HbA_{1c} and Peripheral Arterial Disease in Diabetes

The Atherosclerosis Risk in Communities study

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OBJECTIVE — To assess the relation between HbA_{1c} (A1C) and incident peripheral arterial disease (PAD) in a community-based cohort of diabetic adults from the Atherosclerosis Risk in Communities (ARIC) study. A second aim was to investigate whether the association was stronger for severe, symptomatic disease compared with PAD assessed by low ankle-brachial index (ABI).

RESEARCH DESIGN AND METHODS — This was a prospective cohort study of 1,894 individuals with diabetes using ARIC visit 2 as baseline (1990–1992) with follow-up for incident PAD through 2002. We assessed the relation between A1C and incident PAD, defined by intermittent claudication, PAD-related hospitalization, or a low ABI (<0.9).

RESULTS — During a mean follow-up of 9.8 years, the crude incidence rates were 2.1 per 1,000 person-years for intermittent claudication (n = 41), 2.9 per 1,000 person-years for PAD-related hospitalization (n = 57), and 18.9 per 1,000 person-years for low ABI at visit 3 or 4 (n = 123). The relative risk (RR) (95% CI) of an incident PAD event comparing the second and third tertiles of A1C to the first, respectively, after adjustment for cardiovascular risk factors was strongest for severe, symptomatic forms of disease, e.g., PAD-related hospitalization (RR = 4.56 [1.86–11.18] for the third A1C tertile compared with the first, P trend <0.001) than for low ABI (RR = 1.64 [0.94–2.87], P trend = 0.08).

CONCLUSIONS — We found a positive, graded, and independent association between A1C and PAD risk in diabetic adults. This association was stronger for clinical (symptomatic) PAD, whose manifestations may be related to microvascular insufficiency, than for low ABI. Our results suggest that efforts to improve glycemic control in persons with diabetes may substantially reduce the risk of PAD.

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Peripheral arterial disease (PAD) is more than twice as common among diabetic compared with nondiabetic individuals (1,2) and is a strong predictor of subsequent cardiovascular morbidity and mortality (3–5). Chronic hyperglycemia may contribute to the development of atherosclerosis and subsequent macrovascular events, including PAD, in persons with diabetes, but this relation is controversial. HbA_{1c} (A1C), a measure of long-term glycemic control, is used to monitor and guide clinical treatment in persons with diabetes. Chronic hyperglycemia, as measured by A1C, is an established risk factor for diabetes-associated microvascular disease (6,7). Recent studies have also suggested that A1C may be associated with incident large-vessel disease (coronary heart disease, stroke, and PAD) in persons with diabetes (8–10).

There have been few prospective studies that have examined the association between A1C and PAD in persons with diabetes (11–13). Three previous studies in the literature have shown a positive association between A1C and incident PAD. However, these studies did not consistently adjust for known cardiovascular disease risk factors, including smoking, lipids, and adiposity (8). There is currently no consensus regarding a standard definition for PAD, and prevalence estimates and risk factor associations may differ depending on the definition used. Previous studies have not separately examined the association between A1C and different manifestations of PAD such as low ankle-brachial index (ABI) and intermittent claudication (which are related primarily to stenoses between the aortic bifurcation and the arteries around the knee) or revascularization procedures and amputation (where the effects of inadequate microvascular supply to the skin and peripheral nerves may contribute to clinical recognition of the disease). We conducted this study to test the hypothesis that A1C is positively related to incident PAD in a community-based cohort of persons with diabetes. A secondary hypothesis was that the association would be stronger for severe, symptomatic disease than for asymptomatic PAD individuals assessed by low ABI.

RESEARCH DESIGN AND METHOD

— The Atherosclerosis Risk in Communities (ARIC) study is a community-based cohort study of 15,792 people aged 45–64 years at baseline sampled from four U.S. communities. The baseline clinic examinations (visit 1) took place during 1987–1989, with three follow-up visits approximately every 3 years. A wealth of information on cardiovascular disease risk factors, including lipids,

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Abbreviations: ABI, ankle-brachial index; ARIC, Atherosclerosis Risk in Communities; PAD, peripheral arterial disease.

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

blood pressure, sociodemographic, behavioral, diet, and lifestyle information are available for all participants from the ARIC study (14,15). Visit 2 (1990–1992) was the only visit for which stored whole blood samples were available, and it is the baseline visit for the present study.

We conducted a prospective cohort study using ARIC visit 2 as baseline with follow-up for incident PAD events through 2002. There were 2,337 individuals with diabetes (defined below) at the second ARIC examination. We excluded participants who were non-white or non–African American ($n = 4$), persons with prevalent PAD based on low ABI at visit 1 ($n = 227$) or an incident PAD event between visit 1 and visit 2 ($n = 40$), and participants who were missing A1C data ($n = 12$) or missing covariates of interest ($n = 160$). The final study sample consisted of 1,894 middle-aged adults with diabetes.

Diabetes definition

Participants in the ARIC study were asked to fast for 12 h before each clinical examination. Serum glucose was measured using the hexokinase method (16). Diabetes was defined as a fasting glucose ≥126 mg/dl (minimum of 8 h fasting), a nonfasting glucose ≥200 mg/dl, a self-reported physician diagnosis, or treatment for diabetes at either the first or second ARIC examination.

Exposure: A1C

Frozen whole-blood samples from ARIC visit 2 were thawed and assayed for A1C using a Tosoh high-performance liquid chromatography instrument. The Tosoh assay is certified by the National Glycohemoglobin Standardization Program and traceable to the Diabetes Control and Complications Trial reference method. The within-run coefficient of variation for masked duplicate specimens ($n = 83$) was 2.4%. We have previously demonstrated that measurements from a subset of these stored samples were highly reliable when compared with measurements from a subset of these specimens conducted before long-term storage ($n = 336$, $r = 0.97$) (17,18). Visit 2 A1C measurements were available for all persons with prevalent or incident diabetes in the ARIC study.

Outcome: PAD

Incident PAD was defined according to the following categories: intermittent claudication from ARIC surveillance–based Rose Questionnaire administered annually to ARIC participants by telephone; PAD-related hospitalization, including revascularization or lower-extremity amputation procedure by ICD-9 code, defined as hospital discharge ICD-9 code 443.9 (intermittent claudication, peripheral vascular disease not otherwise specified, peripheral angiopathy not otherwise specified, or spasm of artery) of 84.11 (toe amputation), 84.12 (foot amputation), 84.15 (below knee amputation), 38.18 (leg endarterectomy), and 39.29 (leg bypass surgery); and low ABI, defined as ABI <0.9 in the one leg examined at either visit 3 or 4.

In the ARIC study, intermittent claudication was determined using the Rose Questionnaire (19), which was administered annually to ARIC participants by telephone. The Rose Questionnaire defines intermittent claudication as exertional leg pain relieved by resting within 10 min. Hospitalizations were also identified annually by telephone. If a hospitalization had occurred, a trained abstractor obtained and recorded all ICD-9 hospital discharge diagnoses. Surveillance for symptomatic PAD resulting in hospitalization, revascularization procedures, and amputations occurred through the year 2002. ABI was measured on approximately half of participants at the third clinical examination and on the other half at visit 4. Resting ankle and brachial systolic blood pressures were measured using the Dinamap 1846 SX automated oscillometric device (Criticon, Tampa, FL). The Dinamap device has high validity and reliability compared with the standard Doppler probe (20). Trained technicians measured the ankle blood pressure at the posterior tibial artery in a randomly selected leg, and the brachial artery systolic blood pressure was measured in the right arm. Both were measured while the patient was in the supine position (21,22). ABI was computed by dividing the single ankle systolic blood pressure measurement by the single brachial systolic blood pressure measurement. ABI <0.90 has been shown to have 79% sensitivity and 96% specificity for detecting angiogram-positive PAD (stenosis of ≥50%) (23), although the number of studies that have validated ABI against gold-standard measures of stenosis is small.

Covariates

Other variables of interest included age, race, sex, ARIC field center, HDL and LDL cholesterol, systolic blood pressure, hypertension medication use, diabetes medication use, BMI, waist-to-hip ratio, education level (less than high school, high school graduate or vocational school, or some college or college graduate), smoking status (current, former, or never), and number of pack-years smoked for current and former smokers. Details have been previously described for measurement of plasma lipids (24–26), determination of BMI (kg/m^2), waist-to-hip ratio (27), and systolic and diastolic blood pressure (21). Education level and smoking status were determined from interviews. To ascertain medication use, participants were asked to bring containers of current medications to each examination.

Statistical analysis

Baseline characteristics of the study population were displayed using means (±SD) and proportions for noncases and by each different manifestation of incident PAD (intermittent claudication, PAD-related hospitalization, and low ABI). Cox proportional hazards were used to generate relative risk (RR) estimates (hazard ratios) for incident PAD by tertiles of A1C. We analyzed incident PAD events from ARIC visit 2 through the year 2002. For those who developed PAD, we calculated length of follow-up from the second examination to the time of first PAD diagnosis. The date of event was based on date of visit 3 or 4 (when ABI <0.9), date when intermittent claudication was first classified, or hospitalization discharge date, whichever occurred first. We did not exclude participants with missing ABI measurement at visit 3 or 4 or both, so long as they continued annual telephone contacts to allow intermittent claudication and revascularization procedures to be ascertained. For participants without a PAD event, follow-up ended on the date of death, date of last contact, or else 31 December 2002.

Separate models were constructed to examine whether an A1C-PAD association existed for each of the different manifestations of PAD. We also conducted sensitivity analyses using different definitions of diabetes and in persons with undiagnosed (unreported) and diagnosed diabetes. All statistical analyses were conducted using SAS Version 8.2 (SAS Institute, Cary, NC).

RESULTS — Table 1 displays the characteristics of the study population of people with diabetes comparing individuals

Table 1—*Characteristics of study population of people with diabetes by manifestations of PAD (n = 1,894)*

	PAD			
	No incident PAD	Intermittent claudication	Hospitalization, amputation, or revascularization	Low ABI
n	1,690	41	57	123
Male (%)	48	52	51	38
Age (years)	58 ± 5.7	60 ± 5.0	60 ± 5.1	58 ± 6.1
White (%)	60	78	61	59
Current smoking (%)	18.4	20.0	35.1	24.6
Pack-years of smoking	16.1 ± 23.4	27.7 ± 29.5	23.3 ± 23.9	18.9 ± 23.8
LDL cholesterol (mmol/l)	3.5 ± 1.0	3.4 ± 0.9	3.7 ± 0.9	3.6 ± 1.0
HDL cholesterol (mmol/l)	1.1 ± 0.4	1.0 ± 0.3	1.1 ± 0.2	1.1 ± 0.4
Systolic blood pressure (mmHg)	128 ± 19	125 ± 15	131 ± 22	131 ± 20
Hypertension medication (%)	45.9	43.9	54.4	60.2
BMI (kg/m^2)	31.0 ± 5.9	30.2 ± 4.9	30.2 ± 6.	32.2 ± 6.3
Waist-to-hip ratio	0.97 ± 0.07	0.99 ± 0.06	0.98 ± 0.05	0.97 ± 0.07
Less than high school education (%)	31.6	39.0	36.8	38.2
Use of sulfonylurea (%)	21.9	46.3	17.5	22.8
Use of insulin (%)	16.0	19.5	31.6	17.1
A1C (%)	7.0 (2.1)	8.3 (2.2)	8.2 (2.5)	7.3 (2.1)

Data are % or means ± SD, unless otherwise indicated.

who did not develop PAD during follow-up to those who developed different manifestations of the disease. Major baseline differences observed in this table include a much higher prevalence of current smoking among persons who developed PAD, lower education level, higher prevalence of diabetes medication use, and higher A1C levels.

During a mean follow-up of 9.8 years, the crude incidence rates for the different manifestations of PAD were as follows: 2.1 per 1,000 person-years for intermittent claudication ($n = 41$), 2.9 per 1,000 person-years for PAD-related hospital discharge (symptoms, revascularization, or lower-extremity amputation) ($n = 57$), and 18.9 per 1,000 person-years for low ABI at visit 3 or 4 ($n = 123$). Figure 1 presents the cumulative probabilities for developing a PAD-related hospitalization

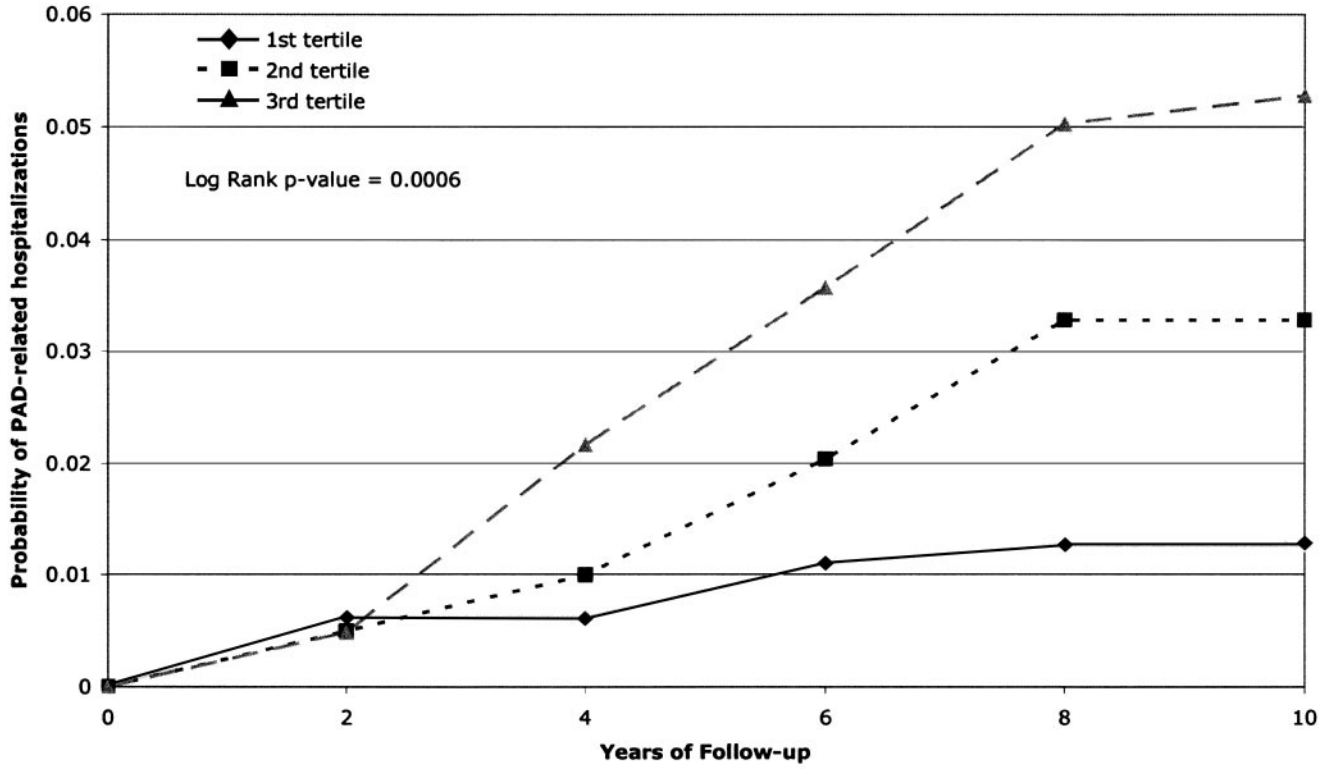

Figure 1—*Risk of PAD-related hospitalizations by tertile of A1C (%) in people with diabetes during 10 years of follow-up* (n = *1,894*).

Table 2—*Tertiles of A1C different manifestations of PAD in people with diabetes*

	A1C			
	<5.9%	6.0–7.4%	>7.5%	*P* value for trend
n	651	611	632	
Intermittent claudication cases (*n* = 41)				
Model 1	1.00 (ref)	3.31 (1.19–9.21)	6.32 (2.37–16.85)	<0.001
Model 2	1.00 (ref)	3.14 (1.07–9.15)	4.55 (1.52–13.06)	0.007
Hospitalization, amputation, or revascularization cases (*n* = 57)				
Model 1	1.00 (ref)	2.49 (1.09–5.72)	4.38 (1.98–9.68)	<0.001
Model 2	1.00 (ref)	2.73 (1.16–6.40)	4.56 (1.86–11.18)	<0.001
Low ABI cases (*n* = 123)				
Model 1	1.00 (ref)	1.66 (1.05–2.63)	1.61 (1.01–2.58)	0.05
Model 2	1.00 (ref)	1.53 (0.95–2.47)	1.64 (0.94–2.87)	0.08

Data are RR (95% CI), unless otherwise indicated. Model 1: adjusted for age, sex, race, and ARIC field center. Model 2: adjusted for age, sex, race, and ARIC field center, LDL and HDL cholesterol, systolic blood pressure, hypertension medication use, diabetes medication, cigarette pack-years, smoking status (ever/never/former), waist-to-hip ratio, BMI, and education level.

by tertile of A1C during the 10 years of follow-up. There was clear separation of risk by tertile of A1C as indicated by the log-rank test (*P* value <0.001).

Table 2 displays the results of the Cox proportional hazards models of risk of PAD by tertile of A1C. Model 1 was adjusted for age, sex, race, and ARIC field center. Model 2 was additionally adjusted for LDL and HDL cholesterol, systolic blood pressure, hypertension medication use, smoking status, pack-years of cigarette use, waist-to-hip ratio, BMI, and education level. The RRs of intermittent claudication cases defined from the Rose Questionnaire were 3.14 (95% CI 1.07–9.15) and 4.55 (1.52–13.06) comparing the second and third tertiles to the first, respectively, in the fully adjusted model (model 2) (*P* value for trend = 0.007).

The RRs for PAD-related hospitalization based on ICD-9 codes by tertile of A1C were 2.73 (95% CI 1.16–6.40) and 4.56 (1.86–11.18) (*P* value for trend <0.001). The wide CIs for intermittent claudication and PAD-related hospitalizations reflect the small number of events for these groups (*n* = 41 and 57 events, respectively). For individuals with PAD defined solely on the basis of a low ABI (ABI <0.9), the comparable RRs were 1.53 (0.95–2.47) and 1.64 (0.94–2.87) (*P* value for trend = 0.08).

Trends toward higher risk of PAD with higher A1C level were evident for all manifestations of PAD and in subgroup analyses in persons with unrecognized (undiagnosed) diabetes and in persons with diagnosed diabetes (data not shown). Fasting glucose levels were also related to incident PAD in a similar manner as A1C (data not shown); however, this association was much weaker compared with that observed for A1C level.

CONCLUSIONS — Our results suggest that poor glycemic control as indicated by elevated A1C levels in individuals with diabetes is associated with an increased risk of PAD independently of known risk factors. This association was particularly strong for the symptomatic, more severe manifestations of the disease, including intermittent claudication and PAD-related hospitalizations. Individuals with poor glucose control (A1C >7.5%) were more than five times as likely to develop intermittent claudication and also five times as likely to have a hospitalization for PAD compared with comparable individuals with good glycemic control (A1C <6%). It has been previously shown in the ARIC cohort that A1C is associated with incident coronary heart disease (10), stroke (28), and cross-sectionally related to atherosclerosis measured using carotid ultrasound imaging (29) in persons with diabetes. The present study suggests that A1C also predicts symptomatic and asymptomatic PAD in individuals with diabetes.

The Diabetes Control and Complications Trial and U.K. Prospective Diabetes Study trials in people with type 1 and type 2 diabetes, respectively, demonstrated that glycemic control is more strongly associated with microvascular disease than macrovascular disease. It may be that pathologic changes occurring in small vessels are more sensitive to chronically elevated glucose levels than is atherosclerosis occurring in larger arteries. Furthermore, it has been hypothesized that some cardiovascular (large vessel) outcomes have microvascular components (30). The U.K. Prospective Diabetes Study showed a decrease in PAD incidence (defined as amputation or death from PAD) in the intensive glycemic control compared with the conventional treatment group (median difference in A1C = 0.9%); however, this result was not statistically significant (35% risk reduction [95% CI −18 to 64]) probably owing to the small numbers of PAD events in this trial.

In our study, A1C was associated with both low ABI and clinical measures of PAD (amputation/revascularization procedures and intermittent claudication). The magnitude of the association between A1C and clinical (symptomatic) measures of PAD was stronger than that for PAD defined solely on the basis of low ABI. This is consistent with clinical trial data that show that A1C is more highly associated with microvascular disease than macrovascular disease. A low ABI reflects atherosclerotic occlusion in the lower extremities and is an important risk factor for cardiovascular events. Amputation and leg revascularization procedures, however, may also reflect the contributions of microvascular disease to the symptoms of the ischemic limb. Indeed, neuropathy, cutaneous ulceration, and wound healing failure underlie the great majority of lower-limb amputations (31). We suspect that definitions of PAD that incorporate the clinical presentation of the disease are more highly associated with A1C than a definition that includes

only ABI because a low ABI measurement does not capture the microvascular component of the condition.

An important limitation of this study was the infrequency with which ABI was measured in the ARIC study. We had annual follow-up of participants for intermittent claudication (Rose Questionnaire) and comprehensive and continuous surveillance for hospitalizations related to PAD, revascularization, and lower-extremity amputations, but ABI data were only available for two clinic visits (discrete times), so exact time of onset for low ABI cases was unknown. Additionally, there were no ABI data at visit 2, the visit for which A1C data were available and the baseline in our study. As a result, exclusion of prevalent disease was limited to all prevalent cases at visit 1 and clinical (hospitalizations and symptomatic) cases occurring at or before visit 2. Thus, although we believe most incident PAD cases occurred after A1C measurement, the temporality of the association between A1C and PAD as defined by low ABI could not be definitively established in this study. Furthermore, ABI was measured in one randomly selected leg, which could have resulted in misclassification of PAD cases as noncases. This misclassification may have resulted in underestimation of the true incidence of ABI cases and corresponding RR estimates. Additionally, the Rose Questionnaire has high specificity but low sensitivity, which may have also contributed to the misclassification of intermittent claudication cases as noncases (32)

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 ≥140 mg/dl. Thus, a number of people (~20%) classified as having diabetes in the present study would not have been classified as having diabetes 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). Despite rigorous measurement and adjustment for a wide range of known cardiovascular risk factors, we also cannot rule out the possibility of residual confounding in this observational study.

Strengths of this study include the large, community-derived study population, comprehensive surveillance for incident PAD-related hospitalizations, and detailed information on important cardiovascular risk factors for all participants. The availability of A1C data on all participants with diabetes at visit 2 provided for a rigorous prospective cohort study of a large sample of persons with diabetes followed for over a decade, permitting us to separately examine associations between A1C and different manifestations of PAD.

We found a positive, graded association between A1C and PAD risk in persons with diabetes in this community-based study. This association was independent of other known cardiovascular disease risk factors. Further, A1C was associated with all manifestations of PAD (symptomatic and asymptomatic), especially intermittent claudication symptoms and hospitalizations for PAD-related events such as leg revascularization or lower-extremity amputation. Our results suggest that efforts to improve glycemic control in persons with diabetes may substantially reduce the risk of PAD development.

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