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Original Contribution

Association between Glycosylated Hemoglobin Level and Cardiovascular and All-Cause Mortality in Type 1 Diabetes

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Hyperglycemia is implicated in the development and progression of microvascular complications in type 1 diabetes. In contrast, the association between hyperglycemia and macrovascular complications or mortality in type 1 diabetes is not clear. The authors studied a population-based cohort of 879 individuals with type 1 diabetes from Wisconsin, free of cardiovascular disease and end-stage renal disease at the baseline examination (1980–1982). The main outcome of interest was all-cause ($n = 201$) and cardiovascular ($n = 132$) mortality as of December 31, 2001. Elevated glycosylated hemoglobin levels were associated with all-cause and cardiovascular mortality, independent of duration of diabetes, smoking, hypertension, and proteinuria. The multivariable relative risks comparing the highest quartile of glycosylated hemoglobin ($\geq$12.1%) with the lowest quartile ($\leq$9.4%) were 2.42 (95% confidence interval: 1.54, 3.82; p-trend $= 0.0006$) for all-cause mortality and 3.28 (95% confidence interval: 1.77, 6.08; p-trend < 0.0001) for cardiovascular mortality. This association was present among both sexes and persisted in subgroup analyses by categories of diabetes duration, smoking, body mass index, proteinuria, and retinopathy. These data suggest that hyperglycemia is associated with all-cause and cardiovascular mortality among individuals with type 1 diabetes.

cardiovascular diseases; diabetes mellitus, type 1; glycosylation; hyperglycemia; mortality; Wisconsin

Abbreviations: CI, confidence interval; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; eGFR, estimated glomerular filtration rate; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Hyperglycemia is implicated in the development and progression of microvascular complications in type 1 diabetes according to data from the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study (1, 2). However, it is not clear whether hyperglycemia is related to macrovascular complications and mortality (3). An association of hyperglycemia with cardiovascular disease and mortality has been suggested in some (4, 5), but not all (6–11), previous studies of individuals with type 1 diabetes. Recent observational analyses from the DCCT/EDIC cohort suggest long-term beneficial effects for previous intensive diabetes therapy, including thinner carotid walls, as measured by intima-media thickness (12), and incident cardiovascular disease, compared with conventional treatment (13).

Using a population-based cohort of individuals in Wisconsin with type 1 diabetes, originally designed to study ocular complications of diabetes, we previously reported a positive association between glycosylated hemoglobin and 10-year cause-specific mortality, including coronary heart

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disease deaths (5, 14); however, we were limited by the number of outcomes available at that time to perform a detailed categorical analysis. Furthermore, in a more recent report (15) examining retinal microvascular characteristics and mortality in type 1 diabetes over a 15-year interval, glycosylated hemoglobin was a significant confounder of that association. We now have 20 years of follow-up data, including repeated measurements of glycosylated hemoglobin and information from active mortality surveillance of the cohort. In this study, we specifically examined in detail the hypothesis that high glycosylated hemoglobin levels are prospectively associated with all-cause and cardiovascular mortality in type 1 diabetes.

MATERIALS AND METHODS

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) has been described in detail in previous publications (16–19). In brief, 10,135 diabetic patients who received primary care in an 11-county area of southwestern Wisconsin were identified following an initial chart review from July 1, 1979, to June 30, 1980. A two-part sample of these patients was selected for the baseline examination from 1980 to 1982: the ''younger-onset'' group (all diabetes patients diagnosed before 30 years of age and who took insulin, $n = 1{,}210$) and the ''older-onset'' group (a probability sample of diabetes patients diagnosed at 30 years of age or older, $n = 1{,}780$). The subject of this study is the younger-onset group, all of whom, based on C-peptide measurements, were later confirmed to have type 1 diabetes mellitus (18). Ninety-nine percent of the younger-onset group was White. The first examination of our cohort (1980–1982) was followed by evaluations 4 years (1984–1986), 10 years (1990–1992), 14 years (1995–1996), and 20 years (2000–2001) later.

Of the younger-onset group ($n = 1{,}210$), 996 individuals participated in the 1980–1982 examination (baseline); nonparticipants were similar to participants except for shorter duration of diabetes, as per data from the initial chart review from 1979 to 1980 (17). This study followed the recommendations of the Declaration of Helsinki and was approved by the Human Subjects Committee of the University of Wisconsin School of Medicine and Public Health Institutional Review Board, Madison. Written, informed consent was obtained from all participants.

Exposure ascertainment

At the 1984–1986 examination, glycosylated hemoglobin level from a venous blood sample was obtained by using the Isolab resin microcolumn technique following the manufacturer's instructions (20). The hemoglobin fractions measured include hemoglobin A1c, and the minor components hemoglobin A1a and hemoglobin A1b, which in this paper are referred to collectively hereafter as glycosylated hemoglobin. The normal range for glycosylated hemoglobin was 4.6–7.9 percent. The intraassay coefficient of variation was 2.4 percent.

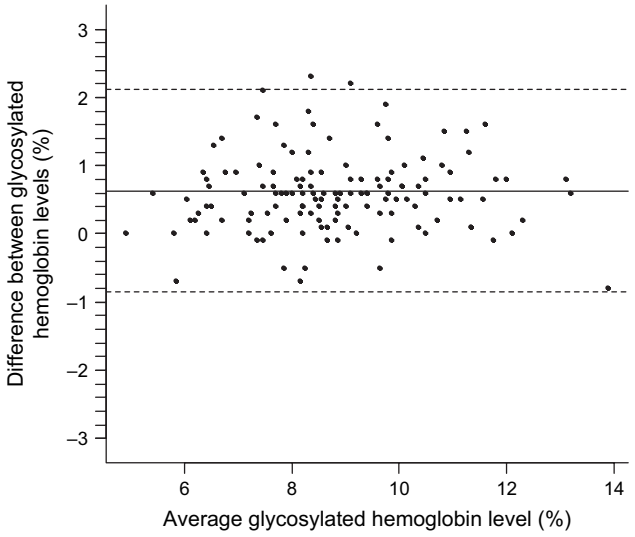

FIGURE 1. Bland-Altman plot comparing paired glycosylated hemoglobin (%) measurements from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) and the Diabetes Control and Complications Trial (DCCT) laboratories in a substudy of 140 type 1 diabetes subjects at one site (Washington University, St. Louis, Missouri), 1995. (Refer to the Materials and Methods section for details of the substudy.) The *x*-axis shows the mean of the two glycosylated hemoglobin (%) measurements (WESDR + DCCT/2). The *y*-axis shows the difference between the two glycosylated hemoglobin (%) measurements (WESDR − DCCT). The solid line represents the mean glycosylated hemoglobin level (%). The dotted lines represent ±2 standard deviations around the mean glycosylated hemoglobin level (%).

Comparability of DCCT glycosylated hemoglobin A1c and WESDR glycosylated hemoglobin was examined in a separate substudy in 1995, as described before (21). Blood samples from 140 type 1 diabetes subjects not included in either study were collected at one site (Washington University, St. Louis, Missouri); samples were split and were shipped to the DCCT Central Biochemistry Laboratory, University of Minnesota, Minneapolis, and to the WESDR Laboratory, University of Wisconsin, Madison. The Pearson correlation between glycosylated hemoglobin measurements from WESDR and DCCT laboratories was 0.91. A Bland-Altman plot comparing the two measurements is presented in figure 1. The WESDR glycosylated hemoglobin microcolumn results compare with the DCCT glycosylated hemoglobin A1c results as follows (21): $\text{DCCT} = 0.003 + 0.935 \times (\text{WESDR})$.

Blood pressure was measured according to the Hypertension Detection and Follow-up Program protocol (22) using a Hawksley random zero sphygmomanometer (Hawksley, Lancing, Sussex, United Kingdom). Phases I and V of the Korotkoff sounds were used to determine systolic and diastolic blood pressures, respectively. The mean of the last two of three readings was the blood pressure measurement used in our analyses. Hypertension was defined as a mean systolic blood pressure of $\geq$140 mmHg and/or a mean diastolic blood pressure of $\geq$90 mmHg and/or a history of

hypertension with antihypertensive medication use; individuals younger than 18 years of age were excluded from the stratified analysis of hypertension status.

Urinary protein levels were measured semiquantitatively by using an agglutination inhibition assay and a reagent strip test (Labstix; Ames, Elkhart, Indiana). Proteinuria was defined as a urine protein level of $\geq$0.3 g/liter. Retinopathy level was determined based on grading of fundus photographs using a modification of the Early Treatment Diabetic Retinopathy Study classification adapted for our study (17). Serum creatinine was measured at the 1984–1986 and subsequent examinations by a method based on a modification of the Jaffe reaction (23). The imprecision of creatinine assay was determined to be 2.73 (standard deviation, 0.03) percent and 1.45 (standard deviation, 0.09) percent on the basis of repeated ($n = 140$) measurement of controls with values of 1.1 mg/dl and 6.2 mg/dl, respectively. The method was linear to >20.0 mg/dl. Estimated glomerular filtration rate (eGFR) was calculated by using the Modification of Diet in Renal Disease Study equation (24). Other pertinent procedures at the 1980–1982 examination included standardized measurement of height and weight and collection of information about each participant's age, sex, years of schooling, year of diabetes diagnosis, details of smoking, and medications taken.

During the 1984–1986 examination (4-year follow-up), in a subset ($n = 400$) of our original cohort, serum total cholesterol and high density lipoprotein cholesterol were measured with the Roche Cobra FARA centrifugal analyzer (Roche Diagnostics, Nutley, New Jersey) using Boehringer Mannheim Diagnostics' (Indianapolis, Indiana) high-performance enzymatic cholesterol reagent. As reported earlier (25), there was little difference between those with and without measured cholesterol levels with regard to age, sex, duration of diabetes, glycosylated hemoglobin, diastolic blood pressure, body mass index, proteinuria, and serum creatinine levels at the 1984–1986 examination.

Outcome measures

Mortality surveillance of the WESDR cohort consisted of reviews of daily newspaper obituaries and regular contact with study participants and their relatives, designated contact persons, or physicians. Deaths were confirmed with death certificate data from annual requests to the Wisconsin Center for Health Statistics, Section of Vital Statistics. For this study, state mortality records through December 31, 2001, were searched. The names of persons who moved out of Wisconsin and those who were lost to follow-up or were suspected to have died were submitted for matching against Wisconsin death records and the National Death Index. For each match made, a copy of the death certificate was secured from the appropriate state. Only those deaths confirmed by death certificates were included in the definition of mortality. Death certificates were collected and coded by trained nosologists by using the *International Classification of Diseases*, Ninth Revision (26). We used these codes to classify deaths as being caused by cardiovascular disease, including coronary heart disease and stroke (codes 401–459), if they were mentioned as the underlying or contributory cause of death on the death certificates. Our preliminary analysis involving deaths due to cardiovascular disease as the ''underlying cause'' of death showed results similar to those based on ''any mention'' of cardiovascular disease as a cause of death on the death certificates, as reported previously in mortality research from our cohort (27) and in the general population (28).

The baseline participants were followed until death (all-cause and cardiovascular), loss to follow-up, or the 2000–2001 examination, whichever occurred first. For a total of 20 years of follow-up, 201 all-cause deaths and 132 cardiovascular deaths occurred in our cohort.

Data analysis

Of the 996 participants at the 1980–1982 examination, we excluded (not mutually exclusive categories) those with preexisting myocardial infarction ($n = 30$), stroke ($n = 11$), angina ($n = 31$), and end-stage renal disease (positive history of dialysis ($n = 8$) or history of renal transplantation ($n = 20$)), as well as those for whom information on important covariates was missing, including systolic or diastolic blood pressure ($n = 18$) or body mass index ($n = 6$). Doing so resulted in 879 type 1 diabetes individuals who formed our baseline cohort. Serum total cholesterol and high density lipoprotein cholesterol were measured at the 1984–1986 examination only for a subset ($n = 400$) of the 879 individuals at risk.

Means and proportions were compared by using analysis of variance and chi-square tests, respectively. Cox proportional hazards regression was used to estimate multivariable-adjusted relative risks and 95 percent confidence intervals (29). Models were run separately for all-cause and cardiovascular mortality as the outcome.

First, baseline glycosylated hemoglobin was categorized into quartiles ($\leq$9.4 percent, 9.5–10.5 percent, 10.6–12.0 percent, $\geq$12.1 percent) and was analyzed in two nested proportional hazards models: the age-, sex-, duration-adjusted model; and the multivariable-adjusted model (further adjusted for education (years of schooling), body mass index (kg/m^2), smoking (never, former, current), hypertension (absent, present), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), proteinuria (absent, present), retinopathy (none, nonproliferative, proliferative), history of neuropathy (absent, present), and history of daily aspirin intake (no, yes)). We ran these models first by including all 20 years of follow-up and then by excluding the first 4 years of follow-up to discount possible effects of preexisting disease on mortality. Second, we performed stratified analyses to determine whether our results were consistent across categories of possible confounders. Third, we analyzed glycosylated hemoglobin as a continuous variable in the following five proportional hazards models: 1) the multivariable model using baseline glycosylated hemoglobin level (whole cohort, $n = 879$); 2) additionally adjusted for serum total cholesterol, high density lipoprotein cholesterol, and eGFR from serum creatinine (ml per minute/1.73 m^2), available from the 1984–1986 examination (subset of baseline cohort, $n = 400$); 3) the multivariable model in a subset of our baseline cohort with ''stable'' glycemic control (defined

as less than a one-unit change in glycosylated hemoglobin levels between the 1980–1982 and 1984–1996 examinations, $n = 268$); 4) the multivariable model considering all covariates as time varying ($n = 879$); and 5) the multivariable model using updated mean glycosylated hemoglobin ($n = 879$). Updated mean glycosylated hemoglobin was calculated as the average of the glycosylated hemoglobin values for a person over his or her entire follow-up period (30).

In a subsidiary analysis, we repeated the main analysis after excluding the first 4 years of follow-up to examine whether our results were biased by subclinical disease at baseline that could be related to mortality. Second, we repeated the main analysis with quartiles of updated mean glycosylated hemoglobin ($\leq$8.9 percent, 9.0–9.8 percent, 9.9–10.8 percent, $\geq$10.9 percent) to examine the effect of an individual's mean glycemic levels during follow-up on mortality. Third, we repeated the main analysis by additionally adjusting for eGFR (ml per minute/1.73 m^2) to further account for the effect of renal function. Because serum creatinine was first measured at the 1984–1986 examination (number of living participants = 903), we performed this analysis among 754 individuals with type 1 diabetes for whom covariate information was complete at the 1984–1986 examination after excluding subjects with myocardial infarction ($n = 25$), stroke ($n = 12$), angina ($n = 26$), and end-stage renal disease (positive history of dialysis ($n = 41$) or history of renal transplantation ($n = 39$)), as well as those for whom information was missing on important covariates, including systolic or diastolic blood pressure ($n = 12$) or body mass index ($n = 36$) (numbers are not mutually exclusive). We examined the association between quartiles of glycosylated hemoglobin ($\leq$8.6 percent, 8.7–9.8 percent, 9.9–11.1 percent, $\geq$11.2 percent) and all-cause ($n = 117$) and cardiovascular ($n = 78$) mortality over a period of 16 years. Finally, since recent clinical practice recommendations suggest a hemoglobin A1c goal of $<$7 percent (31), we calculated the relative risk of all-cause and cardiovascular mortality for updated mean glycosylated hemoglobin levels of $\geq$7 percent, with $<$7 percent as the referent category. For this analysis, we also used the multivariable-adjusted model with additional adjustment for eGFR and therefore the 1984–1986 examination as the baseline. All analyses were performed with SAS version 9 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Characteristics of our cohort are presented in table 1. Those persons in the lowest glycosylated hemoglobin quartile at baseline were less likely to be current smokers, had lower diastolic blood pressure, and were less likely to have proliferative retinopathy and neuropathy.

Higher quartiles of baseline glycosylated hemoglobin were associated with a higher relative risk of all-cause and cardiovascular mortality (table 2). The association was present in the age-, sex-, and duration-adjusted model and in the multivariable model. Corresponding models of trend were also statistically significant. The association between increasing quartiles of glycosylated hemoglobin and all-cause and cardiovascular mortality was consistently present in subgroup analysis by gender (table 3).

Table 4 presents the relative risks of all-cause and cardiovascular mortality comparing the highest versus the lowest glycosylated hemoglobin quartile within categories of selected subgroups, including those based on duration of diabetes, smoking status, body mass index, baseline proteinuria, and retinopathy severity. Consistent with the results for the whole cohort (table 2), the positive association between hyperglycemia and mortality also persisted within these stratified subgroups, and the relative risks ranged from 1.6 to 3.6 for all-cause mortality and from 2.4 to 5.5 for cardiovascular mortality.

As shown in table 5, glycosylated hemoglobin was analyzed as a continuous variable. A one-unit increase in baseline glycosylated hemoglobin level was associated with relative risks of 1.16 (95 percent confidence interval (CI): 1.08, 1.24) for all-cause mortality and 1.20 (95 percent CI: 1.10, 1.30) for cardiovascular mortality. Further adjustment for serum total cholesterol, high density lipoprotein cholesterol, and eGFR measured at the second examination did not materially change the relative risks. When the analysis was confined to cohort members whose glycemic control was stable, defined as less than a one-unit change in glycosylated hemoglobin during the initial 4-year follow-up period, these associations remained essentially similar. The association was similar when glycosylated hemoglobin and other covariates were considered as time-varying covariates and when updated mean glycosylated hemoglobin was used.

As noted in the Materials and Methods section, in a subsidiary analysis, we excluded the first 4 years of follow-up to examine whether our main results (table 2) were biased by subclinical disease at baseline that could be related to mortality. The results were essentially similar. Compared with that for glycosylated hemoglobin quartile 1 (referent), the multivariable relative risk for all-cause mortality was 1.84 (95 percent CI: 1.11, 3.05) in quartile 2, 1.60 (95 percent CI: 0.95, 2.67) in quartile 3, and 2.56 (95 percent CI: 1.54, 4.27) in quartile 4. Similarly, compared with that for glycosylated hemoglobin quartile 1 (referent), the multivariable relative risk for cardiovascular mortality was 2.49 (95 percent CI: 1.21, 5.10) in quartile 2, 2.99 (95 percent CI: 1.47, 6.08) in quartile 3, and 3.96 (95 percent CI: 1.94, 8.11) in quartile 4. We also repeated the main analysis (table 2) by replacing baseline glycosylated hemoglobin quartiles with quartiles of updated mean glycosylated hemoglobin; results were in agreement with our main analyses in which we used baseline glycosylated hemoglobin quartiles. For example, for all-cause mortality, compared with that for glycosylated hemoglobin quartile 1 (referent), the multivariable relative risk was 1.55 (95 percent CI: 0.90, 2.66) in quartile 2, 2.14 (95 percent CI: 1.27, 3.60) in quartile 3, and 5.14 (95 percent CI: 3.17, 8.34) in quartile 4.

To further examine the effect of renal function in the association between glycosylated hemoglobin and mortality, we repeated the main analysis (table 2) by additionally adjusting for eGFR; the 1984–1986 examination was the baseline for this analysis. The results were essentially similar. Compared with that for glycosylated hemoglobin quartile 1 (referent), the multivariable relative risk for all-cause

TABLE 1. Baseline characteristics of the cohort by quartile of glycosylated hemoglobin, Wisconsin, 1980–1982

Characteristic	Baseline glycosylated hemoglobin quartile (range in %)				*p* value*
	Quartile 1 (5.6–9.4)	Quartile 2 (9.5–10.5)	Quartile 3 (10.6–12.0)	Quartile 4 (12.1–19.5)	
No. at risk	225	209	222	223	
Updated mean glycosylated hemoglobin (%)†	8.7	9.7	10.3	11.4	
Age (years)	29.8	34.9	31.9	29.3	<0.001
Sex: male (%)	48.9	56.5	49.6	49.3	0.34
Duration of diabetes (years)	12.2	16.1	14.4	12.2	<0.001
Education (years of schooling)	13.2	12.9	12.8	12.6	0.18
Smoking (%)					
Never	68.5	59.8	59.9	65.5	0.07
Former	13.3	15.8	12.6	8.5	
Current	18.2	24.4	27.5	26.0	
Body mass index (kg/m^2)	23.6	24.1	23.6	22.6	0.002
Hypertension (%)	17.3	18.2	22.1	17.9	0.65
Systolic blood pressure (mmHg)	121.2	125.0	123.5	123.4	0.26
Diastolic blood pressure (mmHg)	76.7	77.6	79.4	79.8	0.009
Proteinuria (%)	21.3	21.5	23.9	20.6	0.85
Estimated glomerular filtration rate (ml per minute/1.73 m^2)‡	91.5	92.7	95.4	96.6	0.31
Retinopathy (%)					
None	40.4	28.7	24.8	27.4	0.002
Nonproliferative	47.6	48.3	55.0	54.2	
Proliferative	12.0	23.0	20.2	18.4	
Neuropathy (%)	15.6	23.4	27.9	26.5	0.009

* Represents the difference in characteristics by quartiles of glycosylated hemoglobin based on analysis of variance or chi-square test, as appropriate.

† Defined as the updated average of the glycosylated hemoglobin values contributed by an individual during his or her entire follow-up.

‡ Rate obtained from serum creatinine measured at the 1984–1986 examination.

mortality was 1.94 (95 percent CI: 0.99, 3.78) in quartile 2, 2.46 (95 percent CI: 1.25, 4.84) in quartile 3, and 4.18 (95 percent CI: 2.18, 8.01) in quartile 4 (p-trend < 0.0001). Similarly, compared with that for glycosylated hemoglobin quartile 1 (referent), the multivariable relative risk for cardiovascular mortality was 3.05 (95 percent CI: 1.20, 7.72) in quartile 2, 3.66 (95 percent CI: 1.42, 9.46) in quartile 3, and 7.54 (95 percent CI: 3.03, 18.74) in quartile 4 (p-trend < 0.0001).

Finally, we performed multivariable analysis with additional adjustment for eGFR, using updated mean glycosylated hemoglobin of <7 percent as the referent group. At the 1984–1986 examination, 114 of 754 eligible study participants belonged to this referent group. Compared with subjects whose glycosylated hemoglobin levels were <7 percent, type 1 diabetic subjects with glycosylated hemoglobin levels of ≥7 percent had a multivariable relative risk of 2.66 (95 percent CI: 1.16, 6.11) for all-cause mortality and 3.50 (95 percent CI: 1.09, 11.23) for cardiovascular mortality.

DISCUSSION

In a population-based sample of individuals with type 1 diabetes from Wisconsin, increasing quartiles of glycosylated hemoglobin were associated with all-cause and cardiovascular mortality in a dose-dependent manner. When glycosylated hemoglobin was analyzed as a continuous variable, the observed positive association with mortality remained. This association was present even after adjusting for the main potential confounders and in analyses stratified by various related variables. Our results from a stable, long-followed cohort of individuals with type 1 diabetes complement and further extend recent evidence from the DCCT/EDIC cohort on the beneficial effect of previous intensive diabetes treatment on carotid intima-media thickness (12) and cardiovascular disease (13) by suggesting that hyperglycemia is also related to mortality.

In the current study, the magnitude of association between glycosylated hemoglobin and mortality; its independence from traditional risk factors, including duration of

TABLE 2. Association between baseline glycosylated hemoglobin level and all-cause and cardiovascular mortality, Wisconsin, 1980–1982 to 2001

Glycosylated hemoglobin level (range in %)	No. at risk ($n = 879$)	All-cause mortality					Cardiovascular mortality				
		All-cause deaths ($n = 201$)	Age-, sex-, and duration-adjusted model*		Multivariable model*,†		Cardiovascular deaths ($n = 132$)	Age-, sex-, and duration-adjusted model*		Multivariable model*,†	
			RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Quartile 1 (5.6–9.4)	225	30	1	Referent	1	Referent	14	1	Referent	1	Referent
Quartile 2 (9.5–10.5)	209	57	1.46	0.94, 2.29	1.76	1.12, 2.78	37	2.03	1.09, 3.78	1.90	1.02, 3.55
Quartile 3 (10.6–12.0)	222	52	1.54	0.98, 2.42	1.57	0.99, 2.50	42	2.59	1.41, 4.76	2.56	1.39, 4.72
Quartile 4 (12.1–19.5)	223	62	2.43	1.57, 3.76	2.42	1.54, 3.82	39	3.41	1.85, 6.28	3.28	1.77, 6.08
p trend				<0.0001		0.0006			<0.0001		<0.0001
One-quartile increase	879	201	1.31	1.15, 1.50	1.27	1.11, 1.46	132	1.44	1.22, 1.70	1.43	1.20, 1.69

* Relative risks (RRs) and 95% confidence intervals (CIs) were adjusted for age (years), sex (male, female), and duration of diabetes (years).
† Additionally adjusted for education (years of schooling), body mass index (kg/m^2), smoking (never, former, current), hypertension (absent, present), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), proteinuria (absent, present), retinopathy (none, nonproliferative, proliferative), history of neuropathy (absent, present), and history of daily aspirin intake (no, yes).

diabetes, smoking, body mass index, and proteinuria; and the consistency within subgroup analysis by gender and other related variables suggest that these findings are less likely to be due to chance. Proteinuria and dyslipidemia are also direct effects of glycemia (1, 32, 33) and may be seen as intermediate steps in the association between

TABLE 3. Sex-specific analysis of the association between baseline glycosylated hemoglobin quartile and all-cause and cardiovascular mortality, Wisconsin, 1980–1982 to 2001

Glycosylated hemoglobin level (range in %)	No. at risk	All-cause mortality					Cardiovascular mortality				
		All-cause deaths ($n = 201$)	Age- and duration-adjusted model*		Multivariable model*,†		Cardiovascular deaths	Age- and duration-adjusted model*		Multivariable model*,†	
			RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Men ($n = 448$)											
Quartile 1 (5.6–9.4)	110	17	1	Referent	1	Referent	7	1	Referent	1	Referent
Quartile 2 (9.5–10.5)	118	32	1.30	0.71, 2.36	1.71	0.93, 3.16	21	1.92	0.81, 4.57	1.96	0.82, 4.68
Quartile 3 (10.6–12.0)	110	32	1.69	0.93, 3.05	2.00	1.09, 3.69	26	3.39	1.47, 7.82	3.17	1.36, 7.38
Quartile 4 (12.1–19.5)	110	34	2.73	1.52, 4.92	2.46	1.33, 4.57	23	4.19	1.79, 9.80	4.59	1.95, 10.82
p trend				0.0004		0.004			0.0001		<0.0001
Women ($n = 431$)											
Quartile 1 (5.6–9.4)	115	13	1	Referent	1	Referent	7	1	Referent	1	Referent
Quartile 2 (9.5–10.5)	91	25	1.82	0.93, 3.59	1.92	0.96, 3.86	16	2.11	0.86, 5.18	2.02	0.82, 4.95
Quartile 3 (10.6–12.0)	112	20	1.30	0.64, 2.63	1.22	0.59, 2.56	16	1.78	0.73, 4.38	1.80	0.73, 4.43
Quartile 4 (12.1–19.5)	113	28	2.34	1.20, 4.56	2.48	1.24, 4.99	16	2.62	1.07, 6.39	2.37	0.95, 5.90
p trend				0.04		0.05			0.06		0.10

* Relative risks (RRs) and 95% confidence intervals (CIs) were adjusted for age (years) and duration of diabetes (years).
† Additionally adjusted for education (years of schooling), body mass index (kg/m^2), smoking (never, former, current), hypertension (absent, present), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), proteinuria (absent, present), retinopathy (none, nonproliferative, proliferative), history of neuropathy (absent, present), and history of daily aspirin intake (no, yes).

TABLE 4. Association between baseline glycosylated hemoglobin quartiles and all-cause and cardiovascular mortality within selected subgroups, Wisconsin, 1980–1982 to 2001

Stratified subgroup	All-cause mortality						Cardiovascular mortality					
	Quartile 1		Quartile 4		Comparison of quartile 4 with quartile 1*		Quartile 1		Quartile 4		Comparison of quartile 4 with quartile 1*	
	No. at risk	All-cause deaths	No. at risk	All-cause deaths	RR	95% CI	No. at risk	Cardiovascular deaths	No. at risk	Cardiovascular deaths	RR	95% CI
Duration of diabetes (years)												
≤15	155	10	159	24	2.39	1.10, 5.22	155	2	159	11	5.51	1.22, 24.91
>15	70	20	64	38	2.59	1.47, 4.57	70	12	64	28	3.02	1.53, 6.0
Smoking												
Never	154	14	146	32	2.29	1.19, 4.44	154	6	146	19	3.55	1.40, 9.03
Current/former	71	16	77	30	2.86	1.49, 5.48	71	8	77	20	3.76	1.62, 8.74
Body mass index (kg/m^2)												
<25	149	19	180	45	2.10	1.20, 3.68	149	7	180	28	4.06	1.77, 9.32
≥25	76	11	43	17	3.64	1.52, 8.70	76	7	43	11	2.37	0.88, 6.37
Proteinuria												
Absent	177	11	177	38	4.00	2.01, 7.95	177	6	177	22	4.30	1.73, 10.68
Present	48	19	46	24	1.60	0.85, 3.00	48	8	46	17	2.80	1.20, 6.55
Retinopathy												
None	91	5	61	6	2.21	0.61, 8.04	91	2	61	3	2.77	0.45, 17.03
Nonproliferative	107	13	121	29	2.47	1.25, 4.87	107	7	121	16	2.51	1.02, 6.21
Proliferative	27	12	41	27	2.34	1.10, 4.96	27	5	41	20	3.54	1.31, 9.58
History of neuropathy												
Absent	190	16	164	35	2.72	1.46, 5.06	190	7	164	18	3.60	1.49, 8.69
Present	35	14	59	27	2.20	1.05, 4.59	35	7	59	21	2.75	1.13, 6.68

* Except for the corresponding stratifying variable for subgroup analysis by smoking, proteinuria, retinopathy, and history of neuropathy, relative risks (RRs) and 95% confidence intervals (CIs) were adjusted for age (years), sex (male, female), duration of diabetes (years), education (years of schooling), body mass index (kg/m^2), smoking (never, former, current), hypertension (absent, present), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), proteinuria (absent, present), retinopathy (none, nonproliferative, proliferative), history of neuropathy (absent, present), and history of daily aspirin intake (no, yes).

TABLE 5. Association between glycosylated hemoglobin as a continuous variable and all-cause and cardiovascular mortality, Wisconsin, 1980–1982 to 2001

Model for a one-unit increase in glycosylated hemoglobin	No. at risk	No. of deaths		Multivariable model			
		All-cause deaths	Cardiovascular deaths	All-cause mortality		Cardiovascular mortality	
				RR*	95% CI*	RR	95% CI
Multivariable model†	879	201	132	1.16	1.08, 1.24	1.20	1.10, 1.30
Multivariable model with further adjustment for lipids and eGFR‡	400	82	54	1.18	1.02, 1.37	1.23	1.06, 1.43
Multivariable model among the "stable" glycemic control group§	268	52	35	1.22	1.01, 1.47	1.29	1.04, 1.60
Multivariable model with time-varying covariates¶	879	201	132	1.18	1.10, 1.27	1.22	1.12, 1.33
Multivariable model with updated mean glycosylated hemoglobin#	879	201	132	1.19	1.10, 1.29	1.23	1.12, 1.35

* RR, relative risk; CI, confidence interval.

† Proportional hazards model was adjusted for age (years), sex (male, female), duration of diabetes (years), education (years of schooling), body mass index (kg/m^2), smoking (never, former, current), hypertension (absent, present), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), proteinuria (absent, present), retinopathy (none, nonproliferative, proliferative), history of neuropathy (absent, present), and history of daily aspirin intake (no, yes).

‡ Multivariable-adjusted model was additionally adjusted for serum total cholesterol (mg/dl), high density lipoprotein cholesterol (mg/dl), and estimated glomerular filtration rate (eGFR), estimated from serum creatinine (eGFR) (ml per minute/1.73 m^2) from the 1984–1986 examination.

§ "Stable" glycemic control was defined as less than or equal to a one-unit change in glycosylated hemoglobin between the 1980–1982 and 1984–1986 examinations.

¶ Time-varying covariates for all variables in the multivariable-adjusted model.

Defined as the average of the glycosylated hemoglobin values contributed by an individual during his or her entire follow-up.

hyperglycemia and mortality (34, 35). However, when these variables were added to multivariable models, the relation between glycemia and mortality was not eliminated.

The observed association between glycemia and mortality can be explained by several plausible mechanisms, including nonenzymatic glycation and oxidation of plasma and arterial wall structural proteins (36, 37) and low density lipoprotein (38); production of advanced glycation end products (39); development of hypertriglyceridemia (40); effects of hyperglycemia on platelet aggregation (41), hemocoagulation, and fibrinolysis (42, 43); and development of proteinuria (1, 27). These findings are analogous to the relation between hyperglycemia and mortality in the general population (44, 45) and those persons with type 2 diabetes (30, 35, 44, 46–49).

However, similar data on the association of hyperglycemia with macrovascular disease and/or mortality in type 1 diabetes are limited. An association of hyperglycemia with cardiovascular disease and mortality has been suggested by some (4, 5, 12, 13), but not all (3, 6–11), previous studies. On the basis of a 10-year follow-up of our cohort, we previously reported (5, 14) a positive association between a one-unit increase in glycosylated hemoglobin and coronary heart disease mortality (relative risk = 1.2). It could be argued that a reported positive association in observational studies between glycosylated hemoglobin and short-term mortality (5, 14) or cardiovascular disease incidence (4, 14) could be explained by undetected/subclinical disease at baseline. Our results on long-term mortality are important in this context. In the current study, the association persisted even after excluding the initial 4 years of follow-up, suggesting these findings to be relatively robust. Furthermore, our findings are consistent with recent analyses from the DCCT/EDIC cohort suggesting long-term beneficial effects of previous intensive diabetes therapy regarding lower carotid intima-media thickness (12) and incident cardiovascular disease, compared with the conventionally treated group (13).

Recent clinical practice recommendations (31) suggest a hemoglobin A1c goal of <7 percent. In the current study, we observed a statistically significant, moderately strong association for all-cause and cardiovascular mortality among type 1 diabetic subjects whose glycosylated hemoglobin levels were ≥ 7 percent compared with <7 percent. Our observational results are therefore in agreement with recent recommendations on glycemic control in type 1 diabetes (31).

Strengths of our study include its high participation rate and the standardized measurement of exposure. As reported previously (19, 21), our method of measuring glycosylated hemoglobin is reliable, validated, and also calibrated to DCCT levels. We used previously validated methods to identify deaths (50, 51) and estimate that more than 98 percent of suspected deaths in our cohort were confirmed through death records. Surveillance bias is less likely given the uniform vital status follow-up procedures used by our staff masked to participants' glycosylated hemoglobin levels. Causes of death were also assigned without any knowledge of participants' exposure status.

Several study limitations need to be considered. First, our study results may not be generalizable, because 99 percent of this cohort was White. However, this factor increases our internal validity because potential biases from confounding variables correlated with race (52) were minimized.

Because our results were based on 20-year follow-up of the cohort, changes in diabetes treatment and health care could have affected mortality results. However, when updated mean glycosylated hemoglobin was used in the analyses, the main results remained similar. Measurement errors in glycosylated hemoglobin and other exposure estimation are more likely to be nondifferential and would probably have underestimated the observed relative risks. Finally, it is possible that our results were biased by residual confounding by factors not measured in the study but potentially related to cardiovascular disease in type 1 diabetes (3), including plasma triglycerides (53), lipoprotein subclasses (53), and markers of endothelial dysfunction (54).

In conclusion, results from our study suggest that higher glycosylated hemoglobin levels are associated with all-cause and cardiovascular mortality in type 1 diabetes. A corollary observation to our results is that the current recommendation for near-normal glycemic control, in addition to preventing microvascular complications, may also enhance survival in individuals with type 1 diabetes.

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The guarantor, A. S., accepts full responsibility for the work and/or the conduct of the study, 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. All authors contributed to the intellectual development of this paper. A. S. had the original idea for the study, analyzed the data, wrote the first draft paper, and is the guarantor. R. K., B. E. K. K., and S. E. M. provided statistical expertise, made critical corrections to the manuscript, and were involved in manuscript revision. R. K. and B. E. K. K. procured funding for the study and supervised data collection.

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