Glycemic Control and Coronary Heart Disease Risk in Persons With and Without Diabetes

The Atherosclerosis Risk in Communities Study

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Background: Chronic hyperglycemia has been hypothesized to contribute to coronary heart disease (CHD), but the extent to which hemoglobin A_{1c} (HbA_{1c}) level, a marker of long-term glycemic control, is independently related to CHD risk is uncertain.

Methods: We conducted a prospective case-cohort study of 1321 adults without diabetes and a cohort study of 1626 adults with diabetes from the Atherosclerosis Risk in Communities Study. Using proportional hazards models, we assessed the relation between HbA_{1c} level and incident CHD during 8 to 10 years of follow-up.

Results: In adults with diabetes, the relative risk (RR) of CHD was 2.37 (95% confidence interval [CI], 1.50-3.72) for the highest quintile of HbA_{1c} level compared with the lowest after adjustment for CHD risk factors. In persons without diabetes, the adjusted RR of CHD in the highest quintile of HbA_{1c} level was 1.41 (95% CI, 0.90-2.30); however, there was evidence of a nonlinear relationship in this group. In nondiabetic adults, HbA_{1c} level was not related to CHD risk below a level of 4.6% but was significantly related to risk above that level ($P<.001$). In diabetic adults, the risk of CHD increased throughout the range of HbA_{1c} levels. In the adjusted model, the RR of CHD for a 1–percentage point increase in HbA_{1c} level was 2.36 (95% CI, 1.43-3.90) in persons without diabetes but with an HbA_{1c} level greater than 4.6%. In diabetic adults, the RR was 1.14 (95% CI, 1.07-1.21) per 1–percentage point increase in HbA_{1c} across the full range of HbA_{1c} values.

Conclusion: Elevated HbA_{1c} level is an independent risk factor for CHD in persons with and without diabetes.

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CHRONIC HYPERGLYCEMIA has been hypothesized to contribute to coronary heart disease (CHD) in individuals with diabetes and nondiabetic individuals, but there is debate regarding whether this relationship is independent of known CHD risk factors. Hemoglobin A_{1c} (HbA_{1c}) reflects long-term glycemic control and tracks well in individuals over time,[1] especially when compared with fasting glucose. In persons with diabetes, HbA_{1c} is related to the development of microvascular disease[2-4] and is at the center of the clinical management of hyperglycemia. Although there is evidence that HbA_{1c} level is also associated with macrovascular disease in persons with diabetes,[5] this relation is controversial.

In persons with type 2 diabetes mellitus, the United Kingdom Prospective Diabetes Study (UKPDS) showed a 16% reduction ($P=.052$) in myocardial infarction (MI) in the intensive glucose-control group compared with the conventionally treated group after 10 years of follow-up.[2] However, because the results for cardiovascular outcomes were not statistically significant at the usual .05 level, the findings of the UKPDS are largely considered negative by the medical community and failed to resolve the debate regarding the effect of glycemic control on cardiovascular risk. The results of the UKPDS and subsequent prospective analyses of the trial data that showed a relation between HbA_{1c} level and cardiovascular risk[6-11] provide evidence of glycemic control as a possible modifiable risk factor for macrovascular disease. A few epidemiologic cohort studies examining the association in persons with diabetes suggest a positive association between HbA_{1c} level and CHD risk, but previous epidemiologic studies have been limited by lack of standardized measurement and adjustment for known CHD risk factors.[5]

It seems likely that if chronic hyperglycemia is important in the pathogenesis of CHD, any such relationship would extend to those individuals with elevated

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HbA_{1c} levels but without a diabetes diagnosis. Indeed, nondiabetic individuals with impaired glucose tolerance or borderline hyperglycemia have an elevated cardiovascular disease risk.[12-15] In persons without diabetes, several recent studies have shown that HbA_{1c} level predicts cardiovascular disease events prospectively and atherosclerosis cross-sectionally, independent of known risk factors.[16-21] However, previous studies have not rigorously examined the association between HbA_{1c} level and CHD risk separately in persons with and without diabetes after adjustment for known CHD risk factors, and no previous study to our knowledge has explicitly addressed whether the risk relation between HbA_{1c} and CHD risk is possibly nonlinear.

The present study was undertaken to test the hypothesis that glycemic control (HbA_{1c}) is positively associated with incident CHD independent of other known risk factors in persons with and without diabetes in a community-based cohort of middle-aged adults. A second aim of this study was to assess whether any relationship between HbA_{1c} and CHD risk is linear, as has been assumed in previous studies, that is, is there a level below which HbA_{1c} does not predict CHD (a threshold), or does risk increase across the full range of HbA_{1c} values (dose response)?

METHODS

STUDY DESIGN AND POPULATION

The Atherosclerosis Risk in Communities (ARIC) Study is a community-based cohort study of 15 792 people aged 45 to 64 years at baseline sampled from 4 US communities. The baseline clinic examinations (visit 1) took place during 1987-1989, with 3 follow-up visits approximately every 3 years. A wealth of information on cardiovascular disease risk factors, including information on lipid levels, blood pressure, sociodemographics, behavior, diet, and lifestyle, is available for all participants from the ARIC Study.[22,23] Visit 2 (1990-1992) was the only visit for which stored whole blood samples were available and was the baseline visit for the present study.

In persons without diabetes, we conducted a case-cohort study nested within the ARIC cohort. We selected all incident CHD cases occurring in persons without diabetes, as defined in the subsection "Outcome: CHD," with follow-up through the year 2000. The reference group (subcohort) was a stratified random sample of the ARIC visit 2 cohort. Persons with diabetes or prevalent cardiovascular disease, based on self-report, clinical examination, or hospital records, were excluded from the cohort random sample. We further excluded those participants who were missing covariates of interest (n=93) and those who fasted less than 8 hours prior to the visit or who were missing information on fasting status (n=26).

In persons with diabetes, we conducted a prospective cohort study using ARIC visit 2 as baseline with follow-up for incident CHD through 2000. We excluded persons with prevalent cardiovascular disease (n=393), missing covariates of interest (n=165), and those who fasted less than 8 hours prior to the visit or who were missing information on fasting status (n=152).

EXPOSURE: HbA_{1c}

Frozen whole blood samples from ARIC visit 2 were thawed and assayed for HbA_{1c} using a high performance liquid chromatography instrument (Tosoh Corporation, Tokyo, Japan). For this study, we measured HbA_{1c} on all post–visit 2 CHD cases with follow-up through 2000, the visit 2 cohort random sample, and all participants with diabetes at visit 2. The within-batch coefficient of variation for the Tosoh assay was 2.4%. We have previously demonstrated that measurements from these stored samples were highly reliable compared with measurements from these same specimens conducted prior to long-term storage (n=336, r=0.97).[19,24]

OUTCOME: CHD

Potential incident CHD events were identified by contacting ARIC participants annually to determine recent hospitalizations for cardiovascular events, procedures, and deaths. Possible hospital events were abstracted for information related to symptoms, signs, times of onset and admission, enzymes, electrocardiogram, and treatment. This information was used in a diagnostic algorithm to classify each individual as "definite MI," "possible MI," or "no MI" using standardized criteria.[25] Sources of validation for cardiovascular out-of-hospital deaths included interviews with family members, questionnaires to physicians, coroner or medical examiner reports, or hospital records. Deaths were classified as "definite fatal CHD," "possible fatal CHD," or "other." Events were reviewed by a committee of physicians for final classification. We included in this analysis incident CHD events (possible MI, cardiovascular revascularization, or definite fatal CHD) occurring among ARIC participants after visit 2 with follow-up through the year 2000.

OTHER VARIABLES OF INTEREST

Participants were asked to fast for 12 hours prior to each visit. To determine medication use, participants were asked to bring containers of current medications to each examination. Serum glucose level was measured using the hexokinase method.[26] Diabetes was defined as a fasting glucose level of 126 mg/dL or greater (≥7.0 mmol/L) (minimum of 8 hours of fasting prior to visit), a nonfasting glucose level of 200 mg/dL or greater (≥11.1 mmol/L), a self-reported physician diagnosis of diabetes, or treatment for diabetes at either the first or second ARIC examination. Persons without diabetes had a fasting glucose level less than 126 mg/dL (<7.0 mmol/L) at both visit 1 and visit 2.

Details have been previously described for measurement and estimation of plasma lipid levels including high-density lipoprotein and low-density lipoprotein cholesterol and triglycerides,[27-29] determination of body mass index (calculated as weight in kilograms divided by height in meters squared), waist-hip ratio,[30] and systolic and diastolic blood pressures.[31] Education level (high school or less, high school graduate or equivalent, or college or above) and smoking status (current, former, or never) were determined from interviews. Physical activity was only available from the first ARIC visit (1987-1989) and was assessed with the questionnaire used by Baecke et al,[32] from which a sport index, ranging from 1 (low) to 5 (high), was derived.

STATISTICAL ANALYSES

We performed all analyses separately in the samples of persons with and without diabetes. In persons without diabetes, we calculated weighted age-, sex-, and race-adjusted means and proportions to compare baseline characteristics by CHD status while accounting for the case-cohort design. Relative risk (RR) estimates (hazard ratios) and their 95% confidence intervals (CIs) for CHD risk were calculated using a weighted Cox proportional hazards model, accounting for the weighted case-cohort sampling design using the Barlow method.[33] In per-

Table 1. Adjusted* Baseline Characteristics of CHD Cases and Noncases in Persons With and Without Diabetes†

Characteristic	Persons Without Diabetes‡ (n = 1321)			Persons with Diabetes (n = 1626)		
	No CHD	CHD Cases	*P* Value	No CHD	CHD Cases	*P* Value
HbA_{1c}, %	4.8	4.9	<.001	6.6	7.3	<.001
Fasting glucose, mg/dL	101	103	.005	167	186	<.001
Systolic blood pressure, mm Hg	120	125	<.001	127	132	.001
Diastolic blood pressure, mm Hg	72.2	73.5	.02	73.2	72.8	.54
LDL-C, mg/dL	131	144	<.001	135	147	<.001
HDL-C, mg/dL	52.3	47.0	<.001	44.8	42.4	.007
Geometric mean triglycerides, mg/dL	106	122	<.001	138	150	.01
Body mass index, kg/m^2	27.5	27.8	.24	31.1	31.1	.87
Waist-hip ratio	0.91	0.93	<.001	0.96	0.98	.001
Baecke physical activity score	2.54	2.37	<.001	2.33	2.23	.048
Current smokers, %	20.3	30.4	<.001	18.6	24.2	.051
Taking hypertension medication, %	18.5	30.7	<.001	42.9	56.0	<.001
High school education or less, %	20.3	30.4	<.001	29.4	28.6	.81

Abbreviations: CHD, coronary heart disease; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.
*Adjusted for age, sex, and race.
†Data are given as mean value unless otherwise specified
‡Adjusted means in persons without diabetes are weighted to account for the case-cohort sampling design.

Table 2. Adjusted Relative Risk of CHD by Quintiles of HbA_{1c} in 1321 Persons Without Diabetes*

Model	HbA_{1c} Quintile, %					*P* Value for Trend	LRT *P* Value
	<4.5	4.5 to <4.8	4.8 to <4.9	4.9 to <5.2	≥5.2		
A (age, sex, and race adjusted)	1.00 (Referent)	0.89 (0.60-1.30)	0.77 (0.51-1.17)	1.45 (1.03-2.06)	1.91 (1.29-2.83)	<.001	<.001
B (model A + smoking)	1.00 (Referent)	0.92 (0.63-1.36)	0.74 (0.49-1.13)	1.33 (0.94-1.90)	1.78 (1.19-2.67)	<.001	<.001
C (model B + body mass index, waist-hip ratio, education, and physical activity)	1.00 (Referent)	0.91 (0.61-1.36)	0.73 (0.47-1.12)	1.30 (0.91-1.87)	1.61 (1.06-2.45)	.003	<.001
D (model C + systolic and diastolic blood pressure and hypertension medication)	1.00 (Referent)	0.78 (0.51-1.19)	0.72 (0.46-1.12)	1.33 (0.92-1.91)	1.71 (1.11-2.63)	.001	<.001
E (model D + lipids†)	1.00 (Referent)	0.67 (0.43-1.05)	0.66 (0.42-1.04)	1.08 (0.74-1.60)	1.41 (0.90-2.30)	.02	<.001

Abbreviations: CHD, coronary heart disease; HbA_{1c}, hemoglobin A_{1c}; LRT, likelihood ratio test of significance of all quintiles combined.
*Data are given as adjusted relative risk (95% confidence interval) unless otherwise specified.
†Low-density lipoprotein and high-density lipoprotein cholesterol and log-transformed triglycerides.

sons with diabetes, we calculated age-, sex-, and race-adjusted means and proportions to compare characteristics by CHD status. Relative risk estimates and 95% CIs for CHD risk were calculated using a Cox proportional hazards model.

We used higher-order polynomial and piecewise spline models to explore the possibility of nonlinear relationships between HbA_{1c} level and CHD risk in persons with and without diabetes. Data analysis indicated the presence of a single changepoint consistent with a single-knot spline model in persons without diabetes (ie, a threshold effect). In persons with diabetes, the relationship appeared to be roughly linear in all models. To display visually the relationship between HbA_{1c} level and CHD risk, we graphed age-, sex-, and race-adjusted relative hazard estimates. In persons without diabetes, we graphed estimates from a piecewise linear spline model with a 2-segment slope and a single knot placed at the maximum likelihood location. We generated a 95% CI corresponding for the location of the knot in the 2-segment spline model.[34,35] In persons with diabetes, we used a linear model and graphed the age-, sex-, and race-adjusted relative hazard of CHD with HbA_{1c} modeled as a continuous variable (per 1–percentage point increment in HbA_{1c}). For persons both with and without diabetes, we also graphed linear spline models with knots at quintiles for comparison and consistency with quintile models presented in the tables. Relative hazard estimates in all graphs use an HbA_{1c} value of 5.2% as a reference relative hazard of 1.0.

RESULTS

In persons without diabetes, the final study sample included 1321 participants, including, by design, all 661 incident CHD events that occurred from visit 2 through the year 2000 in this sample after exclusions. In persons with diabetes, the final study sample included 1626 participants, including 235 incident CHD events that occurred in this sample during follow-up through 2000.

At baseline, CHD cases had significantly higher age-, sex-, and race-adjusted HbA_{1c} levels compared with noncases in persons with and without diabetes (**Table 1**).

Table 3. Adjusted Relative Risk of CHD by Quintiles of HbA_{1c} in 1626 Persons With Diabetes*

Model	HbA_{1c} Quintile, %					*P* Value for Trend	LRT *P* Value†
	<5.2	5.2 to <5.7	5.7 to <6.5	6.5 to <8.2	≥8.2		
A (age, sex, and race adjusted)	1.00 (Referent)	1.36 (0.85-2.17)	1.66 (1.05-2.63)	2.29 (1.48-3.53)	2.80 (1.80-4.34)	<.001	<.001
B (model A + smoking)	1.00 (Referent)	1.32 (0.83-2.10)	1.66 (1.05-2.63)	2.26 (1.47-3.49)	2.75 (1.77-4.28)	<.001	<.001
C (model B + body mass index, waist-hip ratio education, and physical activity)	1.00 (Referent)	1.28 (0.80-2.04)	1.67 (1.05-2.66)	2.27 (1.46-3.52)	2.63 (1.68-4.11)	<.001	<.001
D (model C + systolic and diastolic blood pressure and hypertension medication)	1.00 (Referent)	1.27 (0.79-2.03)	1.68 (1.05-2.68)	2.29 (1.47-3.56)	2.59 (1.65-4.05)	<.001	<.001
E (model D + lipids†)	1.00 (Referent)	1.24 (0.77-1.98)	1.57 (0.98-2.52)	2.04 (1.30-3.19)	2.37 (1.50-3.72)	<.001	.001

Abbreviations: CHD, coronary heart disease; HbA_{1c}, hemoglobin A_{1c}; LRT, likelihood ratio test of significance of all quintiles combined.
*Data are given as adjusted relative risk (95% confidence interval) unless otherwise specified.
†Low-density lipoprotein and high-density lipoprotein cholesterol and log-transformed triglycerides.

In persons with and without diabetes, CHD cases and noncases also differed on other important baseline factors. In persons without diabetes, CHD cases, compared with noncases, had significantly higher systolic blood pressure, low-density lipoprotein cholesterol and triglyceride levels, and waist-hip ratio; more current smokers and higher hypertension-lowering medication use; and lower high-density lipoprotein cholesterol levels. Similar patterns were observed among people with diabetes.

Table 2 gives the results of the weighted proportional hazards models in persons without diabetes. In the model adjusted for age, sex, and race only (model A, Table 2), persons without diabetes in the highest quintile of HbA_{1c} level had approximately twice the risk of CHD compared with persons in the lowest quintile (RR, 1.91; 95% CI, 1.29-2.83). Adjustment for all cardiovascular risk factors (model E) attenuated the relation (RR, 1.41; 95% CI, 0.90-2.30), although this association was still statistically significant when all quintiles were tested simultaneously (likelihood ratio *P* value, <.001).

In persons with diabetes (**Table 3**), a graded relationship was observed for increasing CHD risk with increasing HbA_{1c} level in a minimally adjusted model that contained only age, sex, and race (RR, 2.80; 95% CI, 1.80-4.34 for the highest quintile compared with the lowest [model A]). In a model that included all cardiovascular risk factors (model E), the association was attenuated but remained significant (RR, 2.37; 95% CI, 1.50-3.72). Trends toward higher risk of CHD with higher HbA_{1c} level were evident in all models and in subgroup analyses in persons with unrecognized (undiagnosed) diabetes, persons with diagnosed diabetes, and persons with diagnosed diabetes receiving pharmacological treatment (data not shown).

As can be seen in the **Figure**, A, in persons without diabetes, the relationship between HbA_{1c} level and CHD risk appeared to be nonlinear; HbA_{1c} level was not related to CHD risk below an HbA_{1c} level of 4.6% (95% CI for the location of this knot, 4.4%-4.8%) but was significantly related to risk above that level. This can also be seen in the spline model with knots at the quintiles (Figure, A) and the model using quintiles presented in Table 2.

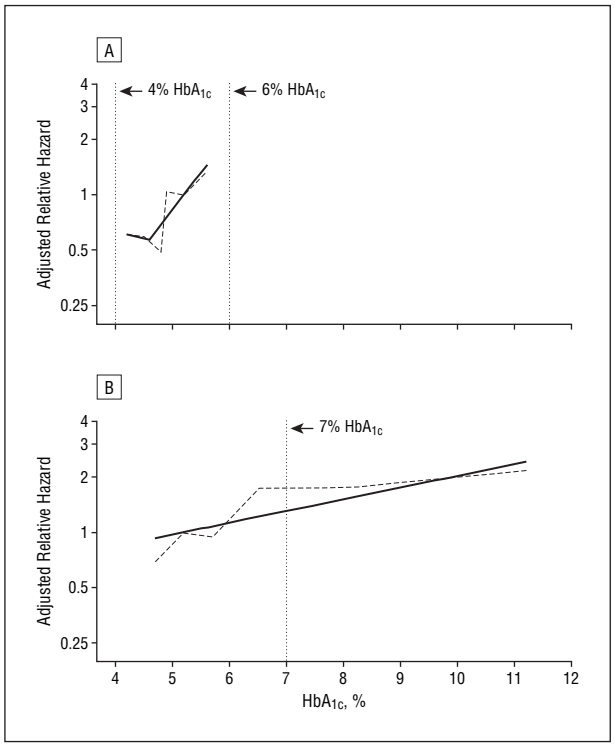

Figure. Adjusted relative hazard of coronary heart disease in 1321 individuals without diabetes (A) and 1626 individuals with diabetes (B), adjusted for age, sex, and race and plotted on the log scale. All adjusted relative hazards are centered at hemoglobin A_{1c} (HbA_{1c})=5.2%, and the graphed lines are shown for the fifth to 95th percentiles of HbA_{1c} level. The solid black line in A is from a single-knot linear spline model (knot at HbA_{1c}=4.6%). The dotted gray line is from a linear spline model with knots at the quintiles of HbA_{1c}. In B, the solid black line is from a linear model; the gray dotted line is from a linear spline model with knots at the quintiles of HbA_{1c} level. The normal range for HbA_{1c} in persons without diabetes (4%-6%) is indicated by the dotted vertical lines in A. The current target for glycemic control in persons with diabetes (HbA_{1c}=7%) is indicated by the vertical dotted line in B.

At HbA_{1c} values greater than 4.6%, the RR of CHD in persons without diabetes was 2.36 (95% CI, 1.43-3.90) per 1–percentage point increase in HbA_{1c} in a model adjusted for all covariates. Because previous studies have not considered a nonlinear relationship, the comparable RR estimate ignoring the nonlinear relationship be-

Table 4. Adjusted Relative Risk of CHD by Quintiles of Fasting Glucose in 1328 Persons Without Diabetes*

Model	Fasting Glucose Quintile, mg/dL					*P* Value†
	<94	94 to <99	99 to <104	104 to <110	≥110	
A (age, sex, and race adjusted)	1.00 (Referent)	1.08 (0.73-1.59)	1.34 (0.94-1.91)	1.42 (0.98-2.05)	1.40 (0.99-1.99)	.02
B (model A + smoking)	1.00 (Referent)	1.04 (0.70-1.54)	1.28 (0.90-1.83)	1.41 (0.97-2.05)	1.37 (0.96-1.95)	.02
C (model B + body mass index and waist-hip ratio)	1.00 (Referent)	0.98 (0.65-1.48)	1.12 (0.77-1.62)	1.26 (0.85-1.86)	1.13 (0.77-1.65)	.34
D (model C + blood pressure and hypertension medication)	1.00 (Referent)	1.02 (0.67-1.56)	1.17 (0.79-1.73)	1.19 (0.79-1.80)	1.09 (0.73-1.61)	.57
E (model D + lipids†)	1.00 (Referent)	1.05 (0.66-1.66)	1.13 (0.74-1.73)	1.17 (0.75-1.82)	1.06 (0.70-1.62)	.77

Abbreviation: CHD, coronary heart disease.
SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0259.
*Data are given as adjusted relative risk (95% confidence interval) unless otherwise specified.
†Low-density lipoprotein and high-density lipoprotein cholesterol and log-transformed triglycerides.

Table 5. Adjusted Relative Risk of CHD by Quintiles of Fasting Glucose in 1638 Persons With Diabetes*

Model	Fasting Glucose Quintile, mg/dL					*P* Value†
	<126	126 to <135	135 to <154	154 to <214	≥214	
A (age, sex, and race adjusted)	1.00 (Referent)	0.68 (0.43-1.07)	0.99 (0.65-1.51)	1.32 (0.88-2.00)	1.59 (1.05-2.41)	<.001
B (model A + smoking)	1.00 (Referent)	0.69 (0.43-1.09)	1.02 (0.67-1.57)	1.38 (0.91-2.08)	1.63 (1.08-2.47)	<.001
C (model B + body mass index and waist-hip ratio)	1.00 (Referent)	0.67 (0.42-1.06)	0.99 (0.64-1.52)	1.37 (0.90-2.07)	1.54 (1.01-2.33)	<.001
D (model C + blood pressure and hypertension medication)	1.00 (Referent)	0.71 (0.45-1.12)	1.04 (0.68-1.60)	1.36 (0.89-2.06)	1.55 (1.02-2.36)	.003
E (model D + lipids†)	1.00 (Referent)	0.66 (0.41-1.05)	0.97 (0.63-1.50)	1.25 (0.82-1.91)	1.34 (0.87-2.07)	.009

Abbreviation: CHD, coronary heart disease.
SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0259.
*Data are given as adjusted relative risk (95% confidence interval) unless otherwise specified.
†Low-density lipoprotein and high-density lipoprotein cholesterol and log-transformed triglycerides.

tween HbA_{1c} level and CHD risk (ie, assuming no change in slope) in our study was 1.68 (95% CI, 1.15-2.45) per 1–percentage point increase in HbA_{1c} level after adjustment for all other risk factors.

In persons with diabetes, the relationship between HbA_{1c} level and CHD risk increased throughout the range of HbA_{1c} values (Figure, B). In an adjusted linear model in persons with diabetes that included all covariates, the RR of CHD per 1–percentage point increase in HbA_{1c} level was 1.14 (95% CI, 1.07-1.21).

Subsequent development of diabetes did not seem to explain the association between HbA_{1c} and CHD in persons without diabetes. When time to development of diabetes was included as a time-varying covariate in the model, the coefficients for HbA_{1c} remained unaltered (data not shown). Fasting glucose level was also related to CHD risk in a similar manner as HbA_{1c} level (**Table 4** and **Table 5**); however, this association was much weaker than that observed for HbA_{1c} level and CHD risk, particularly in nondiabetic individuals.

COMMENT

Our prospective study demonstrates that HbA_{1c} level is related to CHD risk in persons with diabetes in a linear fashion after adjustment for other CHD risk factors. Our analysis suggests that the risk for CHD begins to increase at HbA_{1c} levels even below 7%, the usual target for good glycemic control.[36] In persons without diabetes, the relation between HbA_{1c} level and CHD appears more complicated. For an HbA_{1c} level below 4.6%, there was no clear association between HbA_{1c} and CHD risk. However, a level of 4.6% and above was associated with an increased risk of CHD even after adjustment for other CHD risk factors (RR, 2.36; 95% CI, 1.43-3.90). Thus, HbA_{1c} level is associated with CHD well into the "normal" range of HbA_{1c} values (ie, between 4.6% and 6.0%). However, very low levels of HbA_{1c} are not associated with an elevated CHD risk. Our finding provides guidance on the range of HbA_{1c} informative for CHD risk and suggests that subsequent studies of HbA_{1c} and cardiovascular risk in nondiabetic individuals should consider the possibility of a nonlinear relation.

The magnitude of the association we observed in persons with diabetes is consistent with those shown in previous epidemiologic studies and with limited clinical trial data.[5] In a study of women without diabetes, Blake and colleagues[18] found a crude association between HbA_{1c} levels and CHD risk, but this association was attenuated considerably after adjustment for age and smoking. We did not observe a similar attenuation with control for age and smoking. Indeed, smoking did not appear to be a particularly important confounding factor in our models, even when pack-years smoked and ever, never, and former

smoking categories were included simultaneously in the models to comprehensively adjust for this risk factor (analysis not shown). In a study of persons without self-reported diabetes and an HbA_{1c} level lower than 7% in the European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk) cohort, Khaw and colleagues[37] found that the RR of incident CHD was 1.40 (95% CI, 1.14-1.73) per 1–percentage point increase in HbA_{1c} level after adjustment for cardiovascular risk factors.

A limitation of our study was that we only had a single HbA_{1c} measurement. Hemoglobin A_{1c} is an inherently time-dependent variable; thus, baseline HbA_{1c} level may not most accurately reflect long-term glycemic control. In a prospective analysis of data from the UKPDS, the authors showed that updated mean HbA_{1c} level was more strongly related to increased risk of MI compared with baseline HbA_{1c} level.[8] This suggests that the present study is likely to have underestimated any true association between HbA_{1c} level and CHD.

Due to the observational nature of this investigation, the possibility of residual confounding cannot be completely eliminated. While elevated glucose levels are the clinically defining feature of diabetes, other metabolic abnormalities accompany the diabetic condition. In addition, HbA_{1c} measurements may be distal to the actual pathological effects of chronically elevated glucose levels on vascular tissues that contribute to the development of atherosclerosis and CHD. It is possible that direct markers of the pathologic changes resulting from hyperglycemia would be more strongly associated with CHD events.

The ARIC Study includes comprehensive surveillance for incident CHD and detailed information on important CHD risk factors from all participants. The availability of HbA_{1c} data on all participants with diabetes at visit 2 provided a rigorous prospective cohort study with a large sample of persons with diabetes followed for nearly a decade. The prospective cohort study is generally considered the gold standard for an observational epidemiologic investigation into the relationship between a risk factor and disease such as CHD.

In persons without diabetes, we used a prospective case-cohort design. The case-cohort design is an efficient alternative to a cohort study because measurements are made on all cases but only a random sample of the baseline study population at visit 2. Prospective analyses of these data can still be conducted, but the number of subjects for which HbA_{1c} needed to be measured was minimized. Previous prospective epidemiologic studies have not had extensive information by which to separate persons with and without diabetes. Furthermore, using a fasting glucose level less than 126 mg/dL (<7.0 mmol/L) on 2 separate occasions helped ensure that individuals with undiagnosed diabetes were excluded from our nondiabetic population.

Our analyses suggest that HbA_{1c} level is a marker for important pathological processes related to elevated glucose levels that contribute to vascular disease risk in diabetic adults and persons without diabetes (defined by a fasting glucose level <126 mg/dL [<7.0 mmol/L] at 2 different time points). Known risk factors for CHD such as smoking, hypertension, and hypercholesterolemia should be treated aggressively in persons with diabetes and persons without diabetes who are at high risk for cardiovascular disease. However, elevated HbA_{1c} level is associated with CHD independent of these risk factors, supporting a harmful role for hyperglycemia through other mechanisms that deserve further study.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of approximately 10 000 adults with diabetes, scheduled to be published in 2010, should provide a definitive answer to the question of the efficacy of glucose-lowering treatments in the prevention of cardiovascular complications in persons with diabetes.[38] In the interim, our results suggest that strategies for lowering blood glucose levels in persons with diabetes may reduce the incidence of heart disease, aiding in the interpretation of the equivocal UKPDS trial results for CHD. Our results also suggest that in persons without diabetes, a "high normal" HbA_{1c} level predicts elevated CHD risk and that, in addition to diabetes prevention, strategies to lower glucose levels should be investigated for reducing heart disease risk.

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