Brief Report—Endocrine Research

HbA1c and Heart Failure Risk Among Diabetic Patients

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Context: Diabetes is an independent risk factor for heart failure (HF); however, it is not known whether tight glycemic control can reduce the occurrence of HF among diabetic patients.

Objective: The aim of the study was to investigate the race-specific association of different levels of glycosylated hemoglobin (HbA1c) with the risk of HF among patients with diabetes.

Design, Setting, and Participants: We prospectively investigated the race-specific association of different levels of HbA1c at baseline and during an average of 6.5 years of follow-up with incident HF risk among 17 181 African American and 12 446 white diabetic patients within the Louisiana State University Hospital System.

Main Outcome Measure: We measured incident HF until May 31, 2012.

Results: During follow-up, 5089 HF incident cases were identified. The multivariable-adjusted hazard ratios of HF associated with different levels of HbA1c at baseline (<6.0% [reference group], 6.0–6.9%, 7.0–7.9%, 8.0–8.9%, 9.0–9.9%, and ≥10.0%,) were 1.00, 1.02 (95% confidence interval, 0.91–1.15), 1.21 (1.05–1.38), 1.29 (1.12–1.50), 1.37 (1.17–1.61), and 1.49 (1.31–1.69) (*P* trend < .001) for African American diabetic patients, and 1.00, 1.09 (0.96–1.22), 1.09 (0.95–1.26), 1.43 (1.22–1.67), 1.49 (1.25–1.77), and 1.61 (1.38–1.87) (*P* trend < .001) for white diabetic patients, respectively. This graded positive association was also present in diabetic patients with and without glucose-lowering agent treatment; in diabetic patients with different age, gender, and smoking status; and in incident HF defined as systolic HF (ejection fraction ≤ 40%) and HF with a preserved ejection fraction (ejection fraction > 40%).

Conclusions: The current study suggests a graded positive association of HbA1c with the risk of HF among both African American and white patients with diabetes. **(*J Clin Endocrinol Metab* 99: 0000–0000, 2014)**

Diabetes is an independent risk factor for heart failure (HF) (1). The current American Heart Association HF classification schema designates the presence of diabetes as stage A HF (patients at high risk for developing HF) (2). Several (3–5), but not all (6), observational studies suggest that the degree of glycemic control is inversely associated with the risk of HF among diabetic patients. Several large randomized controlled trials (RCTs) failed to confirm the hypothesis that tight glycemic control might reduce HF risk among diabetic patients (7–9). Thus, there is still an urgent need for more observational data to support the causality, given the lack of conclusive evidence from RCTs. We aim to examine the race-specific association between different levels of glycosylated hemoglobin (HbA1c) at baseline and during follow-up and HF risk among African American and white diabetic patients.

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Abbreviations: BMI, body mass index; CI, confidence interval; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HF, heart failure; LDL, low-density lipoprotein; RCT, randomized controlled trial.

Subjects and Methods

Study population

Louisiana State University (LSU) Health Care Services Division (LSUHCSD) operates seven public hospitals and affiliated clinics in Louisiana (10–12). Administrative, anthropometric, laboratory, clinical diagnosis, and medication data collected at these facilities are available in electronic form for both inpatients and outpatients from 1997. Using these data, we have established the LSU Hospital-Based Longitudinal Study (LSUHLS) (10). A cohort of diabetic patients was established by using the International Classification of Disease (ICD) code-9 (code 250) through the LSUHLS database between January 1, 1999, and December 31, 2009.

LSUHCSD's internal diabetes disease management guidelines call for physician confirmation of diabetes diagnoses by applying the American Diabetes Association criteria (13). The first record of diabetes diagnosis was used to establish the baseline for each patient in the present analyses due to the design of the cohort study.

The present study included 29 627 diabetic patients (12 446 white and 17 181 African American) who were 30 to 94 years of age, had no history of coronary heart disease or HF, and had complete repeated data on all risk factor variables. The study and analysis plan, including the procedure of data coding, were approved by both the Pennington Biomedical Research Center and LSU Health Sciences Center Institutional Review Boards (IRBs), LSU System. IRBs granted a waiver of informed consent for this perspective study, which used a limited data set.

Baseline and follow-up measurements

The patient's characteristics, including age of diabetes diagnosis, gender, race/ethnicity, family income, smoking status, type of health insurance, body mass index (BMI), blood pressure, low-density lipoprotein (LDL) cholesterol, HbA1c, estimated glomerular filtration rate (eGFR), history of obstructive sleep apnea and heart valve disease, and medication (antihypertensive drug, cholesterol-lowering drug, and antidiabetic drug) within a half year after the diabetes diagnosis (baseline) and during follow-up after the diabetes diagnosis (follow-up) were extracted from the computerized hospitalization records. The laboratory methods had been described in our previous paper (14). The updated mean values of HbA1c, LDL cholesterol, BMI, blood pressure, and eGFR over time were measured first at baseline and secondly as an updated mean of annual measurement, calculated for each participant from baseline to each year of follow-up. The average number of HbA1c measurements during the follow-up period was 7.7.

Prospective follow-up

Follow-up information was obtained from the LSUHLS inpatient and outpatient database by using the unique number assigned to every patient who visits the LSUHCSD hospitals. Of 29 627 diabetic patients in the present study, about 97% of patients alive had continuously used LSUHCSD hospitals >1 year after the diagnosis of diabetes. Since 1997, diagnosis of HF in the LSUHCSD hospitals has been made by the treating physicians using the Framingham Criteria for Heart Failure diagnosis (15). After clinical diagnosis of HF, echocardiogram has been used for each HF patient to support the clinical diagnosis, classify HF (ejection fraction [EF] $\leq$ 40% or $>$ 40%), and guide the treatment according to the classification. The diagnosis of HF was the primary endpoint of interest for the study and was defined according to the ICD-9: HF (ICD-9 codes 402.01, 402.11, 402.91, and 428). We have conducted a validation study among 4380 HF patients (not only diabetic patients but also nondiabetic patients) in LSUHCSD hospitals; of 4380 HF patients, 2353 had EF $\leq$40%, and 2027 had EF $>$40%; 2246 (95%) of 2353 HF patients were confirmed by using both the Framingham Criteria for Heart Failure diagnosis and EF ($\leq$40%), and 1430 (71%) of 2027 HF patients were confirmed by using both the Framingham Criteria for Heart Failure diagnosis and EF ($>$40%) (15). Follow-up of each cohort member continued until the date of the diagnosis of HF, the date of the last visit if the subject stopped using LSUHCSD hospitals, death, or May 31, 2012 (11).

Statistical analyses

The association between HbA1c and the risk of HF was analyzed by using Cox proportional hazards models. HbA1c was evaluated in the following two ways: 1) as six categories (HbA1c $<$ 6.0% [reference group], 6.0–6.9%, 7.0–7.9%, 8.0–8.9%, 9.0–9.9%, and $\geq$ 10.0%); and 2) as a continuous variable. All analyses were adjusted for age and sex, and further for smoking, income, type of insurance, BMI, systolic blood pressure, LDL cholesterol, eGFR, history of obstructive sleep apnea and heart valve disease, use of antihypertensive drugs, use of diabetes medications, and use of cholesterol-lowering agents. All statistical analyses were performed with PASW for Windows, version 20.0 (IBM SPSS Inc).

Results

General characteristics of the study population are presented by race in Supplemental Table 1 (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). During a mean follow-up period of 6.5 years, 5089 subjects (2229 white and 2860 African American) developed incident HF. After further adjustment for all confounding factors, there was a significantly positive association between HbA1a and HF risk among whites (P trend $<$ .001) and African Americans (P trend $<$ .001) (Table 1). When HbA1c was considered as a continuous variable, each 1% increase in baseline HbA1c was associated with a 6% (95% confidence interval [CI], 1.04–1.07) increased risk of HF in African Americans and a 9% (95% CI, 1.06–1.11) increased risk of HF in whites.

There was a significant interaction between age and HbA1c on HF risk (Table 2). When stratified by age, the graded positive association of HbA1c at baseline with HF risk was present (P for interaction $<$ .005). When we stratified by gender and smoking status, the graded positive association of baseline HbA1c with HF risk did not change (Table 2). The graded positive association of HbA1c with HF risk was also confirmed among diabetic patients using glucose-lowering agents or not (all P trend $<$ .01) (Table 2). We also conducted additional analyses on HbA1c with

Table 1. Hazard Ratio (95% CI) of HF According to Different Levels of HbA1c at Baseline and During Follow-Up Among African American and White Patients with Diabetes

	HbA1c, %						*P* for trend	Each 1% Increase (Continuous Variable)
	<6.0	6.0–6.9	7.0–7.9	8.0–8.9	9.0–9.9	≥10.0		
Baseline								
African Americans	4146	4192	2296	1541	1216	3790		
No. of cases	543	665	433	305	239	675		
Person-years	25 610	28 408	16 275	11 498	8814	25 825		
Age adjustment HR (95% CI)	1.00	1.07 (0.95–1.20)	1.24 (1.09–1.41)	1.32 (1.15–1.53)	1.39 (1.19–1.62)	1.42 (1.27–1.60)	<.001	1.04 (1.03–1.06)
Multivariable adjustment HR (95% CI)[a]	1.00	1.02 (0.91–1.14)	1.20 (1.06–1.36)	1.28 (1.11–1.48)	1.35 (1.16–1.58)	1.47 (1.31–1.65)	<.001	1.05 (1.04–1.07)
Multivariable adjustment HR (95% CI)[b]	1.00	1.02 (0.91–1.15)	1.21 (1.05–1.38)	1.29 (1.12–1.50)	1.37 (1.17–1.61)	1.49 (1.31–1.69)	<.001	1.06 (1.04–1.07)
Whites	4166	2968	1706	1109	839	1658		
No. of cases	618	566	332	242	176	295		
Person-years	23 051	18 276	11 075	7058	5257	9988		
Age adjustment HR (95% CI)	1.00	1.11 (0.99–1.25)	1.16 (1.01–1.33)	1.46 (1.25–1.69)	1.52 (1.28–1.80)	1.41 (1.23–1.63)	<.001	1.07 (1.04–1.09)
Multivariable adjustment HR (95% CI)[a]	1.00	1.10 (0.98–1.23)	1.10 (0.96–1.26)	1.44 (1.23–1.67)	1.49 (1.26–1.77)	1.62 (1.40–1.87)	<.001	1.09 (1.06–1.11)
Multivariable adjustment HR (95% CI)[b]	1.00	1.09 (0.96–1.22)	1.09 (0.95–1.26)	1.43 (1.22–1.67)	1.49 (1.25–1.77)	1.61 (1.38–1.87)	<.001	1.09 (1.06–1.11)
Follow-up								
African Americans	3368	4284	3176	2171	1606	2576		
No. of cases	437	644	609	447	322	401		
Person-years	19 411	28 029	22 495	16 094	12 088	18 315		
Age adjustment HR (95% CI)	1.00	0.97 (0.86–1.09)	1.19 (1.05–1.34)	1.30 (1.14–1.49)	1.32 (1.14–1.49)	1.18 (1.02–1.35)	<.001	1.04 (1.02–1.06)
Multivariable adjustment HR (95% CI)[a]	1.00	0.92 (0.81–1.04)	1.14 (1.01–1.29)	1.28 (1.11–1.46)	1.32 (1.14–1.53)	1.32 (1.14–1.53)	<.001	1.06 (1.04–1.09)
Multivariable adjustment HR (95% CI)[b]	1.00	0.92 (0.80–1.04)	1.14 (0.99–1.31)	1.27 (1.10–1.47)	1.31 (1.12–1.54)	1.34 (1.15–1.57)	<.001	1.07 (1.04–1.09)
Whites	3301	3405	2,39962	1453	949	976		
No. of cases	445	628	510	283	187	176		
Person-years	16 900	20 585	15 432	9564	6291	5931		
Age adjustment HR (95% CI)	1.00	1.12 (0.99–1.26)	1.34 (1.18–1.53)	1.38 (1.18–1.61)	1.48 (1.25–1.77)	1.65 (1.37–1.97)	<.001	1.10 (1.07–1.13)
Multivariable adjustment HR (95% CI)[a]	1.00	1.04 (0.92–1.18)	1.24 (1.09–1.41)	1.34 (1.15–1.57)	1.47 (1.23–1.76)	1.89 (1.57–2.28)	<.001	1.13 (1.09–1.16)
Multivariable adjustment HR (95% CI)[b]	1.00	1.05 (0.92–1.20)	1.26 (1.09–1.45)	1.36 (1.15–1.60)	1.50 (1.24–1.81)	1.93 (1.59–2.35)	<.001	1.13 (1.10–1.17)

Abbreviation: HR, hazard ratio.

[a] Adjusted for age, gender, BMI, LDL cholesterol, systolic blood pressure, glomerular filtration rate, history of obstructive sleep apnea, history of heart valve disease, type of insurance, income, and smoking.

[b] Adjusted for age, gender, BMI, LDL cholesterol, systolic blood pressure, glomerular filtration rate, history of obstructive sleep apnea, history of heart valve disease, type of insurance, income, smoking, use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents.

incident HF stratified by EF ≤40% (systolic HF) and >40% (HF with a preserved EF— diastolic dysfunction) (Table 2). The U-shaped association was found in incident HF defined as either systolic HF or HF with a preserved EF. After excluding the subjects who were diagnosed with HF during the first 2 years of follow-up (n = 1370) and after excluding the subjects with thiazolidinedione treatment (n = 4099), the multivariable-adjusted hazard ratios of HF associated with different levels of HbA1c at baseline did not change (data not shown).

When we performed an additional analysis by using an updated mean of HbA1c during follow-up, we found almost the same graded positive associations between baseline HbA1c levels and updated mean levels of HbA1c with HF risk among both African American and white diabetic patients (Tables 1 and 2).

Discussion

Our study found a graded positive association between HbA1c at baseline and during follow-up with the risk of HF among both African American and white diabetic patients. In addition, we found that this graded positive association was present in diabetic patients with and without glucose-lowering agent treatment and in diabetic patients with different age, gender, and smoking status, and in incident HF defined as systolic HF (EF ≤ 40%) and HF with a preserved EF (EF > 40%).

Diabetes has been recognized as playing an important role in the development of HF for a long time. Several observational studies (3–5), but not (6) all, suggested a positive association between glycemia and the risk of HF among diabetic patients. However, RCTs always failed to

Table 2. Hazard Ratio (95% CI) of HF According to Different Levels of HbA1c at Baseline and During Follow-Up Among Various Subpopulations

	HbA1c, %							
	<6.0	6.0–6.9	7.0–7.9	8.0–8.9	9.0–9.9	≥10.0	*P* for trend	*P* for interaction
Baseline								
Age groups, y								<.005
<50	1.00	1.05 (0.90–1.23)	1.08 (0.90–1.29)	1.08 (0.90–1.30)	1.31 (1.08–1.57)	1.35 (1.16–1.57)	<.001	
50–59	1.00	1.05 (0.92–1.21)	1.20 (1.03–1.40)	1.49 (1.25–1.76)	1.34 (1.10–1.64)	1.55 (1.33–1.81)	<.001	
60–94	1.00	1.05 (0.90–1.21)	1.09 (0.91–1.29)	1.49 (1.21–1.84)	1.55 (1.20–1.99)	1.56 (1.23–1.97)	<.001	
Gender								>.1
Male	1.00	1.05 (0.91–1.20)	1.10 (0.94–1.29)	1.40 (1.18–1.67)	1.45 (1.20–1.74)	1.47 (1.27–1.70)	<.001	
Female	1.00	1.06 (0.95–1.17)	1.17 (1.03–1.32)	1.32 (1.15–1.51)	1.40 (1.20–1.63)	1.59 (1.40–1.80)	<.001	
Smoking status								>.1
Never	1.00	1.11 (1.01–1.23)	1.20 (1.08–1.35)	1.44 (1.27–1.63)	1.48 (1.28–1.70)	1.65 (1.48–1.85)	<.001	
Ever or current	1.00	0.89 (0.75–1.04)	0.98 (0.81–1.19)	1.11 (0.90–1.37)	1.25 (1.01–1.55)	1.26 (1.05–1.50)	.001	
Using glucose-lowering agents								<.001
No	1.00	1.10 (0.96–1.27)	1.13 (0.95–1.35)	1.40 (1.15–1.70)	1.33 (1.04–1.71)	1.82 (1.54–2.16)	<.001	
Yes	1.00	1.02 (0.91–1.13)	1.14 (1.01–1.28)	1.31 (1.15–1.49)	1.41 (1.23–1.62)	1.43 (1.28–1.61)	<.001	
EF								NA
≤40%	1.00	1.25 (1.04–1.51)	1.45 (1.17–1.79)	1.89 (1.50–2.38)	2.14 (1.69–2.72)	2.35 (1.93–2.86)	<.001	
>40%	1.00	0.97 (0.86–1.09)	1.05 (0.92–1.20)	1.34 (1.16–1.57)	1.38 (1.175–1.63)	1.36 (1.19–1.56)	<.001	
Follow-up								
Age groups, y								<.01
<50	1.00	1.06 (0.89–1.27)	1.13 (0.94–1.36)	1.04 (0.86–1.26)	1.16 (0.95–1.41)	1.29 (1.07–1.55)	.053	
50–59	1.00	0.92 (0.79–1.08)	1.18 (1.00–1.40)	1.44 (1.21–1.72)	1.49 (1.22–1.82)	1.57 (1.28–1.92)	<.001	
60–94	1.00	0.99 (0.85–1.16)	1.21 (1.02–1.44)	1.42 (1.14–1.77)	1.52 (1.15–2.01)	1.32 (0.85–2.06)	<.001	
Gender								>.1
Male	1.00	0.92 (0.79–1.08)	1.13 (0.97–1.33)	1.34 (1.13–1.59)	1.36 (1.12–1.65)	1.53 (1.27–1.85)	<.001	
Female	1.00	0.99 (0.88–1.11)	1.19 (1.05–1.35)	1.25 (1.09–1.44)	1.37 (1.18–1.60)	1.49 (1.28–1.75)	<.001	
Smoking status								>.1
Never	1.00	1.02 (0.92–1.14)	1.24 (1.11–1.40)	1.29 (1.13–1.46)	1.42 (1.23–1.64)	1.61 (1.40–1.86)	<.001	
Ever or current	1.00	0.84 (0.69–1.01)	1.00 (0.82–1.21)	1.31 (1.07–1.61)	1.29 (1.03–1.61)	1.33 (1.05–1.67)	<.001	
Using glucose-lowering agents								<.001
No	1.00	1.04 (0.91–1.19)	1.25 (1.06–1.48)	1.38 (1.14–1.68)	1.36 (1.08–1.71)	1.75 (1.43–2.15)	<.001	
Yes	1.00	0.91 (0.81–1.04)	1.11 (0.98–1.26)	1.23 (1.07–1.41)	1.34 (1.15–1.56)	1.39 (1.19–1.62)	<.001	
EF								NA
≤40%	1.00	1.11 (0.89–1.37)	1.73 (1.39–2.16)	2.18 (1.72–2.76)	2.59 (2.01–3.34)	2.94 (2.29–3.77)	<.001	
>40%	1.00	0.89 (0.79–1.01)	1.07 (0.93–1.22)	1.13 (0.97–1.32)	1.14 (0.96–1.36)	1.26 (1.05–1.51)	<.001	

Abbreviation: NA, not available. Adjusted for age, gender, race, BMI, LDL cholesterol, systolic blood pressure, glomerular filtration rate at baseline (in the baseline analyses) and during follow-up (in the follow-up analyses), history of obstructive sleep apnea, history of heart valve disease, type of insurance, income, smoking, and use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents, other than the variable for stratification.

confirm this association (7–9). A recent meta-analysis of RCTs including 37 299 patients demonstrated that intensive glycemic control did not prevent HF among diabetic patients (16). Several reasons for the inconsistent finding between epidemiological studies and RCTs can be considered. First, small sample sizes, short follow-up, and few cardiovascular disease cases in some studies may limit the statistical power. Second, most epidemiological studies only assess a single baseline measurement of HbA1c with cardiovascular disease risk, which may produce potential bias. Third, thiazolidinediones were used as glucose-lowering agents in most RCTs (8, 9), and they were known to cause HF. In the present study, we found a graded positive association by various HbA1c intervals of clinical relevance at baseline and during follow-up with HF risk among both African American and white diabetic patients in a large sample size database. Each 1% increase in baseline HbA1c was associated with a 6% increased risk of HF in African Americans and 8% in whites. This magnitude of risk increase is lower than the recent meta-analyses that show an 11–15% risk increase (17, 18). In addition, we found that the graded positive association did not change after excluding the subjects with thiazolidinedione treatment, and this positive association was present in diabetic patients with and without glucose-lowering agent treatment and in incident HF defined as systolic HF (EF ≤ 40%) and HF with a preserved EF (EF > 40%).

The mechanisms of poor glycemic control increasing the risk of incident HF in diabetes patients have been well documented. The underlying mechanism for the association between HF and diabetes is thought to involve both macrovascular and microvascular injury. The increased risk of atherosclerosis in diabetic patients contributes significantly to the increased risk of HF. Elevated HbA1c can

increase the risk of HF in part through its association with coronary heart disease (19). Hyperglycemia has considerable effects on myocardium. Some studies also suggest that diabetes may predispose to HF development through the existence of a specific diabetic cardiomyopathy (20).

There are several limitations in our study. One is that our analysis was not performed on a representative sample of the population, which limits the generalizability of this study. Second, there is the possibility that some diastolic HF or asymptomatic coronary heart disease patients were not excluded from the diabetes cohort. Third, residual confounding due to the measurement error in the assessment of confounding factors, unmeasured factors such as physical activity, education, and dietary factors cannot be excluded.

In summary, our study demonstrates that there is a graded positive association between HbA1c at baseline and during follow-up with the risk of HF among both African American and white diabetic patients. In the absence of conclusive evidence from randomized intervention trials, our study provides further epidemiological support for glucose lowering as a strategy to reduce HF in diabetic patients.

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