Relationship of Retinal Vessel Caliber to Cardiovascular Disease and Mortality in African Americans With Type 1 Diabetes Mellitus

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Objective: To examine the relationship between retinal arteriolar and venular diameter and the 6-year incidence of cardiovascular disease and mortality among African Americans with type 1 diabetes mellitus.

Methods: Included were 468 African Americans with type 1 diabetes mellitus who participated in the New Jersey 725 and who had undergone a 6-year follow-up examination. At both baseline and 6-year follow-up, hypertension and presence of heart disease, stroke, or lower extremity arterial disease (LEAD) were documented and confirmed by review of hospital admission and medical records. Computer-assisted grading from digitized images of retinal photographs was accomplished to determine the average diameter of retinal arterioles (central retinal arteriolar equivalent) and venules (central retinal venular equivalent). Retinal vessel diameter size was examined in relation to the 6-year incidence of hypertension, *any* cardiovascular disease (heart disease, stroke, or LEAD), heart disease or stroke, LEAD, and mortality.

Results: Narrower central retinal arteriolar equivalent at baseline significantly and independently predicted 6-year incidence of *any* cardiovascular disease and LEAD, whereas larger retinal venular diameter at baseline significantly and independently predicted 6-year incidence of hypertension. Proteinuria and retinopathy severity at baseline were stronger predictors of mortality than retinal vascular diameter.

Conclusion: In African Americans with type 1 diabetes mellitus, baseline retinal vessel caliber is an independent predictor of incident hypertension and LEAD.

Arch Ophthalmol. 2012;130(5):561-567

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RETINAL ARTERIOLAR NARROWING has long been described as one of the characteristic changes associated with hypertension and cardiovascular disease (CVD).[1-3] In fact, hypertensive and sclerotic changes in the retinal vasculature have been used clinically to predict the severity of hypertension and generalized arterial disease.[2] Retinal vascular changes are thought to provide a window onto arterial vessels elsewhere in the body.

More recently, computerized measurements of retinal vessel diameter from digitized retinal photographs make it possible to quantify retinal vessel diameter.[4-6] By use of this method in nondiabetic populations, the presence of either narrower retinal arteriolar diameter or larger retinal venular diameter has been shown to be significantly and independently associated with the incidence of hypertension, CVD (either heart disease or stroke), and mortality from either vascular or nonvascular causes.[7-22]

In persons with type 2 diabetes mellitus (DM), narrower retinal arteriolar diameter was significantly and independently associated with 14-year incidence of lower extremity arterial disease (LEAD) and 22-year mortality from either stroke or all causes; larger venular diameter was associated with 22-year mortality from stroke.[23] There have been relatively few prospective studies of retinal vessel caliber changes as predictors of CVD in persons with type 1 DM.[24-26]

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We previously assembled, examined, and subsequently reexamined (6 years later) a large group of African Americans with type 1 DM (the New Jersey 725).[27-29] At both visits, 7 standard retinal photographs were obtained and graded for retinopathy severity in a masked fashion by the Ocular Epidemiology Reading Center in Madison. Blood pressure was measured. Detailed clinical information (ie, sociodemographic characteristics and diabetic complications, including heart disease, stroke, and LEAD) were obtained. In addition, the vital status of all participants was ascertained annually since the

beginning of the study by review of the Social Security Death Index. We thus had a unique opportunity to examine whether retinal vessel diameter size is a predictor of 6-year incidence of hypertension, CVD, and mortality in this cohort.

We hypothesized that smaller retinal arteriolar and larger retinal venular diameters, as measured on retinal photographs obtained at the baseline examination, would predict incidence (6-year) of hypertension, CVD, and mortality in these African Americans with type 1 DM.

METHODS

STUDY POPULATION

The original cohort consisted of 725 African Americans with type 1 DM who participated in the New Jersey 725 study from August 25, 1993, through November 7, 1997.[27] Patients diagnosed as having DM and treated with insulin before 30 years of age and currently receiving insulin were identified from a random review of 13 615 medical records. Excluded were patients with type 2 DM, those diagnosed after age 30, and patients with maturity-onset diabetes of youth.[30,31] Of the 875 eligible patients, 725 participated in the baseline examination.[27,28]

Of the 725 in the original cohort, 508 (70.1%) participated in the 6-year follow-up examination, 44 (6.1%) could not be located, 34 (4.7%) refused examination, and 139 (19.2%) had died in the 6-year interval.[29] At follow-up, 25 of the 508 patients (4.9%) were no longer receiving insulin and had not received a pancreas transplant. Because these patients may not be truly insulin-dependent, they were excluded, leaving 483 of the 508 patients (95.1%) available for analysis. Also excluded from the current analyses are patients with either Buerger disease (n=1) or systemic lupus (n=3) and patients who had no gradable eye at baseline (n=11). Data reported here pertain to the remaining 468 patients. The mean (SD) length of follow-up was 6.1 (0.5) years (median, 6.0 years).

PROCEDURES

Patients were examined in the Eye Clinic at University Hospital in Newark. On arrival, informed written consent was obtained. Patients underwent a complete eye examination, including dilated retinal examination and 7 standard stereoscopic Diabetic Retinopathy Study retinal photographs.[32] Also obtained were height and weight measurements. Blood pressure was measured twice in the sitting and standing positions using a random zero sphygmomanometer according to the Hypertension Detection and Follow-up Program protocol.[33] The average of the 4 measurements was used for either the systolic or diastolic pressures. A structured clinical interview included detailed medical and ophthalmologic histories as well as sociodemographic factors and lifestyle variables (ie, self-reported measures of cigarette smoking, alcohol consumption, and illicit drug abuse). Copies of medical records from previous hospital admissions were obtained and reviewed by the principal investigator (M.S.R.) to ascertain history of heart disease, stroke, or LEAD.

Venous blood was drawn for measurement of total glycosylated hemoglobin using high-pressure liquid chromatography (Bio-Rad; Labcorp Laboratory) and high- and low-density lipoprotein cholesterol and total cholesterol using an enzymatic assay and separation spectrophotometry (Genzyme Diagnostics). The normal range for total glycosylated hemoglobin is 4.2% to 7.0%, and the intra-assay coefficient of variation is 0.38% to 1.47%. A 4-hour timed urine collection was obtained for measurement of albumin excretion rate and creatinuria using spectrophotometry (SmithKline Beecham Clinical Laboratory). The institutional review board of the University of Medicine and Dentistry of New Jersey, New Jersey Medical School, approved the study.

DIABETIC RETINOPATHY GRADING

Color fundus photographs obtained at both baseline and 6-year follow-up were graded for diabetic retinopathy (DR) severity in a masked fashion by the Ocular Epidemiology Reading Center in Madison. The modified Early Treatment Diabetic Retinopathy Study Airlie House classification of DR was used.[34,35] Level 10 equals no DR, levels 20 to 53 equal nonproliferative DR of increasing severity, levels 61 to 85 equal proliferative DR (PDR) of increasing severity, and levels 71 to 85 equal PDR with high-risk characteristics. For each eye, the maximum grade in any of the 7 standard photographic fields was used to define the retinopathy level according to the Early Treatment Diabetic Retinopathy Study severity scale.[35] The retinopathy level for a patient was determined using the severity level in the worse eye. If retinopathy severity could not be graded in one eye, the person was considered to have a score equivalent to that in the gradable eye.

Eyes that could not be graded—because of opacities of the media, phthisis, or enucleation—were initially classified as "cannot grade." For such persons, review of all previous medical records was performed by one of us (M.S.R.). When a history of pan-retinal photocoagulation for PDR or pars plana vitrectomy for complications of PDR was documented by chart review, then the DR level was scored as 85. Persons who had an Early Treatment Diabetic Retinopathy Study grading of less than 61 at the time of examination and had previously received laser photocoagulation for PDR, as documented by chart review, were classified as grade 61.

ASSESSMENT OF THE RETINAL VESSEL DIAMETERS

Retinal vessel diameter measurements were accomplished (Ocular Epidemiology Reading Center in Madison) using a computer-assisted technique based on a standard protocol and modified formulas established for the Atherosclerosis Risk in Communities Studies and described in detail elsewhere.[4-6,36-38] Baseline retinal photographs of field 1 were converted to digital images using a high-resolution scanner with identical settings for all photographs. Using a computer software program (Retinal Analysis; Optimate), trained graders, masked to participant characteristics, measured the diameters of all arterioles and venules coursing through a specified area one-half to 1 disc diameter surrounding the optic disc. On average, 7 to 14 arterioles and an equal number of venules were measured for each eye. Individual arteriolar and venular measurements were combined into summary indices that reflected the average retinal arteriolar (central retinal arteriolar equivalent [CRAE]) and venular (central retinal venular equivalent [CRVE]) diameter of an eye.[36] The reliability of this retinal vessel grading approach has been shown to be high.[39]

DEFINITIONS

The patient's age was defined as the age at the time of baseline examination. Age at diagnosis of DM was the age at which the diagnosis of DM was first recorded by a physician in the patient's medical record. Duration of DM was the time between age at diagnosis and age at baseline. Systemic hypertension was defined as present if, at baseline, either the systolic pressure was at least 140 mm Hg or the diastolic pressure was at least 90 mm Hg, or if the patient was receiving antihypertensive medications. Microproteinuria was defined as present if the base-

Table 1. CRAE and CRVE in African American Patients With Type 1 DM With and Without Incident Complications at the 6-Year Follow-up[a]

Variable	No.	Any CVD	No.	Heart Disease or Stroke	No.	LEAD	No.	Hypertension[b]	No.	Mortality
CRAE, μm	401	No 169.7 (15.8)	390	169.5 (15.9)	416	169.3 (15.4)	203	172.2 (15.0)	482	167.9 (16.3)
	59	Yes 161.0 (15.0)	37	163.2 (15.0)	22	158.0 (14.4)	78	170.7 (17.9)	106	160.7 (16.3)
CRVE, μm	406	No 254.1 (25.1)	393	254.4 (25.1)	421	253.7 (24.9)	203	252.6 (21.0)	487	254.0 (25.7)
	58	Yes 255.2 (29.6)	37	255.8 (30.6)	21	253.2 (29.1)	79	261.5 (30.3)	106	256.9 (31.3)

Abbreviations: CRAE, central retinal arterial equivalent; CRVE, central retinal venular equivalent; CVD, cardiovascular disease (heart disease, stroke, or lower extremity arterial disease [LEAD]); DM, diabetes mellitus.

[a] Data are given as mean (SD) unless otherwise indicated. Numbers may vary because of missing data.

[b] Either systolic pressure of at least 140 mm Hg, diastolic pressure of at least 90 mm Hg, or receipt of antihypertensive medications.

line albumin excretion rate was 20 to 200 μg/min, and overt proteinuria was defined as present if the baseline albumin excretion rate was more than 200 μg/min. Any CVD was considered present if (1) the patient reported having undergone foot or leg amputation for a circulatory problem (excluding amputation secondary to an infection) or having had a myocardial infarction (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes 410-414) or stroke (*ICD-9-CM* codes 431-433 or 436) and (2) this was confirmed using standardized criteria by review of medical records of all previous hospital admissions.

Socioeconomic factors that were recorded included patient's level of education (for those aged 25 years or older), personal income (for those aged 18 years or older), and family income. The patient's socioeconomic status was classified according to the Goldthorpe and Hope[40] social grading of occupations. Smoking was defined as "pack-years smoked" by dividing the number of cigarettes smoked per day by 20 multiplied by the number of years smoked until baseline examination.

Assessment of mortality was performed annually between 1993 and 1998 by contacting study participants or their relatives or contacts as well as by review of the Social Security Death Index.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS, version 16 (SPSS, Inc). Measures of CRAE and CRVE of right and left eyes were averaged. Bivariate associations between baseline CRAE and CRVE and incident outcomes were assessed with odds ratios (ORs) and 95% CIs. To maximize clinical utility, the continuous average measures of CRAE and CRVE were transformed to quartiles in some of the analyses. Multivariate logistic regression was used to test the unique association of baseline CRAE and CRVE with incidence of *any* CVD, either heart disease or stroke, LEAD, hypertension, or all-cause mortality, after adjusting for several known risks for these outcomes. Three models were built that included 6 common variables and 1 of 3 highly collinear variables: model 1 included CRAE, CRVE, baseline age, socioeconomic status, sex, and proteinuria; model 2 substituted mean arterial blood pressure for proteinuria; and model 3 substituted baseline DR severity for proteinuria.

RESULTS

Baseline characteristics of the 468 participants have been previously reported.[41] Patients who were included were significantly younger, had significantly higher levels of glycosylated hemoglobin and high-density lipoprotein cholesterol, and had less hypertension, proteinuria, or moderate to severe retinopathy than patients who were excluded.[41]

Table 1 shows mean baseline CRAE and CRVE in patients who, at the 6-year follow-up, either did or did not develop any CVD, heart disease or stroke, LEAD, or hypertension, or who had died between the first and second visit.

Bivariate analyses showed that narrower CRAE at baseline was associated with 6-year incidence of any CVD ($P=.001$) (**Table 2**), incidence of LEAD ($P=.007$), and incidence of heart disease or stroke ($P=.01$). Narrower baseline CRAE was also associated with all-cause mortality ($P=.002$). By contrast, the 6-year incidence of hypertension was associated with larger baseline CRVE ($P=.008$).

To evaluate the uniqueness of these associations, multivariate logistic regression was used to adjust these associations for baseline age, sex, body mass index, and socioeconomic status. Several models were also run adding proteinuria (model 1), mean arterial blood pressure (model 2), or retinopathy severity (model 3), because these characteristics are strongly associated with one another. Multiple regression analysis showed that baseline narrower CRAE was significantly and independently associated with 6-year incidence of *any* CVD and LEAD but not of heart disease or stroke, and that larger baseline CRVE was significantly and independently associated with 6-year incidence of hypertension (**Table 3**). Both narrower CRAE and larger CRVE were significantly and independently associated with mortality when adjusting for baseline levels of mean arterial blood pressure (Table 3) but not either proteinuria or retinopathy severity.

Because the number of patients with either incident heart disease or stroke or LEAD was small, discrete logistic regression models were evaluated that included only 3 variables: age, CRAE, and either proteinuria or mean arterial blood pressure or retinopathy severity. They confirmed results presented in Table 3 with the exception that proteinuria ($P<.001$) rather than narrower CRAE remained a significant and independent predictor of incident heart disease or stroke (data not shown). Given the risk of model overfitting with few incident cases, this last result is considered more valid.

COMMENT

Results of the study indicate that narrower retinal arteriolar diameter at baseline is an independent predictor of the 6-year incidence of *any* CVD and LEAD, and base-

Table 2. Relationship of CRAE and CRVE to 6-Year Incidence of Cardiovascular Complications and Mortality in Type 1 Diabetic African Americans: Bivariate Analysis

	CRAE				CRVE			
6-y Incident Outcome	No.[a]	Quartile	OR (95% CI)	*P* Value	No.[a]	Quartile	OR (95% CI)	*P* Value
Any CVD	460	1st	5.79 (2.39-14.06)	.001	464	1st	1 [Reference]	
		2nd	1.92 (0.72-5.15)	.19		2nd	0.65 (0.29-1.45)	.29
		3rd	2.52 (1.00-6.35)	.05		3rd	0.85 (0.39-1.86)	.69
		4th	1 [Reference]			4th	1.15 (0.54-2.43)	.72
Heart disease or stroke	427	1st	3.74 (1.38-10.17)	.01	430	1st	1 [Reference]	
		2nd	1.22 (0.38-3.90)	.74		2nd	0.55 (0.20-1.50)	.24
		3rd	2.06 (0.74-5.77)	.17		3rd	0.69 (0.26-1.83)	.46
		4th	1 [Reference]			4th	1.16 (0.48-2.82)	.74
LEAD	438	1st	8.18 (1.77-37.90)	.007	442	1st	1 [Reference]	
		2nd	2.92 (0.55-15.36)	.21		2nd	1.04 (0.31-3.50)	.96
		3rd	2.07 (0.37-11.52)	.41		3rd	0.75 (0.20-2.86)	.67
		4th	1 [Reference]			4th	1.28 (0.38-4.32)	.70
Hypertension	281	1st	1.12 (0.50-2.53)	.78	282	1st	1 [Reference]	
		2nd	0.61 (0.28-1.31)	.20		2nd	1.23 (0.54-2.77)	.62
		3rd	1.04 (0.55-1.96)	.91		3rd	1.46 (0.65-3.28)	.37
		4th	1 [Reference]			4th	2.95 (1.33-6.55)	.008
Mortality	588	1st	2.66 (1.42-4.98)	.002	593	1st	1 [Reference]	
		2nd	2.21 (1.17-4.18)	.015		2nd	0.59 (0.31-1.12)	.11
		3rd	1.07 (0.53-2.16)	.86		3rd	0.87 (0.48-1.58)	.65
		4th	1 [Reference]			4th	1.33 (0.76-2.32)	.32

Abbreviations: CRAE, central retinal arterial equivalent; CRVE, central retinal venular equivalent; CVD, cardiovascular disease (heart disease, stroke, or lower extremity arterial disease [LEAD]); OR, odds ratio.

[a]Numbers at risk may vary because of missing retinal vascular data.

line larger retinal venular diameter is an independent predictor of the 6-year incidence of hypertension in African Americans with type 1 DM.

Although retinal arteriolar narrowing has been consistently found in association with the prevalence of heart disease, its relationship with incident heart disease is unclear. In whites with type 1 DM who participated in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, a lower retinal arteriovenous ratio was significantly associated with the 20-year incidence of incident myocardial infarction and mortality from heart disease after accounting for systemic confounders.[25] Because CRAE and CRVE were not examined separately, it is difficult to determine whether narrower CRAE, larger CRVE, or both were the significant parameter(s). In the Pittsburgh study, which included mostly white diabetic type 1 patients, lower CRAE was significantly associated with the 18-year incidence of heart disease after adjustment of confounders, but *only* in women.[26] In a meta-analysis of 6 population-based prospective cohort studies, which included both nondiabetic and diabetic adults, narrower CRAE and larger CRVE were independently associated with the incidence of heart disease in women only.[7,10,16,19,21] This sex difference, as well as differences in presentation and outcomes for heart disease between men and women, supports the role of microvascular disease in relation to atherosclerotic heart disease.[42] In our African American patients, narrower CRAE is more consistently associated with the incidence of LEAD than with that of heart disease or stroke (Table 3). In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, generalized and focal retinal arteriolar narrowing were also significantly and independently associated with an increased 20-year incidence of lower extremity amputation, although that association was attenuated when adding retinopathy to the model, unlike what was found in the present study.[24] Thus, systemic microvascular disease may be a precursor of future risk of any CVD and more specifically of LEAD in African Americans with type 1 DM.

In the present study, wider retinal venular diameter was an independent risk for incident hypertension. In nondiabetic populations, both narrower retinal arteriolar caliber and/or narrower venular diameter have been associated with incident hypertension.[13-15,17,43] Subsequently, Liew et al[44] showed that because arteriolar and venular calibers are significantly correlated, wider and not narrower retinal venular caliber is associated with incident hypertension when controlling for arteriolar caliber; this was further confirmed by Ikram et al.[45] Our data are also supported by data from the Multiethnic Study of Atherosclerosis[43] in which both narrower arteriolar and wider venular diameter were associated with an increased risk of developing hypertension. Wider CRVE as a predictor of hypertension is consistent with the venular changes seen in the microcirculation in the prehypertensive stage and may represent a response of the retinal vasculature to chronic hypoxia.[46] Wider retinal venular diameters have also been reported in association with various traditional CVD risk factors, including elevated levels of systemic inflammatory biomarkers, endothelial dysfunction, markers of the metabolic syndrome, and smoking.[21] The mechanisms that may be involved are unclear and may include genetic as well as environmental factors.[21,47] In persons with DM, the reduction in nitric oxide–mediated vasodilatory response of the retinal vessel

Table 3. Relationship of CRAE and CRVE to 6-Year Incidence of Cardiovascular Disease and Mortality in Type 1 Diabetic African Americans[a]

Baseline Characteristic	Any CVD (n = 460)		Heart Disease or Stroke (n = 460)		LEAD (n = 437)		Hypertension[b] (n = 281)		Mortality (n = 588)	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Model 1										
Age, per decade	1.80 (1.17-2.78)	.008	1.61 (0.96-2.71)	.07	2.04 (0.99-4.20)	.05	1.30 (0.95-1.80)	.11	2.24 (1.52-3.31)	<.001
Sex, male vs female	0.79 (0.41-1.49)	.47			2.43 (0.92-6.37)	.07	1.22 (0.68-2.20)	.51	1.19 (0.73-1.94)	.49
BMI, per kg/m^2			2.14 (0.94-4.88)	.07			0.88 (0.49-1.57)	.66		
SES[c]									1.84 (1.11-3.07)	.02
Proteinuria		.001		.002		.13		.15		<.001
Micro vs none	2.55 (1.19-5.45)		2.72 (1.06-6.98)		3.08 (0.94-10.17)		1.52 (0.76-3.04)		3.33 (1.69-6.56)	
Overt vs none	4.18 (1.92-9.09)		5.19 (2.09-12.88)		3.11 (0.89-10.83)		2.43 (0.90-6.54)		7.80 (4.10-14.83)	
CRAE, µm, per quartile decrease	1.54 (1.09-2.17)	.02	1.22 (0.81-1.83)	.33	1.92 (1.11-3.32)	.02	1.13 (0.82-1.56)	.46	1.12 (0.85-1.47)	.42
CRVE, µm, per quartile increase	1.31 (0.95-1.82)	.10	1.16 (0.79-1.71)	.46	1.55 (0.95-2.54)	.08	1.54 (1.12-2.11)	.008	1.22 (0.95-1.57)	.13
Model 2										
Age, per decade	1.89 (1.23-2.91)	.004	1.73 (1.04-2.88)	.04	2.22 (1.07-4.58)	.03	1.20 (0.86-1.66)	.29	2.70 (1.86-3.93)	<.001
Sex, male vs female	0.82 (0.45-1.52)	.54			2.65 (1.02-6.85)	.05	1.08 (0.60-1.93)	.81	1.39 (0.87-2.20)	.17
BMI, per kg/m^2			1.67 (0.77-3.66)	.20			0.80 (0.45-1.44)	.46		
SES[c]									1.43 (0.88-2.30)	.15
Mean arterial BP, per mm Hg	1.34 (1.07-1.68)	.01	1.38 (1.05-1.83)	.02	1.15 (0.82-1.62)	.42	1.59 (1.12-2.26)	.009	1.21 (1.04-1.42)	.01
CRAE, µm, per quartile decrease	1.56 (1.11-2.19)	.01	1.24 (0.84-1.83)	.28	2.06 (1.18-3.58)	.01	1.14 (0.83-1.57)	.42	1.33 (1.03-1.73)	.03
CRVE, µm, per quartile increase	1.35 (0.98-1.86)	.07	1.19 (0.82-1.73)	.37	1.64 (1.00-2.68)	.05	1.51 (1.10-2.07)	.01	1.37 (1.07-1.75)	.01
Model 3										
Age, per decade	1.84 (1.17-2.89)	.008	1.56 (0.91-2.67)	.11	1.83 (0.84-4.00)	.13	1.11 (0.78-1.57)	.58	2.25 (1.51-3.36)	<.001
Sex, male vs female	0.84 (0.45-1.57)	.59			2.77 (1.05-7.30)	.04	1.22 (0.67-2.23)	.52	1.50 (0.94-2.39)	.09
BMI, per kg/m^2			2.15 (0.97-4.78)	.06			1.14 (0.62-2.09)	.68		
SES[c]									1.59 (0.98-2.59)	.06
Retinopathy severity		.05		.05		.18		.002		.001
Mild vs none	0.98 (0.44-2.21)		1.31 (0.50-3.46)		1.11 (0.27-4.56)		1.05 (0.54-2.02)		1.79 (0.89-3.60)	
Moderate vs none	2.69 (1.10-6.61)		3.99 (1.34-11.83)		2.59 (0.59-11.42)		4.04 (1.47-11.13)		2.50 (1.12-5.59)	
Severe vs none	2.00 (0.73-5.46)		2.67 (0.76-9.47)		4.02 (0.88-18.40)		8.38 (1.91-36.66)		4.77 (2.16-10.51)	
CRAE, µm, per quartile decrease	1.60 (1.14-2.26)	.007	1.28 (0.86-1.90)	.23	1.94 (1.10-3.42)	.02	1.08 (0.77-1.49)	.67	1.25 (0.96-1.64)	.10
CRVE, µm, per quartile increase	1.28 (0.92-1.77)	.14	1.11 (0.75-1.63)	.61	1.46 (0.88-2.42)	.15	1.41 (1.03-1.94)	.04	1.26 (0.98-1.62)	.07

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CRAE, central retinal arterial equivalent; CRVE, central retinal venular equivalent; CVD, cardiovascular disease (heart disease, stroke, or lower extremity arterial disease [LEAD]); OR, odds ratio; SES, socioeconomic status.

[a] Numbers at risk may vary because of missing data.

[b] Either systolic pressure of at least 140 mm Hg, diastolic pressure of at least 90 mm Hg, or receipt of antihypertensive medications.

[c] Comparing low with middle to high.

diameters to flicker light stimulation suggests that endothelial dysfunction may be one of the mechanisms.[48] The clinical implication of our finding is that, in addition to retinal arteries, changes in the diameter of retinal veins may be used as an indicator of response to medical treatment of hypertension.

In the present study, there were inconsistent results regarding baseline retinal vessel diameter and mortality. Although narrower CRAE was independently associated with 6-year mortality when adjusting for baseline mean arterial blood pressure, this association was no longer significant when either proteinuria or retinopathy severity was added to the model, suggesting that these 2 factors not only are better predictors of mortality in this population[49] but also may represent a common mechanism. In whites with type 1 DM, narrower arteriovenous ratio was significantly associated with incidence of death from heart disease.[25] However, in that study, the association between retinal vessel diameter and either CVD or mortality was also confounded by either the retinopathy severity or the presence of nephropathy.[25]

Strengths of the study include the prospective design with high rates of follow-up for a large cohort of well-characterized African American patients with type 1 DM, use of standardized protocols to document potential confounding variables, and measurements of the retinal vascular diameters using a previously validated computerized program.

Several limitations of the study may be noted. There were relatively few incident cases of either heart disease or stroke or LEAD. There is also some possibility of error in patients' hypertension status because patients were seen only once at the 2 time points, although standard protocols were used, medical records were reviewed to confirm either CVD or hypertension, and vital status was ascertained annually from the Social Security Death Index. Measurement of the retinal vessel diameters from color retinal photographs may underestimate the true vascular width because only the red blood cell column is being measured; conversely, increased retinal pigmentation, as present in African Americans, may lead to an

overestimation of the retinal diameter sizes because of reduced contrast between background and retinal vessels.[50] We did not take into account variability of the retinal vessel caliber due to cardiac cycle pulsatility.[51] Finally, we cannot exclude the possibility that selective mortality in this cohort may have obscured the relationship between CRAE and the incidence of all end points.

In summary, results of the present study indicate that, in African Americans with type 1 DM, narrower CRAE is an independent predictor of the 6-year incidence of any CVD and LEAD, and larger CRVE is an independent predictor of the incidence of hypertension. Whether such measurements may be used in the future to monitor treatments for hypertension or DM and its complications that specifically target the microvasculature remains to be determined.

Submitted for Publication: August 2, 2011; final revision received November 16, 2011; accepted November 28, 2011.
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Author Contributions: As principal investigator, Dr Roy had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. All authors had full access to all the data in the study, have read, and have approved the submission of the manuscript.
Financial Disclosure: None reported.
Funding/Support: This research was supported by grants RO1 EY 09860 and R21 EY 18114-1 from the National Eye Institute, Bethesda, Maryland; and a Lew Wasserman Merit Award and an unrestricted grant from Research to Prevent Blindness Inc, New York, New York.

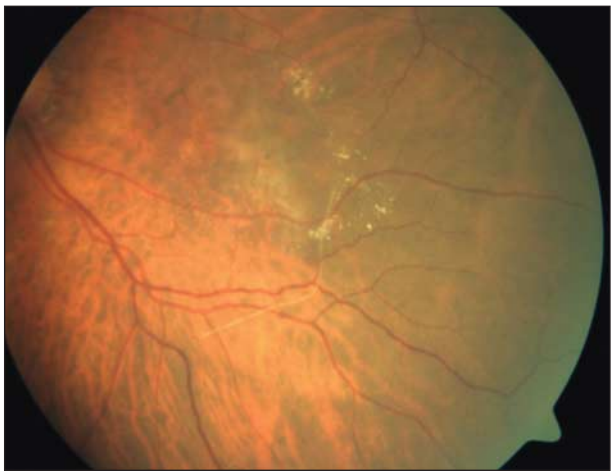
REFERENCES

1. Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. *Am J Med Sci*. 1974;268(6):336-345.
2. Wagener HP, Clay GE, Gipner JF. Classification of retinal lesions in presence of vascular hypertension: report submitted to the American Ophthalmological Society by the Committee on Classification of Hypertensive Disease of the Retina. *Trans Am Ophthalmol Soc*. 1947;45:57-73.
3. Leishman R. The eye in general vascular disease: hypertension and arteriosclerosis. *Br J Ophthalmol*. 1957;41(11):641-701.
4. Parr JC, Spears GF. General caliber of the retinal arteries expressed as the equivalent width of the central retinal artery. *Am J Ophthalmol*. 1974;77(4):472-477.
5. Parr JC, Spears GF. Mathematic relationships between the width of a retinal artery and the widths of its branches. *Am J Ophthalmol*. 1974;77(4):478-483.
6. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology*. 1999;106(12):2269-2280.
7. Wong TY, Klein R, Klein BE, Tielsch JM, Hubbard L, Nieto FJ. Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. *Surv Ophthalmol*. 2001;46(1):59-80.
8. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. *Lancet*. 2001; 358(9288):1134-1140.
9. Ikram MK, de Jong FJ, Bos MJ, et al. Retinal vessel diameters and risk of stroke: the Rotterdam Study. *Neurology*. 2006;66(9):1339-1343.
10. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women: the Atherosclerosis Risk in Communities Study. *JAMA*. 2002;287(9):1153-1159.
11. Wong TY, Klein R, Nieto FJ, et al. Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. *Ophthalmology*. 2003;110(5):933-940.
12. Wong TY, Knudtson MD, Klein R, Klein BE, Hubbard LD. A prospective cohort study of retinal arteriolar narrowing and mortality. *Am J Epidemiol*. 2004;159 (9):819-825.
13. Smith W, Wang JJ, Wong TY, et al. Retinal arteriolar narrowing is associated with 5-year incident severe hypertension: the Blue Mountains Eye Study. *Hypertension*. 2004;44(4):442-447.
14. Wong TY, Shankar A, Klein R, Klein BE, Hubbard LD. Prospective cohort study of retinal vessel diameters and risk of hypertension. *BMJ*. 2004;329(7457): 79-82.
15. Wong TY, Klein R, Sharrett AR, et al; Atherosclerosis Risk in Communities Study. Retinal arteriolar diameter and risk for hypertension. *Ann Intern Med*. 2004; 140(4):248-255.
16. Wong TY, Kamineni A, Klein R, et al. Quantitative retinal venular caliber and risk of cardiovascular disease in older persons: the Cardiovascular Health Study. *Arch Intern Med*. 2006;166(21):2388-2394.
17. Ikram MK, Witteman JC, Vingerling JR, Breteler MM, Hofman A, de Jong PT. Retinal vessel diameters and risk of hypertension: the Rotterdam Study. *Hypertension*. 2006;47(2):189-194.
18. Wang JJ, Liew G, Klein R, et al. Retinal vessel diameter and cardiovascular mortality: pooled data analysis from two older populations. *Eur Heart J*. 2007;28 (16):1984-1992.
19. McGeechan K, Liew G, Macaskill P, et al. Meta-analysis: retinal vessel caliber and risk for coronary heart disease. *Ann Intern Med*. 2009;151(6):404-413.
20. McGeechan K, Liew G, Macaskill P, et al. Prediction of incident stroke events based on retinal vessel caliber: a systematic review and individual-participant meta-analysis. *Am J Epidemiol*. 2009;170(11):1323-1332.
21. Sun C, Wang JJ, Mackey DA, Wong TY. Retinal vascular caliber: systemic, environmental, and genetic associations. *Surv Ophthalmol*. 2009;54(1):74-95.
22. Wieberdink RG, Ikram MK, Koudstaal PJ, Hofman A, Vingerling JR, Breteler MM. Retinal vascular calibers and the risk of intracerebral hemorrhage and cerebral infarction: the Rotterdam Study. *Stroke*. 2010;41(12):2757-2761.
23. Klein R, Klein BE, Moss SE, Wong TY. Retinal vessel caliber and microvascular and macrovascular disease in type 2 diabetes, XXI: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Ophthalmology*. 2007;114(10):1884-1892.
24. Moss SE, Klein R, Klein BE, Wong TY. Retinal vascular changes and 20-year incidence of lower extremity amputations in a cohort with diabetes. *Arch Intern Med*. 2003;163(20):2505-2510.
25. Klein BE, Klein R, McBride PE, et al. Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Arch Intern Med*. 2004;164(17):1917-1924.
26. Miller RG, Prince CT, Klein R, Orchard TJ. Retinal vessel diameter and the incidence of coronary artery disease in type 1 diabetes. *Am J Ophthalmol*. 2009; 147(4):653-660.
27. Roy MS. Diabetic retinopathy in African Americans with type 1 diabetes: the New Jersey 725, I: methodology, population, frequency of retinopathy, and visual impairment. *Arch Ophthalmol*. 2000;118(1):97-104.
28. Roy MS. Diabetic retinopathy in African Americans with type 1 diabetes: the New Jersey 725, II: risk factors. *Arch Ophthalmol*. 2000;118(1):105-115.
29. Roy MS, Affouf M. Six-year progression of retinopathy and associated risk factors in African American patients with type 1 diabetes mellitus: the New Jersey 725. *Arch Ophthalmol*. 2006;124(9):1297-1306.
30. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20(7):1183-1197.
31. Winter WE, Maclaren NK, Riley WJ, Clarke DW, Kappy MS, Spillar RP. Maturity-onset diabetes of youth in black Americans. *N Engl J Med*. 1987;316(6):285-291.
32. The Diabetic Retinopathy Study Research Group. Diabetic Retinopathy Study report number 7: a modification of the Airlie House classification of diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 1981;21(1, pt 2):1-226.
33. Canner PL, Borhani NO, Oberman A, et al. The Hypertension Prevention Trial: assessment of the quality of blood pressure measurements. *Am J Epidemiol*. 1991;134(4):379-392.
34. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification: ETDRS report number 10. *Ophthalmology*. 1991;98(5)(suppl):786-806.
35. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS report number 12. *Ophthalmology*. 1991;98(5)(suppl):823-833.
36. Knudtson MD, Lee KE, Hubbard LD, Wong TY, Klein R, Klein BE. Revised for-

mulas for summarizing retinal vessel diameters. *Curr Eye Res*. 2003;27(3):143-149.
37. Atherosclerosis Risk in Communities (ARIC) Study Research Group. *ARIC Retinal Photography Protocol, Manual 14A*. Chapel Hill: ARIC Coordinating Center, Dept of Biostatistics, University of North Carolina; 1996.
38. Atherosclerosis Risk in Communities (ARIC) Study Research Group. *ARIC Retinal Reading Center Protocol, Manual 14B*. Chapel Hill: ARIC Coordinating Center, Dept of Biostatistics, University of North Carolina; 1996.
39. Couper DJ, Klein R, Hubbard LD, et al. Reliability of retinal photography in the assessment of retinal microvascular characteristics: the Atherosclerosis Risk in Communities Study. *Am J Ophthalmol*. 2002;133(1):78-88.
40. Goldthorpe J, Hope K. *The Social Grading of Occupations: A New Approach and Scale*. New York, NY: Oxford University Press; 1974:134-143.
41. Roy MS, Klein R, Janal MN. Retinal venular diameter as an early indicator of progression to proliferative diabetic retinopathy with and without high-risk characteristics in African Americans with type 1 diabetes mellitus. *Arch Ophthalmol*. 2011;129(1):8-15.
42. Chilian WM. Coronary microcirculation in health and disease: summary of an NHLBI workshop. *Circulation*. 1997;95(2):522-528.
43. Kawasaki R, Cheung N, Wang JJ, et al. Retinal vessel diameters and risk of hypertension: the Multiethnic Study of Atherosclerosis. *J Hypertens*. 2009;27(12):2386-2393.
44. Liew G, Wong TY, Mitchell P, Wang JJ. Are narrower or wider retinal venules associated with incident hypertension? *Hypertension*. 2006;48(2):e10, author reply e11. doi:10.1161/01.HYP.0000231652.97173.4c.
45. Ikram K, Witteman J, Vingerling J, Breteler M, Hofman A, de Jong P. Response to "are narrower or wider retinal venules associated with incident hypertension?" *Hypertension*. 2006;48(2):e11. doi:10.1161/01.HYP.0000231653.74701.6b.
46. Saldívar E, Cabrales P, Tsai AG, Intaglietta M. Microcirculatory changes during chronic adaptation to hypoxia. *Am J Physiol Heart Circ Physiol*. 2003;285(5):H2064-H2071.
47. Fahy SJ, Sun C, Zhu G, et al. The relationship between retinal arteriolar and venular calibers is genetically mediated, and each is associated with risk of cardiovascular disease. *Invest Ophthalmol Vis Sci*. 2011;52(2):975-981.
48. Nguyen TT, Kawasaki R, Kreis AJ, et al. Correlation of light-flicker-induced retinal vasodilation and retinal vascular caliber measurements in diabetes. *Invest Ophthalmol Vis Sci*. 2009;50(12):5609-5613.
49. Roy M, Rendas-Baum R, Skurnick J. Mortality in African Americans with type 1 diabetes: the New Jersey 725. *Diabetes Med*. 2006;23(6):698-706.
50. Rochtchina E, Wang JJ, Taylor B, Wong TY, Mitchell P. Ethnic variability in retinal vessel caliber: a potential source of measurement error from ocular pigmentation?—the Sydney Childhood Eye Study. *Invest Ophthalmol Vis Sci*. 2008;49(4):1362-1366.
51. Knudtson MD, Klein BE, Klein R, et al. Variation associated with measurement of retinal vessel diameters at different points in the pulse cycle. *Br J Ophthalmol*. 2004;88(1):57-61.

Archives Web Quiz Winner

Congratulations to the winner of our December quiz, William D. Sullins III, OD, Woods Memorial Hospital, Athens, Tennessee. The correct answer to our December challenge was intravitreal inoculation of cotton. For a complete discussion of this case, see the Ophthalmic Images section in the January *Archives* (Cassar J, Smith T, Kwan T. Intravitreal inoculation of cotton after bevacizumab [Avastin] injection. *Arch Ophthalmol*. 2012;130[1]:126).



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