal disease	72 (11.1)	31 (16.8)	41 (8.8)	< 0.01
Malignancy	64 (9.9)	21 (11.4)	43 (9.3)	0.42
Medical services	472 (72.6)	133 (71.9)	339 (72.9)	0.79
Surgical services	178 (27.4)	52 (28.1)	126 (27.1)	0.79
Community dweller	548 (84.3)	149 (80.5)	399 (85.8)	0.10
Nursing home resident	102 (15.7)	36 (19.5)	66 (14.2)	0.10
Laboratory Values (mean/SD)*				
Glomerular filtration rate (ml/min/1.73 m^2)	51.2/28.0	44.6/40.5	53.9/27.6	< 0.01
White blood cell count (× 10^3/μl)	9.4/4.2	10.2/5.0	9.0/3.7	< 0.01
Glucose (mg/dl)	169.0/98.3	171/86.4	168.0/102.8	0.68
A1C (%)	7.08/1.24	7.18/1.22	7.04/1.28	0.18

**Laboratory tests were performed on admission except for A1C, which was obtained within 90 days of the admission.*
SD, standard deviation

Table 2. Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for the Effects of Race on Hypoglycemia (n = 650)

	Univariate (HR [95% CI])	Model 1 (HR [95% CI])	Model 2 (HR [95% CI])	Model 3 (HR [95% CI])
African American	**1.7** (1.3–2.3)			
African-American men		**3.0** (2.0–4.6)	**2.3** (1.5–3.6)	**2.5** (1.6–4.0)
African-American women		1.1 (0.77–1.7)*	1.0 (0.7–1.5)	1.0 (0.7–1.5)
Age ≥ 75 years		**1.8** (1.3–2.4)	**1.8** (1.4–2.5)	**2.0** (1.5–1.7)
Sex		1.3 (0.83–1.9)	1.3 (0.8–1.9)	1.3 (0.9–2.1)
Home therapy: oral			1.7 (1.0–3.0)	1.5 (0.9–2.7)
Home therapy: insulin			**4.7** (2.8–7.9)	**2.2** (1.2–3.7)
Home therapy: oral and insulin			**4.1** (2.2–7.6)	**2.1** (1.1–4.0)
Hospital therapy: sliding-scale insulin				**2.4** (1.1–5.3)
Hospital therapy: long- or intermediate-acting insulin				**3.2** (2.1–4.9)
Hospital therapy: insulin infusion				**2.8** (1.5–5.5)
Glucose level				**0.5** (0.4–0.8)

**The race-by-sex interaction was statistically significant at* P < 0.01. *Interactions of race with other model 2 predictors were not significant.*
Coefficients significant at P < 0.05 *are shown in bold. Coefficients significant at* P < 0.01 *are shown in bold and underlined.*

rate, medical history of cognitive impairment, end-stage renal disease, and peripheral vascular disease (Table 2).

Incidence of hypoglycemia and home therapy

In this cohort, 38.3% were treated at home with oral hypoglycemic agents alone, 31.5% with insulin alone, 10.8% with a combination of oral agents and insulin, and 19.4% with no hypoglycemic agents. Newer noninsulin injectable therapies such as pramlintide, exenatide, and liraglutide were rarely prescribed and are not included in the analysis.

In the unadjusted analyses, being on insulin therapy without concurrent oral hypoglycemic agents at home was significantly associated with having one or more hypoglycemic events in the hospital ($P < 0.001$). On the other hand, being on oral therapy alone or on no pharmacological therapy was significantly associated with fewer hypoglycemic episodes during the hospital stay ($P < 0.0001$ for both) (Table 3).

Incidence of hypoglycemia and hospital therapy

Being prescribed sliding-scale insulin, long- or intermediate-acting insulin, or an intravenous insulin infusion during the hospital stay were significantly associated with the incidence of having one or more hypoglycemic episodes ($P < 0.01$). On the other hand, having no hypoglycemic agent prescribed was significantly associated with having fewer hypoglycemic episodes ($P < 0.0001$) (Table 3).

Bivariate and multivariable regression analyses

In model 1, age and sex were added to the model, and race-by-age and race-by-sex interactions were tested. The race-by-sex interaction was significant (HR 2.9, 95% CI 1.9–4.44), indicating that the effect of race was significantly greater among men. We therefore present the effects of race separately for men and women beginning with model 1. Controlling for age and sex, African-American men were three times more likely than white men to experience a hypoglycemic event while hospitalized. Among

Table 3. Outpatient and Inpatient Therapies and Incidence of Hypoglycemia

	All Patients (*n* = 650)	Patients Having One or More Hypoglycemic Episode (*n* = 186)	Patients Having No Hypoglycemic Episodes (*n* = 464)	*P*
Outpatient Therapies (*n* [%])				
Oral therapy only	249 (38.3)	45 (24.2)	204 (44.0)	< 0.0001
Insulin therapy only	205 (31.5)	96 (51.6)	109 (23.5)	< 0.0001
Combination of oral and insulin therapy	70 (10.8)	26 (14.0)	44 (9.5)	< 0.0001
No therapy	126 (19.4)	19 (2.9)	107 (23.1)	< 0.0001
Inpatient Therapies (*n* [%])*				
Sliding-scale insulin	553 (85.1)	179 (96.2)	374 (80.6)	< 0.0001
Long- or intermediate- acting insulin	309 (47.5)	143 (76.7)	166 (35.8)	< 0.0001
Insulin infusion	20 (3.1)	11 (5.9)	9 (2.0)	0.01
No therapy	48 (7.4)	2 (1.1)	46 (9.9)	< 0.0001
Oral agent	121 (18.6)	29 (15.6)	92 (19.8)	0.21

**Ordered within 24 hours of the incidence of hypoglycemia, if any, or admission, if no hypoglycemia*

women, there was no race difference in the hazard of a hypoglycemic event. Being ≥ 75 years of age was also positively related to the risk of hypoglycemia compared to being 65–74 years of age (HR 1.8, 95% CI 1.3–2.4).

In model 2, after controlling for age and race, home therapy with insulin alone and home therapy with a combination of oral antidiabetic agents and insulin were significantly associated with the risk of hypoglycemia (HR 4.7, 95% CI 2.8–7.9 and HR 4.1, 95% CI 2.2–7.6, respectively). The comorbidities that were significant in initial models (peripheral vascular disease, end-stage renal disease, and elevated glomerular filtration rate) became nonsignificant if home therapies were included in the model. The race effect among men was attenuated by 35% when home therapies were added to the model but remained significant.

In model 3, we controlled for all variables that were significantly associated with a hypoglycemic event. Three hospital therapies—sliding-scale insulin, long- or intermediate-acting insulin, and intravenous insulin infusion—were positively associated with a hypoglycemic event. Glucose level at admission, which had been nonsignificant in model 2, became significant in model 3 when adjusted for hospital therapies (Table 2). All model variables were examined for co-linearity, and none was found, including between home and hospital hypoglycemic therapy.

Race effect on hypoglycemia by hospital day

Tests for nonproportionality effect of race were positive; the risk of having one or more hypoglycemic events during hospitalization was at its maximum for African-American men at the first day of hospitalization and declined thereafter (Figure 1).

Discussion

This study explored the impact of race on hypoglycemia in older adults, as well as some of the factors that may explain the race effect. The results are consistent with previously reported associations between an increased incidence of hypoglycemia, older age, and African-American race. However, in our cohort, the effect was limited to men and not apparent in women. This sex difference was reported in the Diabetes Control and Complications Trial[10] in patients with type 1 diabetes but is contrary to what was reported in patients with type 2 diabetes in the Action to Control Cardiovascular Risk in Diabetes trial,[11] in which female sex was associated with an increased risk of hypoglycemia in the outpatient setting.

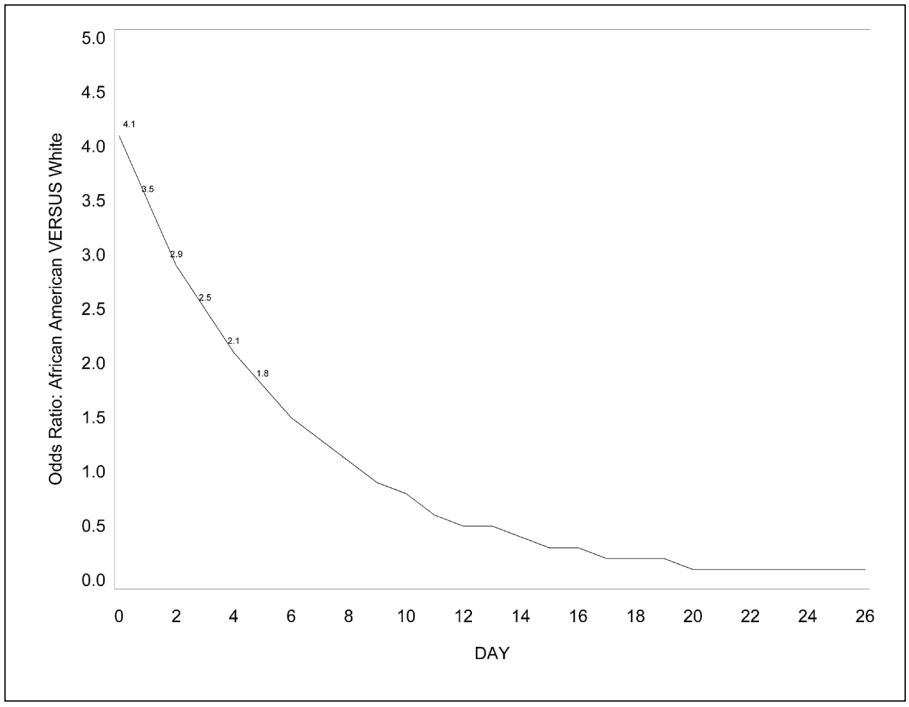

Figure 1. Impact of race on hypoglycemic events among men over the course of hospitalization (in days). Only significant odds ratios are labeled.

Of particular interest are the findings that home diabetes therapy explains part of the increased risk among African-American men, even after controlling for hospital therapy, and that the risk is greatest at admission and decreases throughout the rest of the hospitalization. Several factors could possibly explain these findings, including decreased or inconsistent adherence to medications at home, diminished ability of A1C testing to accurately assess glycemic control in African Americans, and environmental and lifestyle factors.

Nonadherence to home therapy is common in patients with diabetes and has been shown to be higher among older, African-American patients.[12–14] Consequently, these patients' outpatient medication prescriptions do not necessarily reflect what they are actually taking daily.

Medication nonadherence rates have varied widely among studies, mainly because of differences in measurement methods.[15] In a meta-analysis of 569 studies of adherence across a range of medical disorders,[16] the average nonadherence rate was estimated at 24.8% but was significantly higher (32%) among patients with diabetes. In a recent study by Roth et al.,[14] the rate of nonadherence to all medications in African-American older adults was as high as 68%. Therefore, the rate of nonadherence among African Americans seems to be particularly high, rendering them susceptible to hospital doses higher than the doses they usually take at home.

Recent data indicate that A1C values may overestimate actual glucose levels in African Americans.[17] A study of patients with impaired glucose tolerance from different ethnicities[18] showed that African Americans have higher A1C levels than whites after controlling for multiple factors, including glucose level. Other studies[12,19] have come to the same conclusion in patients without diabetes, with prediabetes, and with diabetes.

The existence of higher A1C levels in African Americans has not been fully explained. Snieder et al.[20] found genetic factors that explain about 60% of A1C variability in twins with type 1 diabetes and that could be extrapolated to help understand these ethnic differences. The overestimation of A1C in African Americans may theoretically lead to unnecessary escalation of hypoglycemic agents in the hospital to improve glycemic control, thus leading to hypoglycemia.

Environmental and lifestyle factors could be major contributors to the discrepancy between the overall amount and dose sizes of hypoglycemic agents required to achieve glycemic control at home versus in the hospital. The types and amounts of food consumed are regulated and consistent in the hospital and may differ from home practices, especially in minority populations. Additionally, it has been found that patients may use inappropriately high levels of basal insulin to attempt to control postprandial glucose elevations or between-meal snacking.[21] When such patients decrease food consumption or temporarily go without food in the hospital, this excess basal insulin can precipitate hypoglycemia.

Our study included older adults who have been found to be at a high risk of developing hypoglycemia[7] and its associated adverse outcomes. In a retrospective study using information from 70 hospitals, Curkendall et al.[2] found that hypoglycemia was associated with increased length of hospital stay, hospital mortality, hospital charges, and discharge to a skilled nursing facility. Moreover, hypoglycemia has also been shown to be associated with lower quality of life in older

adults with diabetes[22] and with a higher risk of dementia.[23]

Consequently, clinicians need to be aware of this increased risk and take measures to predict and prevent hypoglycemia in older adults, with particular attention given to African-American patients. Measures should start in the outpatient setting to ensure vigorous medication reconciliation efforts and assessment of adherence at every clinic visit. Blood glucose logs should be carefully examined on a regular basis, and patients should be assessed routinely for symptoms and signs of hypoglycemia. These efforts would avoid the unnecessary addition or dose escalation of hypoglycemic agents.

When these patients are hospitalized, equally vigorous efforts must be instituted to obtain accurate outpatient medication lists, assess outpatient diabetes control, and assess the frequency of hypoglycemia. Careful attention must be directed to changes in nutritional needs, activity levels, and the timing of prandial insulin with meals during hospitalization. For patients with decreased intake and activity who are at high risk for hypoglycemia, modest dose reductions should be considered.

This study has several limitations. Data were extracted from electronic medical records and thus were limited to information collected in routine clinical care. Data involving hospital therapy were extracted from the medication order records rather than actual medication administration records. Additionally, home oral therapy was not further stratified into different subtypes, and hospital-administered prandial short- or rapid-acting insulin was not isolated from that used in the sliding scale. Another limitation is related to the fact that hypoglycemia determination was based merely on laboratory test values in the absence of the ability to identify the coexistence of hypoglycemia symptoms. Other factors that are not studied here but could be potential explanations of a differential risk of hypoglycemia in African Americans include patient-specific factors such as duration of diabetes treatment, BMI, frequency of outpatient hypoglycemia, and problems associated with insulin delivery (e.g., differential absorption at injection sites), as well as hospitalization-specific factors such as weight-based insulin dose prescribed, frequency of blood glucose monitoring, changes in level of activity during the inpatient stay, and nutrition, particularly timing of prandial insulin injections relative to food intake.[24–26] Finally, the generalizability of this single-center study may be limited.

Conclusion

This retrospective cohort study of the impact of race on the incidence of hypoglycemia in hospitalized adults ≥ 65 years of age showed that African-American men, but not women, are at a 2.5–3 times higher risk of hypoglycemic events during hospitalization. About 35% of this effect is explained by home diabetes therapy. Adults ≥ 75 years of age are at a 1.8–2.0 times higher risk of hypoglycemia compared to those aged 65–74 years, correcting for multiple comorbidities and hospital and home therapies. The risk of hypoglycemia is highest at the beginning of a hospitalization and declines thereafter.

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Adline Ghazi, MD, is the director of the diabetes program at Medstar Good Samaritan Hospital in Baltimore, Md. Lawrence R. Landerman, PhD, is an associate professor of medicine at Duke University School of Medicine and an associate research professor in the Duke University School of Nursing in Durham, N.C. Lillian F. Lien, MD, is medical director of Duke inpatient diabetes management and an assistant professor in the Department of Medicine, Division of Endocrinology, Metabolism, and Nutrition and the Sarah W. Stedman Nutrition and Metabolism Center at Duke University Medical Center. Cathleen S. Colon-Emeric, MD, MHS, is an associate professor in the Department of Medicine, Division of Geriatrics at Duke University Medical Center and the Durham VA Medical Center Geriatric Research, Education and Clinical Center.