Glycemic Control, Atherosclerosis, and Risk Factors for Cardiovascular Disease in Individuals With Diabetes

The Atherosclerosis Risk in Communities study

ELIZABETH SELVIN, PHD, MPH[1,2]
JOSEF CORESH, MD, PHD[1,2,3]
SHERITA H. GOLDEN, MD, MHS[1,2,3]
LORI L. BOLAND, MPH[4]
FREDERICK L. BRANCATI, MD, MHS[1,2,3]
MICHAEL W. STEFFES, MD, PHD[5]

OBJECTIVE — Glycemic control (HbA_{1c} [A1C]) is strongly associated with microvascular disease in individuals with diabetes, but its relation to macrovascular disease and atherosclerosis is less clear. This study examines the relationship between A1C, carotid intima-media thickness (IMT), and traditional cardiovascular risk factors in individuals with diabetes.

RESEARCH DESIGN AND METHODS — A cross-sectional study of 2,060 people with diagnosed and undiagnosed (unrecognized) diabetes in the Atherosclerosis Risk in Communities study was performed.

RESULTS — LDL and HDL cholesterol, plasma triglycerides, and waist-to-hip ratio were significantly associated with A1C after multivariable adjustment. African Americans with undiagnosed and diagnosed diabetes had significantly elevated A1C values compared with whites, even after adjustment for potentially confounding factors. There was a graded association between A1C and carotid IMT. In a fully adjusted model in individuals with undiagnosed diabetes, the odds ratio (OR) of being in the highest quartile of IMT versus the lowest was 2.46 (95% CI 1.16–5.03, comparing the highest quartile of A1C to the lowest). In people with diagnosed diabetes, the comparable OR was 2.62 (1.36–5.06).

CONCLUSIONS — This study identified several important associations between A1C and known risk factors for cardiovascular disease and suggested that A1C is independently related to carotid IMT. Chronically elevated glucose levels may contribute to the development of atherosclerosis in people with diabetes, independent of other risk factors.

Diabetes Care **28:1965–1973, 2005**

From the [1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; the [2]Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, Maryland; the [3]Johns Hopkins School of Medicine, Baltimore, Maryland; the [4]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota; and the [5]Department of Laboratory Medicine and Pathology, Medical School, University of Minnesota, Minneapolis, Minnesota.

Address correspondence and reprint requests to Elizabeth Selvin, Ph.D., MPH, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2024 E. Monument St., Suite 2-600, Baltimore, MD 21205. E-mail: lselvin@jhsph.edu.

Received for publication 14 January 2005 and accepted in revised form 24 April 2005.

Abbreviations: ARIC, Atherosclerosis Risk in Communities; IMT, intima-media thickness; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Recent estimates suggest that there are ~18 million individuals with diabetes in the U.S., affecting ~9% of the total adult population (1). Glycemic control is a focus of clinical treatment of diabetes. HbA_{1c} (A1C), a measure of long-term glycemic control, is used to monitor and guide clinical treatment in individuals with diabetes. Elevated A1C levels are strongly associated with diabetes-related microvascular disease (2–4), but whether A1C is independently associated with the progression of atherosclerosis (5) and cardiovascular events (6) in individuals with diabetes remains controversial.

The U.K. Prospective Diabetes Study (UKPDS) showed an overall 25% reduction ($P = 0.0099$) in the risk of microvascular disease end points in the intensively treated group (median A1C = 7.0%) compared with the conventionally treated group (7.9%) after 10 years of follow-up (2). There is some evidence from epidemiologic studies that similar reductions in A1C may also reduce the risk of cardiovascular disease in people with diabetes (6,7). In the UKPDS trial, there was a 16% reduction ($P = 0.052$) in myocardial infarction observed for the intensively treated group compared with the conventionally treated group. Although the findings were only of borderline statistical significance, the UKPDS provided intriguing evidence of glycemic control as a possible modifiable risk factor for coronary heart disease.

Few studies have explicitly examined the association between glycemic control, carotid intima-media thickness (IMT), and known risk factors for cardiovascular disease. We hypothesized that glycemic control as measured by A1C would be positively associated with prevalent cardiovascular disease and carotid IMT even after adjustment for other cardiovascular risk factors in individuals with diagnosed and undiagnosed diabetes. We also hypothesized that A1C would be correlated

with risk factors for cardiovascular disease including lipids, blood pressure, and adiposity.

RESEARCH DESIGN AND METHODS

— The Atherosclerosis Risk in Communities (ARIC) study is a community-based cohort study of nearly 16,000 people aged 45–64 years at baseline (1987–1989). All participants were selected from four U.S. communities: suburban Minneapolis, Minnesota; Forsyth County, North Carolina; Washington County, Maryland; and Jackson, Mississippi. The cohort in Jackson, Mississippi, was sampled and recruited to have an all-black study population. Details on the design and conduct of the ARIC are available elsewhere (8). For the present cross-sectional study, we analyzed data from the second examination (visit 2) of ARIC participants, the only visit for which A1C data are available, which took place from 1990 to 1992. All individuals with diagnosed or undiagnosed diabetes at visit 1 or 2 were eligible for this study. We excluded 51 people who were missing data on A1C, four people who were nonwhite or nonblack, and 222 additional people who did not fast for ≥8 h before visit 2. After exclusions, 2,060 subjects were included in this study.

Diabetes status

Participants were asked to fast for 12 h before the ARIC clinic visits and to bring all current medications to determine mediation use. Glucose was measured using the hexokinase method (9). Individuals were defined as having diagnosed diabetes if they self-reported a physician diagnosis of diabetes or were currently taking diabetes medication. Individuals were classified as having undiagnosed (unreported) diabetes if they had a fasting glucose level ≥126 mg/dl or a nonfasting glucose level ≥200 mg/dl at the first or second ARIC examination but did not self-report a physician diagnosis of diabetes and were not taking diabetes medication. We further classified participants with diagnosed diabetes into the following treatment categories: *1*) no pharmacologic treatment, *2*) insulin treatment, or *3*) sulfonylurea treatment (oral hypoglycemic medication). Data for this study were collected in the early 1990s before metformin and thiazolidinediones were widely available.

A1C assay

Frozen whole blood samples from ARIC visit 2 were thawed and assayed for A1C using a Tosoh high-performance liquid chromatography instrument. The within-batch coefficient of variation for the Tosoh assay was 2.4%. We found that measurements from these long-term stored samples were extremely reliable when compared with measurements from the same samples conducted before long-term storage ($n = 336$, $r = 0.97$) (10,11).

Other variables of interest

Details have been previously described for measurement of lipids (12–14), determination of BMI (weight in kilograms divided by the square of height in meters), waist-to-hip ratio (15), and systolic and diastolic blood pressures (16). Smoking, hormone use (women only), and alcohol consumption (current, former, or never) were assessed by interview. Prevalent cardiovascular disease was based on self-report, ARIC clinical examination, or hospital records (17).

To assess carotid IMT, B-mode carotid ultrasound (Biosound 2000 II SA; Biosound, Indianapolis, IN) evaluations were completed on bilateral segments of the extracranial carotid arteries. The carotid artery was divided into three 1-cm regions and readers measured IMT within these regions. If the participants had missing IMT information from any carotid artery site, values were imputed for missing sites based on sex and race. Mean far wall IMT was also adjusted for reader differences and downward drift. Further details are described in previous articles (18,19).

Variables of interest were categorized using clinically relevant cut points wherever possible. BMI was categorized according to the classification system established by the National Institutes of Health (<25, 25.0–29.9, and ≥30.0 kg/m^2) (20). Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or current use of antihypertensive medication. Carotid IMT and waist-to-hip ratio were categorized according to quartiles.

Statistical analysis

All analyses were stratified by undiagnosed (unrecognized) and diagnosed diabetes status. Pearson's correlation coefficients and scatterplots were used to examine and present the association between A1C and fasting serum glucose.

Mean A1C levels were compared across categories of variables of interest after adjusting for age, sex, and race using a linear prediction model with each adjustment variable set to its mean value. In people with diagnosed diabetes, we also examined the association between A1C level and pharmacologic treatment status (none, sulfonylurea, or insulin). Mean A1C levels by presence of prevalent cardiovascular disease and quartile of IMT were compared separately in individuals with undiagnosed and diagnosed diabetes after adjustment for all other cardiovascular risk factors.

Multivariable linear regression models were used to assess the independent relationship between variables of interest and A1C after adjustment for relevant covariates. Diabetes treatment was assessed in a separate model because glucose-lowering treatment directly affects A1C levels and should not strictly be considered a "confounding" factor. Because information on duration of diabetes was missing for >30% of people with diagnosed diabetes, we did not include it in our final models. We did, however, conduct a subgroup analysis of people with diagnosed diabetes for which information on duration of diabetes was available. We also used a multivariable logistic regression model to compare the odds of being in the highest quartile of IMT ("thick IMT") versus the lowest by quartile of A1C after adjustment for potential confounding factors. These results were displayed graphically (Fig. 2). Because the distributions of both A1C and IMT differed in individuals with undiagnosed and diagnosed diabetes, diagnosis-specific quartiles were used in this analysis. All statistical analyses were conducted using Stata 8.2 (Stata, College Station, TX).

RESULTS

— In this community-based study of people with diabetes, the mean level of A1C in the total study population (diagnosed and undiagnosed diabetic patients combined) was 6.82 ± 2.10%. When stratified by diagnosis status, the average levels of A1C were 5.95 ± 1.41 and 7.56 ± 2.31% in individuals with undiagnosed ($n = 949$) and diagnosed ($n = 1,111$) diabetes, respectively.

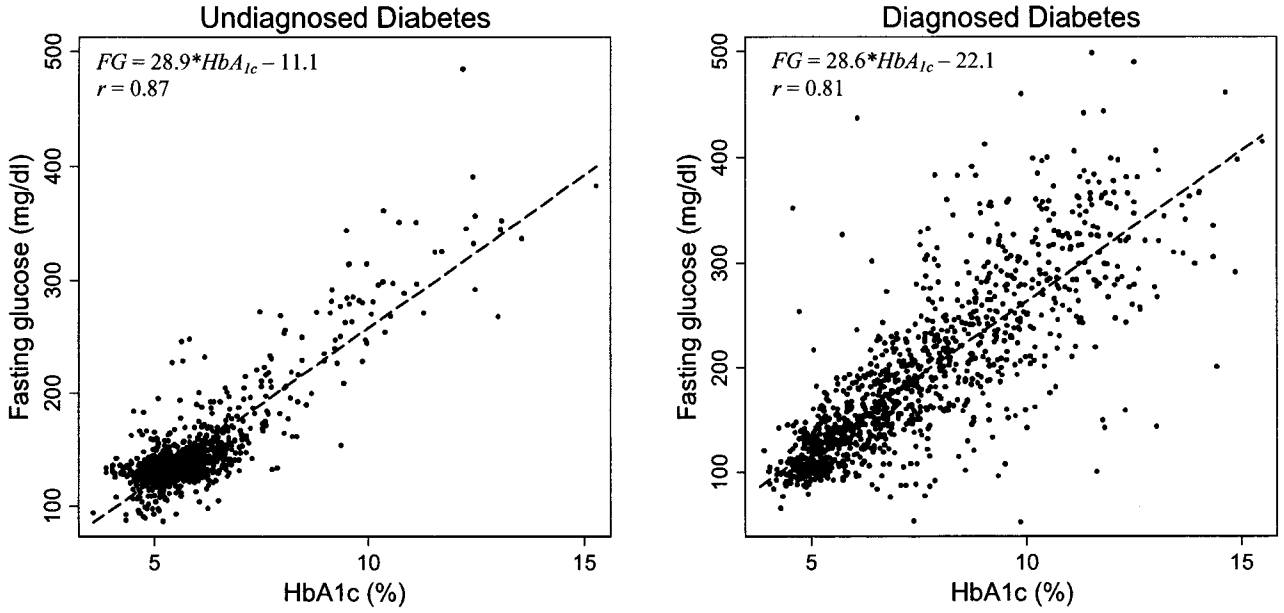

Figure 1—*Scatterplots of fasting glucose (FG; mg/dl) and A1C (HbA_{1c}; %) in individuals with undiagnosed and diagnosed diabetes. Dotted lines are linear regression lines. Regression equations are given in the* upper-left corner *of each graph.*

Fasting glucose and A1C

As expected, the correlation between fasting glucose and A1C was high. Correlations were 0.84 overall and 0.87 and 0.81 for individuals with diagnosed diabetes and undiagnosed diabetes, respectively (Fig. 1). In people with diagnosed diabetes who were not receiving pharmacologic treatment, the correlation was 0.90. The correlations were 0.56 and 0.82 in individuals receiving insulin and sulfonylurea treatment, respectively.

Age-, sex-, and race-adjusted analyses

In age-, sex-, and race-adjusted analyses (Table 1), race, measures of adiposity (BMI and waist-to-hip ratio), smoking status, LDL and HDL cholesterol concentrations, plasma triglyceride levels, and glucose-lowering medications (diagnosed diabetes only) were all significantly associated with glycemic control as measured by A1C ($P < 0.01$). Current smoking and current alcohol consumption were significantly associated with lower A1C levels in individuals with diagnosed diabetes only. Mean A1C levels were also strongly associated with IMT after adjustment for age, sex, and race in individuals with diagnosed and undiagnosed diabetes (Table 2).

Multivariable analyses

Table 2 displays the results of the adjusted multivariable linear regression models in people with undiagnosed and diagnosed diabetes. All models were simultaneously adjusted for age, sex, race, and all other variables in the table except for current hormone use. Current hormone use was examined in a separate model of women only, which included all other variables in the table. Correlations between A1C and BMI and waist-to-hip ratio were similar, so only waist-to-hip ratio was included in the multivariable models.

African-American race was strongly associated with A1C levels even after adjustment for all cardiovascular disease risk factors in individuals with undiagnosed and diagnosed diabetes. In people with diagnosed diabetes, African-American race was associated with ~1% higher mean A1C level compared with whites in this study, even after adjustment for potential confounding factors. HDL cholesterol ($P < 0.01$) was associated inversely with A1C in individuals with undiagnosed diabetes. LDL cholesterol was positively associated with A1C in individuals with diagnosed diabetes ($P < 0.01$). In both diagnosed and undiagnosed diabetic individuals, waist-to-hip ratio was strongly positively associated with A1C ($P < 0.01$). In people with diagnosed diabetes, being in the upper quartile of waist-to-hip ratio was associated with ~0.8% higher A1C level. Plasma triglycerides were associated positively with A1C in individuals with diagnosed and undiagnosed diabetes in a graded fashion. In people with diagnosed diabetes, glucose-lowering medication use was strongly associated with glycemic control ($P < 0.01$). Individuals currently taking sulfonylurea treatment had an ~2% higher mean A1C level than those with diagnosed diabetes who were not receiving any pharmacologic treatment ($P < 0.01$). People with diagnosed diabetes who were currently receiving insulin therapy had a 1.7% higher mean A1C level compared with individuals not taking medication ($P < 0.01$). There was some evidence that current alcohol consumption was associated with lower A1C, but this result was not statistically significant in any of the multivariable models.

In women, current hormone use was associated with lower A1C levels. Women with diagnosed diabetes who were currently taking hormones had ~0.8% lower mean A1C levels compared with women not currently taking hormones ($P < 0.01$). In women with undiagnosed diabetes, those currently taking hormones had 0.4% lower mean A1C levels ($P < 0.01$).

In the subgroup analysis of people with diagnosed diabetes for which information on duration of diabetes was available ($n = 696$), we did not find any association between A1C and diabetes duration after adjusting for cardiovascular risk factors (analysis not shown). We

Table 1—*Adjusted mean A1C by risk factor in undiagnosed and diagnosed diabetic subjects*

	Undiagnosed diabetes		Diagnosed diabetes	
	n	Adjusted mean A1C (%)	*n*	Adjusted mean A1C (%)
Age-group (years)				
45–50	84	5.91	80	7.72
50–55	246	5.93	240	7.66
55–60	222	5.95	265	7.58
60–65	260	5.97	323	7.51
65–70	137	5.99	203	7.44
P value		0.552		0.192
Sex				
Male	476	5.91	493	7.50
Female	473	6.00	618	7.61
P value		0.293		0.403
Race				
White	625	5.76	672	7.15
African American	324	6.33	439	8.19
P value		<0.001		<0.001
BMI (kg/m^2)				
<25	108	5.70	163	7.35
25–29.9	345	5.75	385	7.48
≥30	491	6.12	562	7.68
P value		<0.001		0.020
Quartiles of waist-to-hip ratio				
0.64–0.93	251	5.60	262	7.02
0.93–0.98	253	5.91	262	7.47
0.98–1.00	222	6.07	290	7.70
1.00–1.27	222	6.28	295	7.99
P value		<0.001		<0.001
Smoking status				
Current	200	6.13	217	7.33
Former	378	5.86	417	7.93
Never	368	5.95	475	7.99
P value		0.081		<0.001
Alcohol consumption				
Current	502	5.88	388	7.30
Former	227	6.12	389	7.67
Never	218	5.95	332	7.74
P value		0.120		0.028
Hypertension				
No	420	6.01	452	7.55
Yes	524	5.91	655	7.57
P value		0.264		0.926
Quartiles of LDL cholesterol (mg/dl)				
<110	212	5.81	276	7.12
110–134	239	5.90	255	7.35
134–161	224	5.96	266	7.52
>161	243	6.07	251	7.81
P value		0.023		<0.001
Quartiles of HDL cholesterol (mg/dl)				
<33	196	6.33	266	7.87
33–41	249	6.11	251	7.65
41–51	271	5.92	298	7.45
>51	232	5.51	291	7.03
P value		<0.001		<0.001

Continued on following page

also did not find any evidence that duration of diabetes was an important confounder in the relationship between A1C and any other variables of interest, and therefore, it was not included in any of the final models.

Although A1C was not significantly independently associated with prevalent cardiovascular disease in this study (data not shown), A1C was associated with higher carotid IMT in both undiagnosed and diagnosed diabetes. Figure 2 displays the odds ratios (ORs) of being in the highest quartile of IMT ("thick IMT") versus the lowest quartile of IMT by quartile of A1C after adjustment for cardiovascular risk factors. In people with diagnosed and undiagnosed diabetes, the highest quartile of A1C was significantly associated with having a thick IMT. In individuals with undiagnosed diabetes, the adjusted ORs of thick IMT were 2.42 (95% CI 1.16–5.03), 2.32 (1.14–4.71), and 2.46 (1.16–5.22) comparing the second, third, and fourth quartiles of A1C with the lowest, respectively ($P = 0.051$). For individuals with diagnosed diabetes, a strong trend was observed. In a model adjusted for the same covariates, the ORs of thick IMT were 1.09 (0.58–2.04), 2.04 (1.08–3.87), and 2.62 (1.36–5.06) for the second, third, and fourth quartiles of A1C, respectively ($P = 0.001$). In model 2 (diagnosed diabetes), which included all covariates plus diabetes medication use, the ORs of being in the highest quartile of IMT were 1.18 (0.60–2.33), 2.17 (1.06–4.46), and 2.83 (1.34–5.96) for the second, third, and fourth quartiles of A1C compared with the first ($P = 0.002$).

CONCLUSIONS — African-American race, cholesterol levels, plasma triglycerides, and waist-to-hip ratio were all associated with A1C levels independently of each other and known cardiovascular risk factors. As reported in previous studies (21–24), African-American race was strongly associated with higher A1C levels even after adjustment for potentially confounding factors. Understanding why African Americans are more likely to have poor glycemic control in undiagnosed and diagnosed diabetes warrants further investigation in future epidemiologic and clinical studies.

A1C was strongly associated with atherosclerosis as measured by carotid IMT. Carotid IMT is a widely accepted marker of atherosclerosis. It closely reflects the

Table 1—*Continued*

	Undiagnosed diabetes		Diagnosed diabetes	
	n	Adjusted mean A1C (%)	*n*	Adjusted mean A1C (%)
Quartiles of triglycerides (mg/dl)				
<103	223	5.61	280	6.93
103–146	259	5.86	263	7.36
146–210	247	6.04	266	7.68
>210	219	6.32	300	8.22
P value		<0.001		<0.001
Glucose-lowering medication use				
No pharmacologic treatment			381	6.62
Sulfonylurea treatment			237	7.48
Insulin treatment			493	8.33
P value				<0.001
Duration of diabetes				
<10 years			452	7.79
>10 years			294	7.94
P value				0.363
Current hormone use (women only)				
No	317	6.14	410	7.89
Yes	67	5.71	86	6.82
P value		0.024		<0.001

Data are means adjusted simultaneously for age, sex, and race except age, which was adjusted for race and sex only; sex, which was adjusted for age and race only; and race, which was adjusted for age and sex only.

atherosclerotic process and is strongly related to LDL cholesterol and other cardiovascular risk factors and predicts coronary heart disease events (25–28). Several recent studies have also shown that improvements in glycemic control can slow progression of atherosclerotic disease in individuals with type 1 (5,29,30) and type 2 diabetes (31). Our study provides evidence to suggest that glycemic control as measured by A1C is related to carotid IMT in middle-aged adults with diabetes independent of traditional cardiovascular risk factors. A previous case-control study in people without diabetes in the ARIC suggested that IMT case status was associated with A1C after controlling for age, sex, race, field center, examination date, smoking, BMI, hypertension, LDL and HDL cholesterol concentrations, education, fasting glucose, and fasting insulin (OR 1.88 [95% CI 0.9–4.1]) for the highest quartile of A1C compared with the lowest) (10). Previous studies have proposed that the glycation and oxidation of lipids and

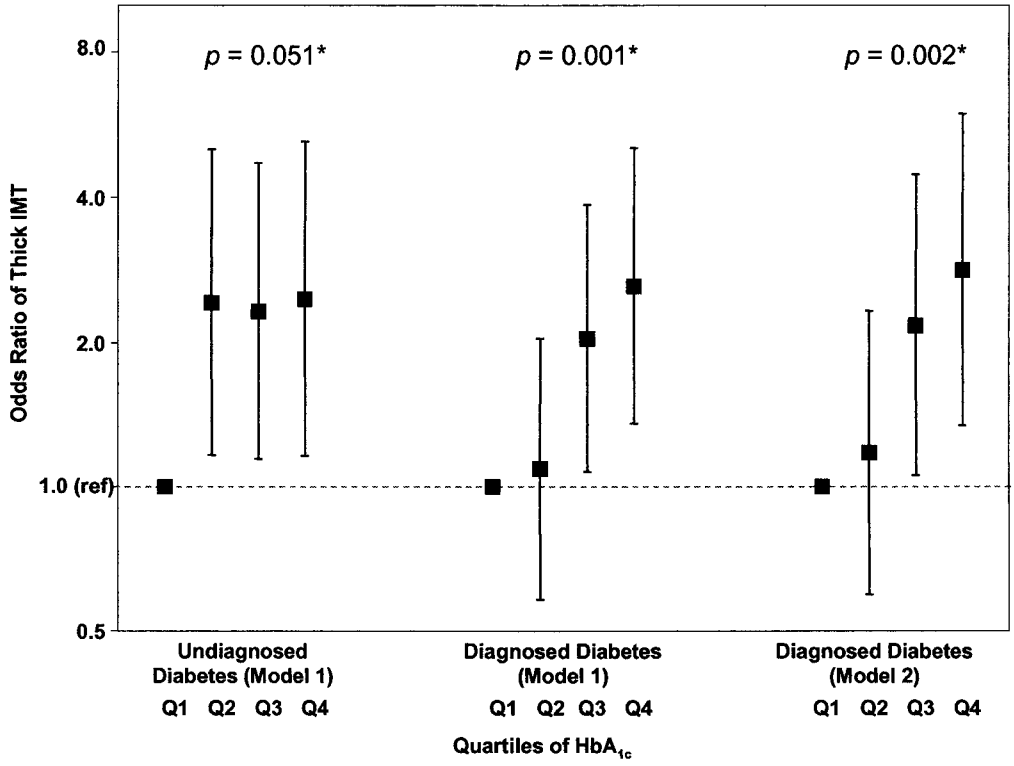

Figure 2—*OR (95% CI) of highest quartile of IMT ("thick IMT") versus the lowest quartile by quartile of A1C (HbA_{1c}) in individuals with undiagnosed and diagnosed diabetes. Model 1 was adjusted for age, sex, race, waist-to-hip ratio, LDL and HDL cholesterol concentrations, hypertension status, log triglyceride levels, smoking status, and alcohol consumption; all continuous variables were modeled as such. Model 2 was additionally adjusted for glucose-lowering medication use and diabetes duration.* P *values are tests for trend. In people with undiagnosed diabetes, the cut points for quartiles of A1C were 5.2, 5.6, and 6.2, respectively. In individuals with diagnosed diabetes, the cut points for quartiles of A1C were 5.7, 7.1, and 9.1 respectively.*

Table 2—*Multivariable adjusted linear regression models of A1C (%) and cardiovascular disease risk factors*

	Undiagnosed diabetes	Diagnosed diabetes	
	Model 1: difference in adjusted mean A1C (%) level by CVD risk factor	Model 1: difference in adjusted mean A1C (%) level by CVD risk factor	Model 2: difference in adjusted mean A1C (%) level by CVD risk factor
Age (per 5 years)	0.004	−0.136*	−0.50*
Sex (female vs. male)	0.300*	−0.057	0.131
Race (African American vs. white)	0.803*	1.28*	0.960*
Hypertension (yes vs. no)	−0.185	−0.185	−0.352*
LDL cholesterol (per 10 mg/dl)	0.013	0.057*	0.049*
HDL cholesterol (per 10 mg/dl)	−0.144*	−0.026	−0.006
Quartiles of waist-to-hip ratio			
Q2 (0.93–0.98) vs.Q1 (0.64–0.93)	0.250	0.520*	0.424*
Q3 (0.98–1.00) vs. Q1 (0.64–0.93)	0.544*	0.685*	0.501*
Q4 (1.00–1.27) vs. Q1 (0.64–0.93)	0.589*	0.812*	0.737*
Quartiles of triglycerides (mg/dl)			
Q2 (103–146) vs. Q1 (<103)	0.202	0.266	0.177
Q3 (146–210) vs. Q1 (<103)	0.317*	0.506*	0.421*
Q4 (>210) vs. Q1 (<103)	0.352*	0.739*	0.468*
Smoking			
Current vs. never	0.171	−0.546*	−0.317
Former vs. never	−0.091	−0.096	−0.031
Alcohol consumption			
Current vs. never	−0.035	−0.263	−0.253
Former vs. never	0.168	−0.041	−0.125
Glucose-lowering medication use			
Sulfonylurea vs. none			1.966*
Insulin vs. none			1.651*
Hormone use (current vs. former/never)†	−0.443*	−0.812*	−0.760*

Model 1 was adjusted for age, sex, race, waist-to-hip ratio, LDL and HDL cholesterol concentration, hypertension status, triglyceride level, smoking status, and alcohol consumption. Model 2 was additionally adjusted for glucose-lowering medication use. *P value <0.05. †Analysis conducted in separate models of women only; these models include all variables listed above for model 1 and model 2 plus hormone use. CVD, cardiovascular disease.

other proteins may contribute to the development of atherosclerosis in individuals with diabetes via the formation of advanced glycation end product and other related mechanisms (32–36).

A1C was not associated with prevalent cardiovascular disease in this study. Because this study was cross sectional, it is possible that individuals with prevalent cardiovascular disease ("survivors") in this cohort had better risk factor profiles (including lower A1C) and less severe disease than people who died of cardiovascular disease before baseline and therefore could not be included in the study. Thus, associations observed here may be affected by "survival bias" and biased toward the null. Nonetheless, age-stratified analyses did not show a stronger relation between A1C and prevalent cardiovascular disease in younger compared with older subjects.

In this middle-aged community-based cohort, there was some evidence of an association between decreased A1C and increasing age in individuals with diagnosed diabetes. In previous studies of people with type 2 diabetes, associations between glycemic control and age have been mixed. Several studies have shown that younger age is associated with higher A1C levels (37–39), whereas other studies have shown a positive association (40) or no association (41).

Similar to our results, previous studies have shown a positive association between glycemic control and adiposity (39,42,43) and cholesterol levels (21,44). Studies in individuals without diabetes have also shown similar correlations between lipids and A1C (45–48).

In this cross-sectional analysis, the strong association between pharmacologic treatment and elevated A1C levels in individuals with diagnosed diabetes most likely reflects severity of diabetes and/or poor medical compliance in people taking sulfonylurea and insulin medication compared with individuals not receiving pharmacologic treatment.

Several previous studies suggested possible beneficial effects of moderate alcohol consumption on glycemic control (40,42,49–51). In our study, there was some evidence of an association between current alcohol consumption and decreased A1C, but this relationship did not persist after adjustment for cardiovascular risk factors.

Similar to our results, previous studies of postmenopausal women with diabetes have shown that hormone use is associated with better glycemic control (22,52–56). Although this could be a direct effect of hormone therapy on glucose metabolism (57,58), it could also reflect a "healthy user" effect because previous studies have shown that women taking hormone replacement therapy are more likely to have a higher education level, have better health status, and engage in health-promoting behaviors compared

with women not taking hormones (59–61).

This study benefited from the rigorous methodology of the ARIC study and the availability of a wide range of risk factor data from a large community-based sample of people with diabetes. Because ARIC is a community-based cohort study, we were able to identify and examine individuals with both undiagnosed and diagnosed diabetes. Previous studies have examined associations between A1C and individual cardiovascular risk factors but few studies have had sufficient sample size or covariate information to be able to examine possible independent relationships after adjustment for multiple risk factors. To our knowledge, no previous study has compared the relationship between A1C and cardiovascular disease risk factors separately in people with diagnosed and undiagnosed diabetes. The availability of information on IMT also allowed us to assess the relationship between A1C and a measure of atherosclerosis, providing further evidence that elevated glucose levels may be contributing to the development of atherosclerosis and possibly subsequent cardiovascular events. There have been few studies of the relationship between A1C and atherosclerosis in individuals with type 2 diabetes.

Nonetheless, the cross-sectional design limited our ability to draw conclusions regarding the temporality of these associations. It is also important to note that during the time of the ARIC examinations for which data in this study were obtained (1990–1992), the criterion for the diagnosis of diabetes was a fasting glucose level ≥140 mg/dl. Thus, a number of people (~20%) classified as diabetic in the present study would not have been classified as diabetic under the clinical criteria at the time. However, similar relationships were observed in an analysis using a cut point of 140 mg/dl to define diabetes (analysis not shown). We were also unable to distinguish between the effects of race and geography in this analysis because most African-American participants (90%) were drawn from a single study center in Jackson, Mississippi. However, as mentioned earlier, previous studies have also shown that African-American race is associated with glycemic control (21–23). Furthermore, we did not have information on fasting insulin at ARIC visit 2, and we cannot eliminate the possibility of a direct effect of hyperinsulinemia. Nonetheless, when measurements of fasting insulin from ARIC visit 1 were included in our analyses (data not shown), no changes were observed.

We know from the results of clinical trials that interventions that decrease A1C levels, even by 1% (e.g., from 8 to 7%) can make an enormous difference in the health and lives of people with diabetes. This study suggests that A1C levels are also related to carotid IMT, race/ethnicity, adiposity, lipid levels, hormone therapy, and diabetes treatment. These results provide useful information for future observational and clinical studies. Understanding which factors are related to A1C is important for the development of appropriate models of glycemic control and risk of clinical events in epidemiologic studies. The results presented here provide evidence that A1C is cross-sectionally related to carotid IMT independent of other risk factors. Chronically elevated glucose levels may contribute to the development of atherosclerosis in individuals with diabetes.

Acknowledgments— 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. E.S. was supported by National Heart, Lung, and Blood Institute Grant T32HL07024.

The authors thank the staff and participants of the ARIC study for their important contributions and Joyce Jordahl for her valuable contributions to this study.

References

1. Centers for Disease Control and Prevention: *National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2002.* Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2003
2. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
3. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
4. Shichiri M, Kishikawa H, Ohkubo Y, Wake N: Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 23:B21–B29, 2000
5. Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, O'Leary DH, Genuth S: Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 348: 2294–2303, 2003
6. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH: Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 21:421–431, 2004
7. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
8. The ARIC Investigators: The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol* 129: 687–702, 1989
9. *Operations Manual No. 10: Clinical Chemistry Determinations, Version 1.0.* Chapel Hill, NC, ARIC Coordinating Center, School of Public Health, University of North Carolina, 1987
10. Vitelli LL, Shahar E, Heiss G, McGovern PG, Brancati FL, Eckfeldt JH, Folsom AR: Glycosylated hemoglobin level and carotid intimal-medial thickening in nondiabetic individuals: the Atherosclerosis Risk in Communities study. *Diabetes Care* 20:1454–1458, 1997
11. Selvin E, Coresh J, Jordahl J, Boland L, Steffes MW: Stability of haemoglobin A1c (HbA1c) measurements from frozen whole blood samples stored for over a decade. *Diabet Med*. In press
12. Siedel J, Hagele EO, Ziegenhorn J, Wahlefeld AW: Reagent for the enzymatic determination of serum total cholesterol with improved lipolytic efficiency. *Clin Chem* 29:1075–1080, 1983
13. Nagele U, Hagele EO, Sauer G, Wiedemann E, Lehmann P, Wahlefeld AW, Gruber W: Reagent for the enzymatic determination of serum total triglycerides with improved lipolytic efficiency. *J Clin Chem Clin Biochem* 22:165–174, 1984
14. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
15. *Operations Manual No. 2: Cohort Component Procedures, Version 1.0.* Chapel Hill, NC, ARIC Coordinating Center, School of Public Health, University of North Caro-

lina, 1987
16. *Operations Manual No. 11: Sitting Blood Pressure, Version 1.0*. Chapel Hill, NC, ARIC Coordinating Center, School of Public Health, University of North Carolina, 1987
17. White AD, Folsom AR, Chambless LE, Sharret AR, Yang K, Conwill D, Higgins M, Williams OD, Tyroler HA: Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *J Clin Epidemiol* 49: 223–233, 1996
18. The ARIC Study Group: High-resolution B-mode ultrasound scanning methods in the Atherosclerosis Risk in Communities Study (ARIC). *J Neuroimaging* 1:68–73, 1991
19. The ARIC Study Group: High-resolution B-mode ultrasound reading methods in the Atherosclerosis Risk in Communities (ARIC) cohort. *J Neuroimaging* 1:168–172, 1991
20. Executive summary of the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. *Arch Intern Med* 68:1855–1867, 1998
21. de Rekeneire N, Rooks RN, Simonsick EM, Shorr RI, Kuller LH, Schwartz AV, Harris TB. Racial differences in glycemic control in a well-functioning older diabetic population: findings from the Health, Aging and Body Composition Study. *Diabetes Care* 26:1986–1992, 2003
22. Ferrara A, Karter AJ, Ackerson LM, Liu JY, Selby JV: Hormone replacement therapy is associated with better glycemic control in women with type 2 diabetes: The Northern California Kaiser Permanente Diabetes Registry. *Diabetes Care* 24:1144–1150,2001
23. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS: Racial and ethnic differences in glycemic control of adults with type 2 diabetes. *Diabetes Care* 22:403–408, 1999
24. Lane JD, McCaskill CC, Williams PG, Parekh PI, Feinglos MN, Surwit RS: Personality correlates of glycemic control in type 2 diabetes. *Diabetes Care* 23:1321–1325, 2000
25. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX: Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol* 146: 483–494, 1997
26. Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, Rosamond WD, Evans G: Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol* 151:478–487, 2000
27. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, The Cardiovascular Health Study Collaborative Research Group: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 340:14–22, 1999
28. Folsom AR, Chambless LE, Duncan BB, Gilbert AC, Pankow JS, the Atherosclerosis Risk in Communities Study Investigators: Prediction of coronary heart disease in middle-aged adults with diabetes. *Diabetes Care* 26:2777–2784, 2003
29. Larsen JL, Colling CW, Ratanasuwan T, Burkman TW, Lynch TG, Erickson JM, Lyden ER, Lane JT, Mack-Shipman LR: Pancreas transplantation improves vascular disease in patients with type 1 diabetes. *Diabetes Care* 27:1706–1711, 2004
30. Larsen JL, Ratanasuwan T, Burkman T, Lynch T, Erickson J, Colling C, Lane J, Mack-Shipman L, Lyden E, Loseke M, Miller S, Leone J: Carotid intima media thickness decreases after pancreas transplantation. *Transplantation* 73:936–940, 2002
31. Wagenknecht LE, Zaccaro D, Espeland MA, Karter AJ, O'Leary DH, Haffner SM: Diabetes and progression of carotid atherosclerosis: the Insulin Resistance Atherosclerosis Study. *Arterioscler Thromb Vasc Biol* 23:1035–1041, 2003
32. Vlassara H: Recent progress in advanced glycation end products and diabetic complications. *Diabetes* 46:S19–S25, 1997
33. Lyons TJ: Glycation, oxidation, and glycoxidation reactions in the development of diabetic complications. *Contrib Nephrol* 112:1–10, 1995
34. Lyons TJ: Glycation and oxidation: a role in the pathogenesis of atherosclerosis. *Am J Cardiol* 25:26B–31B, 1993
35. Beckman JA, Creager MA, Libby P: Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 287: 2570–2581, 2002
36. Sheetz MJ, King GL: Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *JAMA* 287:2579–2588, 2002
37. Carter JS, Gilliland SS, Perez GE, Skipper B, Gilliland FD: Public health and clinical implications of high hemoglobin A1c levels and weight in younger adult Native American people with diabetes. *Arch Intern Med* 160:3471–3476, 2000
38. El Kebbi IM, Cook CB, Ziemer DC, Miller CD, Gallina DL, Phillips LS: Association of younger age with poor glycemic control and obesity in urban African americans with type 2 diabetes. *Arch Intern Med* 13: 69–75, 2003
39. Hu D, Henderson JA, Welty TK, Lee ET, Jablonski KA, Magee MF, Robbins DC, Howard BV: Glycemic control in diabetic American Indians: longitudinal data from the Strong Heart Study. *Diabetes Care* 22:1802–1807, 1999
40. Boeing H, Weisgerber UM, Jeckel A, Rose HJ, Kroke A: Association between glycated hemoglobin and diet and other lifestyle factors in a nondiabetic population: cross-sectional evaluation of data from the Potsdam cohort of the European Prospective Investigation into Cancer and Nutrition Study. *Am J Clin Nutr* 71:1115–1122, 2000
41. Shorr RI, Franse LV, Resnick HE, Di Bari M, Johnson KC, Pahor M: Glycemic control of older adults with type 2 diabetes: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. *J Am Geriatr Soc* 48:264–267, 2000
42. Okosun IS, Dever GE: Abdominal obesity and ethnic differences in diabetes awareness, treatment, and glycemic control. *Obes Res* 10:1241–1250, 2002
43. Harder H, Dinesen B, Astrup A: The effect of a rapid weight loss on lipid profile and glycemic control in obese type 2 diabetic patients. *Int J Obes Relat Metab Disord* 28: 180–182, 2004
44. Wagner AM, Jorba O, Rigla M, Bonet R, de Leiva A, Ordonez-Llanos J, Perez A: Effect of improving glycemic control on low-density lipoprotein particle size in type 2 diabetes. *Metabolism* 52:1576–1578, 2003
45. Blake GJ, Pradhan AD, Manson JE, Williams GR, Buring J, Ridker PM, Glynn RJ: Hemoglobin A1c level and future cardiovascular events among women. *Arch Intern Med* 164:757–761, 2004
46. Jenkins AJ, Lyons TJ, Zheng D, Otvos JD, Lackland DT, McGee D, Garvey WT, Klein RL: Serum lipoproteins in the diabetes control and complications trial/epidemiology of diabetes intervention and complications cohort: associations with gender and glycemia. *Diabetes Care* 26: 810–818, 2003
47. Barrett-Connor E, Criqui MH, Witztum JL, Philippi T, Zettner A: Population-based study of glycosylated hemoglobin, lipids, and lipoproteins in nondiabetic adults. *Arteriosclerosis* 7:66–70, 1987
48. Park S, Barrett-Connor E, Wingard DL, Shan J, Edelstein S: GHb is a better predictor of cardiovascular disease than fasting or postchallenge plasma glucose in women without diabetes: the Rancho Bernardo Study. *Diabetes Care* 19:450–456, 1996
49. Kroenke CH, Chu NF, Rifai N, Spiegelman D, Hankinson SE, Manson JE, Rimm EB: A cross-sectional study of alcohol consumption patterns and biologic

markers of glycemic control among 459 women. *Diabetes Care* 26:1971–1978, 2003
50. Gulliford MC, Ukoumunne OC: Determinants of glycated haemoglobin in the general population: associations with diet, alcohol and cigarette smoking. *Eur J Clin Nutr* 55:615–623, 2001
51. Harding AH, Sargeant LA, Khaw KT, Welch A, Oakes S, Luben RN, Bingham S, Day NE, Wareham NJ: Cross-sectional association between total level and type of alcohol consumption and glycosylated haemoglobin level: the EPIC-Norfolk Study. *Eur J Clin Nutr* 55:882–890, 2002
52. Sargeant LA, Wareham NJ, Khaw KT: Hormone replacement therapy and glucose tolerance in EPIC-Norfolk: a population-based study. *Diabete Metab Res Rev* 16:20–25, 2000
53. Triusu RJ, Cowie CC, Harris MI: Hormone replacement therapy and glucose metabolism. *Obstet Gynecol* 96:665–670, 2000
54. Samaras K, Hayward CS, Sullivan D, Kelly RP, Campbell LV: Effects of postmenopausal hormone replacement therapy on central abdominal fat, glycemic control, lipid metabolism, and vascular factors in type 2 diabetes: a prospective study. *Diabetes Care* 22:1401–1407, 1999
55. Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, Cauley JA, Barrett-Connor E: Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 138: 1–9, 2003
56. Crespo CJ, Smit E, Snelling A, Sempos CT, Andersen RE: Hormone replacement therapy and its relationship to lipid and glucose metabolism in diabetic and nondiabetic postmenopausal women: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care* 25:1675–1680, 2002
57. Andersson B, Mattsson LA: The effect of transdermal estrogen replacement therapy on hyperandrogenicity and glucose homeostasis in postmenopausal women with NIDDM. *Acta Obstet Gynecol Scand* 78:260–261, 1999
58. Andersson B, Mattsson LA, Hahn L, Marin P, Lapidus L, Holm G, Bengtsson BA, Bjorntorp P: Estrogen replacement therapy decreases hyperandrogenicity and improves glucose homeostasis and plasma lipids in postmenopausal women with noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 82:638–643, 1997
59. Brett KM, Madans JH: Use of postmenopausal hormone replacement therapy: estimates from a nationally representative cohort study. *Am J Epidemiol* 145:536–545, 1997
60. Keating NL, Cleary PD, Rossi AS, Zaslavsky AM, Ayanian JZ: Use of hormone replacement therapy by postmenopausal women in the United States. *Ann Intern Med* 130:545–553, 1999
61. Sturgeon SR, Schairer C, Brinton LA, Pearson T, Hoover RN: Evidence of a healthy estrogen user survivor effect. *Epidemiology* 6:227–231, 1995