

Poor Glycemic Control in Diabetes and the Risk of Incident Chronic Kidney Disease Even in the Absence of Albuminuria and Retinopathy

Atherosclerosis Risk in Communities (ARIC) Study

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Background: Diabetic nephropathy is the leading cause of kidney failure in the United States. The extent to which an elevated glycated hemoglobin (HbA_{1c}) concentration is associated with increased risk of chronic kidney disease (CKD) in the absence of albuminuria and retinopathy, the hallmarks of diabetic nephropathy, is uncertain.

Methods: Glycated hemoglobin concentration was measured in 1871 adults with diabetes mellitus followed up for 11 years in the Atherosclerosis Risk in Communities (ARIC) Study. Incident CKD was defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m² after 6 years of follow-up or a kidney disease–related hospitalization. We categorized HbA_{1c} concentrations into 4 clinically relevant categories. Albuminuria and retinopathy were measured midway through follow-up.

Results: Higher HbA_{1c} concentrations were strongly associated with risk of CKD in models adjusted for demographic data, baseline glomerular filtration rate, and cardiovascular risk factors. Compared with HbA_{1c} con-

centrations less than 6%, HbA_{1c} concentrations of 6% to 7%, 7% to 8%, and greater than 8% were associated with adjusted relative hazard ratios (95% confidence intervals) of 1.4 (0.97-1.91), 2.5 (1.70-3.66), and 3.7 (2.76-4.90), respectively. Risk of CKD was higher in individuals with albuminuria and retinopathy, and the association between HbA_{1c} concentration and incident CKD was observed even in participants without either abnormality: adjusted relative hazards, 1.46 (95% confidence intervals, 0.80-2.65), 1.17 (0.43-3.19), and 3.51 (1.67-7.40), respectively; $P_{\text{trend}} = .004$.

Conclusions: We observed a positive association between HbA_{1c} concentration and incident CKD that was strong, graded, independent of traditional risk factors, and present even in the absence of albuminuria and retinopathy. Hyperglycemia is an important indicator of risk of both diabetic nephropathy with albuminuria or retinopathy and of less specific forms of CKD.

Arch Intern Med. 2008;168(22):2440-2447

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MORE THAN 26 MILLION adults in the United States have chronic kidney disease (CKD), defined as decreased glomerular filtration rate (GFR) or increased urinary albumin excretion.¹ Chronic kidney disease is associated with an increased risk of cardiovascular disease, morbidity, and mortality.²⁻⁷ As a major risk factor for cardiovascular disease, the National Kidney Foundation⁸ and the American Heart Association⁹ consider individuals with CKD to be in the highest-risk group for intervention.

Diabetes mellitus (DM) is a leading cause of kidney failure in the United States, accounting for more than 40% of all incident cases of end-stage renal disease.¹⁰⁻¹² Diabetes increases the risk for end-stage

renal disease including disease that is a direct complication of DM and disease from causes other than DM.¹³ Diabetes is closely associated with microvascular disease and is often manifested as albuminuria or retinopathy,^{12,14} although approximately one-third of individuals with DM have decreased kidney function without either albuminuria or retinopathy.¹⁵

The increased concentration of glycated hemoglobin (HbA_{1c}) is related to the development of microvascular disease in DM, and its reduction is at the center of the clinical management of hyperglycemia. Randomized studies in individuals with type 1 DM have shown that intensive treatment slows progression of microvascular complications (nephropathy, retinopathy, and neuropathy) and

reduces the development and progression of microalbuminuria.¹⁶

The continuous relationship between HbA_{1c} concentration and incidence of moderate CKD in individuals with DM, however, has not been well quantified to our knowledge. It is also unknown whether moderately elevated HbA_{1c} concentrations predict a decline in kidney function in the absence of detectable microvascular disease as evidenced by albuminuria, retinopathy, or both. An improved understanding from observational data of the risks and consequences of DM in the absence of albuminuria and retinal damage is particularly important given recent concerns about stringent glycemic control and risk of death in certain individuals with DM who are at high risk.¹⁷

We examined the long-term independent association between moderately elevated concentrations of HbA_{1c} and incident CKD in a population-based observational sample of adults with DM and evaluated the consistency of this association in those with and without albuminuria or retinopathy.

METHODS

STUDY POPULATION

Data were obtained from the Atherosclerosis Risk in Communities (ARIC) Study. This was a prospective biracial observational cohort of 15 792 individuals including 2187 with DM between the ages of 45 and 64. At baseline, their mean (SD) age was 54 (5.8) years; 55% were female, and 74% were white and 26% were African American. Individuals were recruited from a probability sample of 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. Participants took part in examinations starting with a baseline visit (visit 1) between 1987 and 1989. Individuals underwent 3 follow-up examinations at approximately 3-year intervals at community clinics and answered annual follow-up telephone interviews between visits. Hospitalized events were ascertained continuously from ARIC Study inception through December 31, 2004. Details of the ARIC cohort have been published elsewhere.¹⁸

In the present study, we included all participants with DM at the second ARIC visit (visit 2, 1990-1992), the only visit in which the concentration of HbA_{1c} was measured. Diabetes mellitus was defined as a fasting glucose concentration of 126 mg/dL or higher or a nonfasting glucose concentration of 200 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0555), self-reported physician diagnosis of DM, or use of oral hypoglycemic medication or insulin. Of 1871 individuals, 1054 (56%) were identified on the basis of self-reported DM. A total of 1655 individuals (88%) were identified on the basis of elevated plasma glucose concentration: 1556 (83%) had a fasting plasma glucose concentration of at least 126 mg/dL, and 99 (7%) had a nonfasting glucose concentration of at least 200 mg/dL. Only 216 individuals (11.5%) reported having DM without also having an elevated plasma glucose concentration.

We excluded 28 participants with missing HbA_{1c} concentrations at visit 2 and 20 with missing serum creatinine levels at ARIC visit 1 or visit 2; 229 with an estimated GFR (eGFR) less than 60 mL/min/1.73 m² at either ARIC visit 1 or visit 2; 3 participants who reported race as other than white or African American; and 8 African Americans from the Minnesota and Washington County study centers. Analyses are based on the remaining 1871 study participants. The study was

approved by the institutional review boards at each of the sites, and written informed consent was obtained from all participants.

DATA COLLECTION

Demographic and health behavior data, medical history, and measurements of height, weight, and blood pressure were obtained at each clinical examination. Blood was drawn at all clinic visits as described previously.¹⁹

Hemoglobin A_{1c} was assayed from stored whole-blood samples from ARIC visit 2 using high-performance liquid chromatography instruments (Tosoh Bioscience Inc, South San Francisco, California) in a secondary reference laboratory of the National Glycohemoglobin Standardization Program at the University of Minnesota Medical Center, Fairview, and certified by the International Federation of Clinical Chemists.²⁰⁻²² Measurements of HbA_{1c} were available for 2159 of 2187 participants with DM (98.7%). The HbA_{1c} concentrations were recalibrated to correct for an upward bias that was observed in a previous validation study comparing samples before and after long-term storage.²¹

A modified kinetic Jaffe method was used to measure the serum creatinine level at ARIC visits 2 and 4. The serum creatinine level was corrected for interlaboratory differences and indirectly calibrated to the Cleveland Clinic measurement by subtraction of 0.24 mg/dL (to convert to micromoles per liter, multiply by 88.4) from the visit 2 values and the addition of 0.18 mg/dL to the visit 4 values and then used to estimate GFR.^{3,23} The eGFR was calculated using the simplified Modification of Diet in Renal Disease equation developed at the Cleveland Clinic: $eGFR = [186.3 \times (\text{serum creatinine [mg/dL]}^{-1.154}) \times (\text{age}^{-0.203}) \times (0.742 \text{ if female}) \times (1.21 \text{ if African American})]$.²⁴

Three seated blood pressure measurements were obtained by certified technicians using a random-zero sphygmomanometer after 5 minutes of rest. The mean of the second and third readings was recorded. Enzymatic methods were used to obtain total plasma cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations, and the low-density lipoprotein cholesterol concentration was calculated from these using the Friedewald equation.²⁵

Smoking status was determined by self-reported cigarette smoking. Prevalent coronary heart disease (CHD) was defined as a history of physician-diagnosed myocardial infarction, electrocardiographic evidence of a previous myocardial infarction (presence of a major or minor Q-wave abnormality with T-wave or ST-segment abnormality), or self-reported previous coronary revascularization procedure. Self-reported medication use (eg, antihypertensive or antidiabetes agents) was verified by bottle inspection.

Urinary albumin excretion was measured from a spot urine sample at ARIC visit 4 (1996-1998) as the ratio of albumin to creatinine (in milligrams per gram). Albuminuria was defined as an albumin to creatinine ratio of 30 mg/g or greater (which includes both the categories of microalbuminuria and macroalbuminuria). Retinography was conducted at ARIC visit 3 (1993-1995) in 1 randomly selected eye of each participant. A modification of the Airlie House classification system was used to grade lesions typical of diabetic retinopathy from a 45° color fundus photograph of 1 eye from each participant. Severity scores were assigned as follows: level 10, no retinopathy; level 20, minimal nonproliferative retinopathy (microaneurysms only or blot hemorrhages only); level 35, early nonproliferative retinopathy (microaneurysms and at least 1 of the following: venous loops, soft or hard exudate, and questionable intraretinal microvascular abnormalities or venous beading); levels 43 to 47,

Table 1. Characteristics of the Cohort of 1871 Individuals With Diabetes Mellitus According to HbA_{1c} Category at Baseline

Descriptors	HbA _{1c} Concentration Category, %				P _{trend}
	<6 (n=770)	6-7 (n=407)	7-8 (n=193)	>8 (n=501)	
HbA _{1c} concentration					
Mean (SD), %	5.28 (0.43)	6.46 (0.31)	7.73 (0.28)	10.15 (1.50)	
Median (IQR)	5.29 (4.97-5.61)	6.46 (6.14-6.67)	7.52 (7.31-7.73)	9.86 (8.90-11.24)	
Disease progressed to incident CKD, %	11.8	16.5	23.8	31.3	<.001
Male sex, %	52.0	49.6	44.0	41.3	.002
Age, mean (SD), y	58 (5.7)	58 (5.8)	59 (5.7)	57 (5.7)	.98
African American, %	29.5	40.5	35.8	55.3	<.001
Serum creatinine concentration, mean (SD), mg/dL	0.89 (0.18)	0.89 (0.17)	0.87 (0.18)	0.85 (0.19)	.004
Glomerular filtration rate, estimated mean (SD), mL/min/1.73 m ²	89 (18)	91 (18)	91 (18)	97 (23)	<.001
Mildly decreased, 60-89 mL/min/1.73 m ² , %	60.5	55.3	54.9	42.3	<.001
Fasting glucose concentration, mean (SD), mg/dL	134 (24)	156 (27)	195 (48)	270 (67)	<.001
Use of blood glucose medication, %	14.7	39.8	68.2	74.8	<.001
Prevalent CHD, ^a %	8.1	9.8	16.8	12.2	.002
Blood pressure category, %					
Normal	33.9	33.91	36.3	34.33	.94
Prehypertension	39.7	42.5	38.3	41.4	.73
Stage 1 hypertension	18.7	17.4	18.7	17.8	.95
Stage 2 hypertension	7.7	6.1	6.7	6.8	.79
Blood pressure, mean (SD), mm Hg					
Systolic	128 (20)	128 (18)	128 (20)	128 (20)	.98
Diastolic	74 (11)	73 (10)	72 (10)	72 (11)	.047
Hypertension, ^b %	52.6	60.7	54.4	59.1	.03
Smoking status, %					
Current	20.3	20.2	18.7	19.0	.92
Former	41.5	38.3	38.0	37.0	.38
Never	38.2	41.5	43.2	44.0	.18
Body mass index, ^a mean (SD) ^c	30.2 (5.5)	32.3 (6.2)	31.3 (6.0)	31.6 (5.9)	<.001
Cholesterol concentration, mean (SD), mg/dL					
LDL ^a	134 (38)	136 (38)	133 (44)	140 (40)	.07
HDL ^a	44 (14)	41 (13)	43 (15)	43 (14)	.004
Triglyceride concentration, ^a mean (SD), mg/dL	164 (110)	169 (92)	188 (118)	200 (179)	<.001

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

SI conversion factors: To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01; serum creatinine to micromoles per liter, multiply by 88.4; glucose to millimoles per liter, multiply by 0.0555; HDL and LDL to millimoles per liter, multiply by 0.0259; and triglycerides to millimoles per liter, multiply by 0.0113.

^aNumber of missing values: prevalent CHD, 33; body mass index, 7; LDL cholesterol concentration, 87; HDL cholesterol concentration, 6; triglyceride concentration, 3.

^bStage 1 or 2 or receiving antihypertensive agents.

^cCalculated as weight in kilograms divided by height in meters squared.

moderate to severe nonproliferative retinopathy (microaneurysms and at least 1 of the following: intraretinal microvascular abnormalities, venous beading, hemorrhages, and microaneurysms exceeding those of a standard photograph 2A); level 60 or higher, proliferative retinopathy. We considered a severity score of 20 or higher to indicate presence of retinopathy.²⁶⁻²⁸

OUTCOMES

Incident CKD was defined as eGFR less than 60 mL/min/1.73 m² at visit 4 (1996-1998, approximately 6 years after visit 2) or kidney disease noted during a hospitalization or death.²⁹ All hospitalizations and deaths in ARIC participants were ascertained through review of medical records, annual follow-up interviews, and death certificates. Identification of hospital events was limited to those in acute-care hospitals and did not include events in nursing homes, psychiatric hospitals, or other locations. Deaths were recorded regardless of location, and death certificates were abstracted for both underlying and contributory causes of death. Hospitalizations identified through active surveillance and used

to identify cases included the following: hospitalizations (discharges or deaths) coded using the *International Classification of Diseases, Ninth Revision*, for chronic renal disease (codes 581-583 or 585-588), hypertensive renal disease (code 403), hypertensive heart and renal disease (code 404), unspecified disorder of kidney and ureter (code 593.9), DM with renal manifestations (code 250.4), kidney transplantation, renal dialysis, or adjustment/fitting of catheter (code V42.0, V45.1, or V56), hemodialysis (code 39.95) or peritoneal dialysis (code 54.98), and without acute renal failure (codes 584, 586, 788.9, and 958.5) as the primary or secondary hospitalization code.

STATISTICAL ANALYSIS

We categorized HbA_{1c} concentrations into categories (<6%, 6%-7%, 7%-8%, or >8%) corresponding to current American Diabetes Association guideline categories.³⁰ Baseline characteristics of the population were compared across CKD status and HbA_{1c} concentration categories using χ^2 test. Incidence rates of CKD during follow-up were compared across HbA_{1c} concentration categories. Follow-up time was calculated from the

time of the second ARIC examination to the first date of CKD diagnosis, defined as the earliest of either the fourth examination (if GFR decline was indicated) or the discharge date of a CKD-related hospitalization. Participants were censored at death, withdrawal from the study, or December 31, 2004, whichever occurred first. Adjusted hazard ratios and their 95% confidence intervals for the time to development of CKD were computed using Cox proportional hazards models after first testing the assumption of proportionality of hazards over time. Models were developed comparing participants by HbA_{1c} concentration category and by continuous HbA_{1c} measurements. The continuous association between HbA_{1c} concentration and incident CKD was estimated from a Poisson regression model including a fourth-order polynomial for HbA_{1c} adjusted to the incidence rate for a 60-year-old white man with a baseline eGFR of 90 mL/min/1.73 m². Multivariate models included age, sex, race, study center, baseline eGFR, body mass index (calculated as weight in kilograms divided by height in meters squared),

hypertension status, use of antihypertensive agents, prevalent CHD, smoking status, and low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations. Analyses were repeated after stratification by the presence of albuminuria at visit 4 and retinopathy at visit 3 in 1231 participants for whom these data were available. All statistical analyses were conducted using commercially available software (STATA version 9.2; StataCorp, College Station, Texas, or SAS version 9.1; SAS Institute, Inc, Cary, North Carolina).

RESULTS

Among the 1871 participants, higher HbA_{1c} concentrations were directly associated with female sex, African American race, higher eGFR, fasting glucose concentration, prevalent CHD, hypertension, use of antihypertensive or antidiabetes agents, body mass index, and triglyceride concentration (**Table 1**). Higher HbA_{1c} concentration category also was associated with lower high-density lipoprotein cholesterol concentration.

A total of 361 cases of incident CKD occurred during a mean follow-up of 11 years (incidence rate, 17.0 CKD cases per 1000 person-years). A total of 120 cases were identified on the basis of a follow-up eGFR of less than 60 mL/min/1.73 m², and 292 cases were identified on the basis of a kidney-related hospitalization or death (51 individuals met both criteria). **Figure 1** compares the cumulative risk of developing CKD by HbA_{1c} concentration category. From lowest to highest category, 11.8%, 16.5%, 23.8%, and 31.3% of participants developed CKD during the study ($P < .001$, log-rank test). The incidence rate was progressively higher with a higher category of HbA_{1c} (**Table 2**). Cases detected on

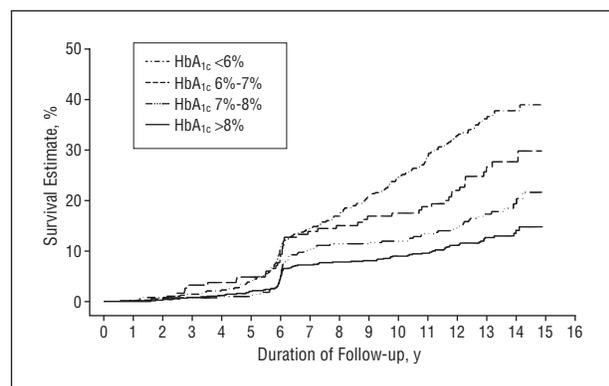


Figure 1. Kaplan-Meier survival estimates for glycated hemoglobin (HbA_{1c}) concentration by category.

Table 2. Incidence of CKD According to HbA_{1c} Concentration Category

Variable	Total Incidence	HbA _{1c} Concentration Category, %				P _{trend}
		<6	6-7	7-8	>8	
HbA _{1c} concentration, mean (SD)	7.07 (2.16)	5.28 (0.43)	6.46 (0.31)	7.53 (0.28)	10.15 (1.50)	
CKD defined by visit 4 eGFR <60 mL/min/1.73 m ² or ICD-9 code hospitalization						
No. of events	361 of 1871	91 of 770	67 of 407	46 of 193	157 of 501	
Incidence per 1000 person-years	17.00	9.87	14.15	21.87	30.29	<.001
Unadjusted HR (95% CI)	1.25 (1.20-1.30) ^a	1 [Reference]	1.44 (1.05-1.97)	2.30 (1.61-3.28)	3.39 (2.62-4.39)	<.001
Adjusted HR ^b (95% CI)	1.31 (1.25-1.38) ^a	1 [Reference]	1.37 (0.97-1.91)	2.49 (1.70-3.66)	3.67 (2.76-4.90)	<.001
CKD defined by visit 4 eGFR <60 mL/min/1.73 m ²						
No. of events	120 of 1871	39 of 770	30 of 407	12 of 193	39 of 501	
Incidence per 1000 person-years	14.92	11.20	16.35	14.83	20.37	.01
Unadjusted HR (95% CI)	1.10 (1.02-1.18) ^a	1 [Reference]	1.48 (0.92-2.39)	1.41 (0.74-2.70)	1.72 (1.10-2.70)	.02
Adjusted HR ^b (95% CI)	1.13 (1.03-1.25) ^a	1 [Reference]	1.31 (0.78-2.20)	1.27 (0.63-2.56)	1.63 (0.95-2.79)	.08
CKD defined by ICD-9 code hospitalization only						
No. of events	292 of 1871	62 of 770	49 of 407	41 of 193	140 of 501	
Incidence per 1000 person-years	13.58	6.68	10.20	19.09	26.56	.68
Unadjusted HR (95% CI)	1.29 (1.23-1.35) ^a	1 [Reference]	1.54 (1.06-2.24)	2.97 (2.00-4.40)	4.36 (3.23-5.88)	<.001
Adjusted HR ^b (95% CI)	1.33 (1.26-1.40) ^a	1 [Reference]	1.43 (0.96-2.12)	3.12 (2.04-4.77)	4.53 (3.26-6.30)	<.001

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HR, hazard ratio; ICD-9, *International Classification of Diseases, Ninth Revision*.

SI conversion factor: To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01.

^aPer 1% increase in HbA_{1c} concentration.

^bAdjusted for age, sex, race, study center, baseline eGFR, body mass index, hypertension status, use of antihypertensive agents, prevalent coronary heart disease, smoking status, low- and high-density lipoprotein cholesterol concentrations, and triglyceride concentration.

the basis of decreased eGFR at visit 4 (6 years after the baseline HbA_{1c} measurement) are indicated by the steeper rise in the cumulative incidence curve at this follow-up visit. The trend for higher risk of decreased kidney function remained after adjustment for age, sex,

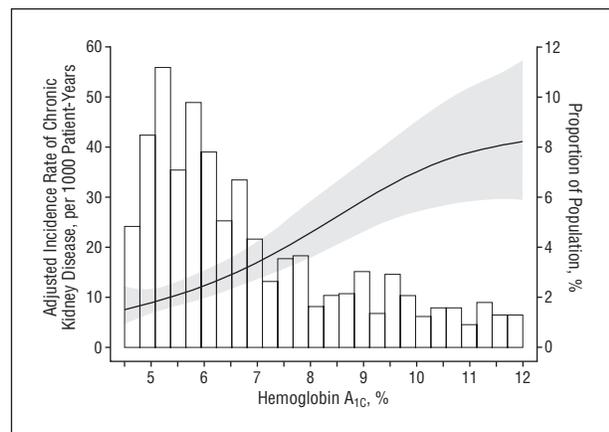


Figure 2. Adjusted incidence rates and 95% confidence intervals (shaded area) of chronic kidney disease according to glycated hemoglobin (HbA_{1c}) concentration. The curve represents minimally adjusted incidence rates based on a Poisson regression model including a fourth-order polynomial for HbA_{1c} concentration adjusted to the incidence rate for a 60-year-old white man with a baseline estimated glomerular filtration rate of 90 mL/min/1.73 m². The histogram represents the frequency distribution of HbA_{1c} concentration in the study sample.

and race as shown by the graded association across the entire range of HbA_{1c} concentrations (**Figure 2**, which caps HbA_{1c} concentrations at an upper limit for the overall sample).

The association between HbA_{1c} and the risk of CKD remained after further adjustment for other CKD risk factors including study center, body mass index, hypertension, use of antihypertensive medications, prevalent CHD, smoking status, low-density and high-density cholesterol concentrations, and triglyceride concentration (Table 2). Individuals with HbA_{1c} concentrations between 6% and 7%, between 7% and 8%, and greater than 8% had hazard ratios (95% confidence intervals) of 1.37 (0.97-1.91), 2.49 (1.70-3.66), and 3.67 (2.76-4.90), respectively, of progressing to incident CKD compared with individuals with DM and HbA_{1c} concentrations of 6% or less. In analyses of HbA_{1c} concentrations as a continuous risk factor, each 1% increase in HbA_{1c} concentration was associated with a 31% higher risk of developing CKD. The association was observed for both components of the combined case definition of incident CKD, though the association was somewhat weaker in analyses limited to events detected by a decrease in eGFR at visit 4 (hazard ratios, 1.13; 95% confidence intervals, 1.03-1.25, per 1% increase in HbA_{1c} concentration) than for kidney disease-related hospitalizations (1.33; 1.26-1.40, per 1% increase in HbA_{1c} concentration). The association was not appreciably altered when

Table 3. Adjusted HR of Incident CKD According to HbA_{1c} Concentration Category, by Adjusted HR Albuminuria and Retinopathy Status^a

Variable	Total Sample	HbA _{1c} Concentration Category, %				P _{trend}
		<6	6-7	7-8	>8	
Albuminuria (93 of 251^b)						
No. of events	103 of 270	15 of 61	14 of 58	13 of 31	61 of 120	
Incidence per 1000 person-years	34.53	20.81	30.32	40.49	48.73	<.001
Adjusted HR ^c (95% CI)	1.27 (1.14-1.41) ^d	1 [Reference]	0.83 (0.38-1.84)	2.19 (0.96-5.00)	2.54 (1.35-4.79)	<.001
No albuminuria (116 of 972^b)						
No. of events	129 of 1035	49 of 504	32 of 239	16 of 100	32 of 192	
Incidence per 1000 person-years	9.78	7.55	10.47	12.66	13.46	<.001
Adjusted HR ^c (95% CI)	1.20 (1.08-1.32) ^d	1 [Reference]	1.34 (0.83-2.15)	1.75 (0.94-3.27)	2.21 (1.32-3.70)	.002
Retinopathy (135 of 467^b)						
No. of events	152 of 512	23 of 127	19 of 92	22 of 66	88 of 227	
Incidence per 1000 person-years	26.14	15.11	17.67	29.78	35.51	<.001
Adjusted HR ^c (95% CI)	1.27 (1.17-1.37) ^d	1 [Reference]	1.01 (0.52-1.97)	2.23 (1.18-4.20)	2.73 (1.65-4.50)	<.001
No retinopathy (123 of 960^b)						
No. of events	134 of 1015	56 of 526	34 of 248	13 of 89	31 of 152	
Incidence per 1000 person-years	10.75	8.55	11.08	12.21	17.38	<.001
Adjusted HR ^c (95% CI)	1.22 (1.10-1.35) ^d	1 [Reference]	1.12 (0.71-1.77)	1.49 (0.75-2.96)	2.44 (1.48-4.01)	.001
Neither albuminuria nor retinopathy (66 of 675^b)						
No. of events	73 of 707	31 of 393	22 of 173	6 of 58	14 of 83	
Incidence per 1000 person-years	8.05	6.10	9.95	8.17	13.42	<.001
Adjusted HR ^c (95% CI)	1.27 (1.08-1.51) ^d	1 [Reference]	1.46 (0.80-2.65)	1.17 (0.43-3.19)	3.51 (1.67-7.39)	.004
Both albuminuria and retinopathy (56 of 104^b)						
No. of events	64 of 116	4 of 12	6 of 12	6 of 12	48 of 80	
Incidence per 1000 person-years	53.15	30.77	44.06	47.41	59.16	<.001
Adjusted HR ^c (95% CI)	1.14 (0.96-1.36) ^d	1 [Reference]	0.74 (0.16-3.39)	2.09 (0.43-10.05)	2.13 (0.63-7.28)	.10

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HbA_{1c}, glycated hemoglobin; HR, hazard ratio.

^aAlbuminuria was measured at the 6-year follow-up visit, and retinopathy at the 3-year follow-up visit.

^bNumber for fully adjusted models.

^cAdjusted for age, sex, race, study center, baseline estimated glomerular filtration rate, body mass index, hypertension status, use of antihypertensive agents, prevalent coronary heart disease, smoking status, low-density and high-density lipoprotein cholesterol concentrations, and triglyceride concentration.

^dPer 1% increase in HbA_{1c} concentration.

controlling for total cholesterol concentration, white blood cell count, or use of angiotensin-converting enzyme inhibitors at baseline (results not shown). The association remained in analyses setting the time of incident CKD to the midpoint between the 2 visit dates for cases defined by a decrease in eGFR (results not shown).

Individuals who had developed either albuminuria or retinopathy by visits 3 and 4, respectively (**Table 3**), were at much higher risk of CKD than those with neither abnormality. Of the 217 cases of incident CKD occurring in participants who had undergone both urinalysis and retinography, almost one-fourth developed in individuals with only retinopathy (24%; n=52), half that in those with only albuminuria (13%; n=28), and the remaining two-thirds developed in individuals with both complications (29.5%; n=64) or neither complication (33.6%; n=73). The association of HbA_{1c} concentration with incident CKD, however, was similar across these subgroups. A hazard ratio of 1.27 (95% confidence interval, 1.08-1.51) for a 1% increase in HbA_{1c} concentration was observed in those without either albuminuria or retinopathy, consistent with the overall observed hazard ratios. Also consistent with overall trends, the trend for higher risk of decreased kidney function remained within each stratum of abnormalities (those developing neither albuminuria nor retinopathy, only 1 complication, or both), after adjustment for age, sex, and race as shown by the graded association across the entire range of HbA_{1c} concentrations (**Figure 3**), capping HbA_{1c} concentration at an upper limit of the stratum-specific 95th percentiles.

We found no statistically significant interactions between HbA_{1c} concentration and any demographic characteristics. We observed higher risk associated with higher HbA_{1c} concentration in analyses even after stratifying by sex, race, hypertension status, history of CHD, and DM treatment status (results not shown).

COMMENT

We observed a strong association between higher HbA_{1c} concentrations and incidence of CKD in adults with DM. This association was independent of traditional CKD risk factors and was observed across the entire range of HbA_{1c} concentrations examined. This is one of few prospective studies to examine the risk of incident CKD in a large biracial community-based cohort. We included all individuals with DM, used an HbA_{1c} assay certified by international programs and used for more than 2 decades in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Study,²² and observed participants on average for more than 11 years. Even in the absence of both modest amounts of albuminuria and retinopathy, 2 hallmarks of diabetic microvascular disease, the concentration of HbA_{1c} was positively associated with incident CKD.

Diabetic nephropathy is diagnosed in the presence of persistent albuminuria (>30 mg per 24 hours) equivalent to 30 mg/g (urinary albumin to creatinine ratio), diabetic retinopathy, and no evidence of other kidney or renal tract disease.¹⁴ These results, however, demonstrate

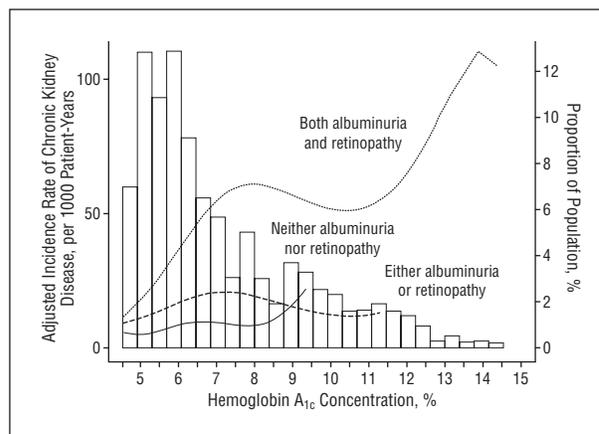


Figure 3. Adjusted incidence rates of chronic kidney disease according to glycated hemoglobin (HbA_{1c}) concentration stratified by albuminuria and retinopathy status. The curves represent minimally adjusted incidence rates based on Poisson regression models including a fourth-order polynomial for HbA_{1c} concentration adjusted to the incidence rate for a 60-year-old white man with a baseline estimated glomerular filtration rate of 90 mL/min/1.73 m² within each stratum. The HbA_{1c} concentrations were capped at an upper limit equivalent to the stratum-specific 95th percentile. The histogram represents the frequency distribution of HbA_{1c} concentration in the study sample.

the importance of identifying the risk of developing kidney disease in individuals with DM even in the absence of albuminuria or retinopathy.

Sixty percent of individuals with type 2 DM and hypertension develop nephropathy.¹² In adults with DM, 13% have a decreased eGFR and 64% have albuminuria.¹⁵ About 1.1 million adults older than 40 years have both type 2 DM and decreased eGFR. More than half of these adults (59%) do not have albuminuria, and an estimated 0.3 million do not have either albuminuria or retinopathy.¹⁵ In this population-based study, among the 217 cases of incident CKD occurring in participants who had undergone both urinary albumin measurements and retinography, one-third (n=73; 33.6%) developed in individuals without albuminuria or retinopathy, nearly one-third (n=64; 29.4%) developed in individuals with both albuminuria and retinopathy, and the remaining cases (80 cases [37%]) developed in individuals with albuminuria (28 cases [13%]) or retinopathy (52 cases [24%]).

The Framingham Heart Study offspring cohort demonstrated an increased odds of developing incident CKD associated with abnormal glycemic status,³¹ and although we know that stringent glycemic control decreases the risk of DM complications, cardiovascular disease, and CKD progression,^{17,32,33} kidney pathology has been underexplored in individuals with type 2 DM.¹⁴ Findings from the Multiple Risk Factor Intervention Trial, a multicenter prospective cohort of men, showed that men with DM are at increased risk of end-stage renal disease from all causes and from causes other than DM.¹³ Although this study cannot address the specific pathophysiologic mechanisms relating elevated HbA_{1c} concentrations to incident CKD, there are a number of biologically plausible explanations for observed associations, many potentially acting through damage to the glomerular basement membrane. Hemodynamic factors and advanced glycation end products also may have important roles in kidney disease progression in both individuals

with and without DM.³⁴⁻³⁷ Evidence links glucose excursions,³⁸ insulin resistance,³⁹ and DM^{40,41} to decreased diurnal blood pressure decline (nondipping). Evidence also suggests that non-dippers with DM have poorer cardiovascular prognoses,³⁸ more target organ damage,⁴² and sympathetic activation in diabetic nephropathy.⁴³ In our analysis, adjusting for blood pressure and antihypertensive medication use did not change the association. We could not, however, account for intraindividual physiologic variation over time or diurnal variations in systemic pressure. Glycemia also may affect intrarenal pressure. Intraglomerular hypertension can contribute to progression of diabetic nephropathy even in the absence of systemic hypertension.³⁴

The ARIC Study did not collect information on type of DM in participants. The age at first DM diagnosis was asked of ARIC participants at the ARIC visit 3 (3 years after visit 2, the baseline of these analyses). Among 773 participants having a diagnosis of DM at visit 2, the mean (SD) time from diagnosis to visit 2 was 10 (9) years. Only 43 (3.8% of 1134 asked) reported having DM diagnosed at age 30 years or younger, which suggests that few had type 1 DM.

The present study is also limited by the lack of a direct measure of kidney function. Direct measurement of kidney function is impractical in large cohorts, and most studies have relied on serum creatinine-based estimates of GFR. Estimated GFR was based on single measurements of creatinine at 3 different visits (measurements at visits 1 and 2 to exclude prevalent cases and at visit 4 to define incident cases). The association of higher HbA_{1c} concentrations and CKD was also observed in analyses limited to hospitalizations involving a kidney diagnosis.

Approximately 20% of individuals classified as having DM according to our definition did not meet the American Diabetes Association criteria for DM in place at the time (fasting glucose concentration ≥ 140 mg/dL), and only approximately 40% of our sample was prescribed medications to treat DM. Because of these early cases of DM, there are many individuals with HbA_{1c} concentrations in the normal range. Risks across HbA_{1c} concentrations were consistent across all population subgroups and did not differ by DM treatment status.

Because measurements for albuminuria were available only at visit 4, we could only exclude prevalent cases of CKD stage 3 or greater, and, therefore, our sample may include individuals with prevalent CKD stage 1 or 2 at baseline. Measurements of HbA_{1c} and urinary albumin excretion and retinography were performed only once, at 3 different intervals (urinalysis at visit 4, retinography at visit 3, and HbA_{1c} at visit 2). By relying on a single measurement taken to detect either albuminuria or retinopathy, some cases may be missed. Those individuals without albuminuria at visit 4 are unlikely to have had albuminuria 6 years earlier.⁴⁴ Likewise, if damage was not detected on retinal images obtained at visit 3, it is unlikely that substantial damage was present at visit 2. Though specific findings of retinal damage may not be consistently observed over time, previous data from the ARIC Study found regression of identified damage to be uncommon in individuals with DM.⁴⁵ As in any study such as this, there is potential for residual confounding owing to unmeasured or mismeasured variables.

In summary, we observed a positive association between HbA_{1c} concentration and incident CKD that was strong, graded, independent of traditional risk factors, and present even at mildly elevated concentrations of HbA_{1c}. In this population-based setting, approximately one-third of CKD incidence occurred in the presence of both albuminuria and retinopathy and one-third occurred in the absence of both conditions. These data suggest that glycemic control is an important modifiable risk factor in the pathology of kidney disease in individuals with DM, both in the presence and absence of other microvascular damage. These results also suggest that urinary albumin screening alone may not be adequate for CKD detection in individuals with type 2 DM.

Accepted for Publication: May 19, 2008.

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Author Contributions: Ms Bash had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Selvin and Coresh. *Acquisition of data:* Selvin, Steffes, and Coresh. *Analysis and interpretation of data:* Bash, Selvin, and Astor. *Drafting of the manuscript:* Bash. *Critical revision of the manuscript for important intellectual content:* Bash, Selvin, Steffes, Coresh, and Astor. *Statistical analysis:* Bash, Selvin, and Astor. *Obtained funding:* Coresh. *Administrative, technical, and material support:* Bash, Steffes, and Coresh. *Study supervision:* Astor.

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by grants 5R01-DK-076770-02, 5T32-HL-007024-33 (Ms Bash) and 5T32-RR-023253-02 (Ms Bash) from the National Institutes of Health.

Additional Information: The ARIC Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022.

Additional Contributions: The staff and participants of the ARIC Study made important contributions to our study.

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