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Retinal Microvascular Signs and Incidence of Abdominal Aortic Aneurysm: the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Purpose: To test the hypothesis that retinal microvascular abnormalities known to predict other cardiovascular diseases are associated prospectively with risk of abdominal aortic aneurysm. The rationale is that aortic aneurysm involves small vessel pathology that parallels, to some degree, retinal vasculopathy.

Methods: In 1993–1995, the Atherosclerosis Risk in Communities (ARIC) Study, a prospective population-based cohort, took retinal photographs of a randomly selected eye of 10,911 ARIC participants (initial mean age 60 years). Staff centrally graded the photographs using central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) indices. We followed participants for incidence of abdominal aortic aneurysm (n=378 events), measured via medical record linkage from 1993 −1995 through 2011.

Results: Wider venular diameters were associated with increased incidence of abdominal aortic aneurysm, with the hazard ratio (95% CI) being 1.61 (1.20, 2.16) for the highest versus lowest quartile of CRVE. However, adjustment for other abdominal aortic aneurysm risk factors, particularly smoking, eliminated the association of CRVE with abdominal aortic aneurysm. CRAE and frank retinopathy showed no association with abdominal aortic aneurysm incidence.

Conclusion: This prospective study found that retinal vascular diameters and retinopathy are not associated with incidence of abdominal aortic aneurysm.

Keywords

Abdominal aortic aneurysm; ARIC Study; epidemiology; prospective study; retinal vasculature

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INTRODUCTION

Abdominal aortic aneurysm (AAA) is an important public health concern whose risk factors include advanced age, smoking, male sex, white race, and family history, with hypertension and hypercholesterolemia playing less important roles.[1] Diabetes is associated with reduced AAA risk.[1] The pathophysiology of AAA involves infiltration of the aortic wall by inflammatory and immune cells, proteolysis of elastin and collagen in the media and adventitia, and smooth muscle cell apoptosis with thinning of the media.[1] Additionally, arteriolosclerosis of the aortic vaso vasorum caused by hypertension and inflammation may contribute to AAA.[2]

Inflammation, hypertension, and other processes likewise promote retinal vasculopathy, including retinal arteriolosclerosis and venular dilation. These retinal microvascular signs are markers of increased risk of clinical cardiovascular events.[3] In the Atherosclerosis Risk in Communities (ARIC) Study, for example, retinal microvascular abnormalities were associated with increased risk of stroke,[4,5] congestive heart failure,[6] coronary heart disease (women only),[7] and brain microvascular disease.[8]

Given the several commonalities of vasculopathy in the retina and the aortic vaso vasorum, it is possible that retinal microvascular abnormalities also serve as an early indicator of increased AAA risk. Yet, no epidemiologic study has examined the association between retinal microvascular signs and incidence of AAA. We hypothesized that narrower arteriolar diameters, wider venular diameters, and other manifestations of retinopathy are associated with increased incidence of AAA.

METHODS

The longitudinal ARIC Study[9] recruited a population-based cohort of 15,792 persons between 45 and 64 years of age in 1987 through 1989, from Forsyth County, North Carolina; Jackson, Mississippi (African Americans only); the northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland. ARIC performed a baseline examination of participants and followed them by annual telephone contact and up to four reexaminations in 1990–1992, 1993–1995, 1996–1998, and 2011–2013. The study adhered to the guidelines of the Declaration of Helsinki, the Institutional Review Boards of each participating center (University of North Carolina, University of Minnesota, University of Mississippi, Johns Hopkins University) approved the study protocol, and all participants gave written informed consent. The present study is based on retinal photographic data from the third examination (1993–1995), which included 12,887 participants (86% of baseline).

Trained technicians performed retinal photography according to standardized procedures.[10] After 5 minutes of dark adaptation, they obtained a 45 degree-retinal photograph of 1 randomly selected eye. These photographs were digitized, and trained graders estimated the caliber of individual retinal arterioles and venules by a computer-assisted technique. These measurements yielded two indices: central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE).[3,10] Trained graders also evaluated the retinal photographs

for signs of retinopathy: microaneurysms, flame-shaped hemorrhages, blot hemorrhages, or soft exudates. The graders' retinal vascular measurements had high reproducibility.[10,11]

The ARIC study protocols have been described previously.[9] Participants at ARIC exam 3 reported smoking status and provided prescription bottles for staff to record whether they took blood pressure, cholesterol, or glucose lowering medications. Trained technicians obtained measurements of height and weight in a scrub suit. ARIC measured sitting blood pressure 3 times using a random-zero sphygmomanometer after a 5-minute rest and used the mean of the last 2 measurements for analysis. ARIC asked participants to fast overnight, and certified phlebotomists collected blood to measure plasma total and HDL cholesterol and serum glucose concentrations. We defined diabetes as a fasting glucose ⩾126 mg/dL, nonfasting glucose ⩾200 mg/dL, use of glucose lowering medication, or self-report of a physician diagnosis of diabetes.

ARIC identified incident clinical AAAs by several strategies. In the annual telephone calls with ARIC participants (or their proxy respondents), interviewers asked about any interim hospitalizations and identified deaths, and ARIC requested these records. ARIC also conducted surveillance of local hospitals to identify additional hospitalizations or deaths. In addition, ARIC linked participant identifiers with fee-for-service Medicare data from the Centers for Medicare and Medicaid Services (CMS) for 1991–2011, to find any missing hospital or outpatient events for those over 65 years. We identified clinical AAAs as those with a hospital discharge diagnosis from any source, or two Medicare outpatient claims that occurred at least one week apart, with *ICD-9-CM* codes of 441.3 (ruptured AAA), 441.4 (AAA without mention of rupture) or 441.02 (AAA dissection), or procedure codes of 38.44 (AAA resection and replacement) or 39.71 (AAA endovascular repair), or a listed cause of death coded as *ICD-9* 441.3 or 441.4 or *ICD-10* code I71.02 (AAA dissection), I71.3 (ruptured AAA), or I71.4 (AAA without mention of rupture). Although labeled "clinical AAAs" these diagnoses would include both symptomatic and asymptomatic AAAs that were medically documented. We treated thoracic, thoracoabdominal, or unspecified aortic aneurysms as not being AAA.

Of the 12,887 participants at ARIC visit 3, we excluded participants whose race was neither black nor white (n=38); who were blacks in Minneapolis and Washington County, due to small numbers (n=42); who reported prior AAA surgery or aortic angioplasty at ARIC baseline or incident AAA before visit 3 (n=60); or who had ungradable photographs or missing data for retinal vessel caliber and other retinal signs (n=1,836). This left 10,911 participants for analysis. We analyzed CRAE and CRVE using quartiles, and categorized retinopathy as (yes, no). Person-years of follow-up for AAA were computed from visit 3 to the first of: AAA occurrence, loss to follow-up, death, or else through December 2011. We used Cox proportional hazards regression to calculate hazard ratios and adjust for major AAA risk factors. Tests of interaction by sex were nonsignificant ($p>0.15$), so men and women were pooled for analyses.

RESULTS

Among the 10,911 ARIC participants with retinal vascular data and free of AAA, the mean (SD) CRAE was 193 (17) μm and CRVE was 159 (15) μm. As shown in Table 1, most AAA risk factors were associated positively with CRAE but less consistently with CRVE.

Over a mean (SD) of 15.3 (4.1) years of follow-up (maximum 18.8 years), we identified 378 incident AAA events. As shown in Table 2, in Model 1, wider venular diameters were associated with increased incidence of AAA, with the hazard ratio (95% CI) being 1.61 (1.20, 2.16) for the highest versus lowest quartile of CRVE. Adjusting for Model 2 variables, particularly smoking, eliminated the association of CRVE with AAA. CRAE showed no association with AAA incidence. Further adjustment of CRVE and CRAE for each other did not alter these conclusions.

Participants with frank retinopathy had a 23–33 percent greater risk of AAA than those free of retinopathy, but these estimates were nonsignificant, as there were few incident AAA events in those with retinopathy.

DISCUSSION

This population-based cohort study found no independent association between retinal arteriolar or venular diameters and incident AAA. A crude association observed between CRVE and AAA was confounded by major AAA risk factors, particularly smoking. The study also found no association between retinopathy and AAA. Although retinal abnormalities predict other cardiovascular events,[3–8] and small vessel pathology contributes to both retinal vasculopathy and AAA, there is no apparent link between these two diseases.

Although our study was large and carefully done, it had some limitations. Firstly, ARIC obtained the retinal data on a single eye, which would have led to an underestimate of retinopathy prevalence. Secondly, retinopathy and AAA occurrence were uncommon enough that we might have detected only sizable hazard ratios as statistically significant with our sample size. Thirdly, retinal data were missing on 14 percent of participants, but ARIC has previously reported that risk factors were similar for those with versus without retinal data. Thus, it seems unlikely that missing data affected our conclusions. Fourthly, we had only one retinal assessment; any biological variability or change over time most likely would have attenuated the reported hazard ratios. Finally, to capture AAAs during follow-up, we employed discharge diagnoses of hospitalizations reported by ARIC participants or discharges found through surveillance of local hospitals. Some AAA hospital discharges may have been overlooked, and the AAAs we captured were a mix of symptomatic AAAs and clinically recognized asymptomatic AAAs. Additional subclinical AAAs were undoubtedly missed in the absence of uniform screening. Yet, an abdominal ultrasound performed in 5,911 surviving ARIC participants in 2011–2013 found only 74 additional, clinically unrecognized AAAs.[12] In general, misclassification of AAA status during follow-up is likely to be unrelated to retinal vascular findings and therefore would have attenuated our hazard ratio estimates.

In conclusion, this prospective study found that retinal vascular diameters and retinopathy are not associated with incident AAA.

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Table 1.

Participant characteristics by venular diameters and arterial diameters: ARIC Study, 1993–1995.

	Venular diameters (CRVE), μm				Arterial diameters (CRAE), μm			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Range	127–182	182–193	193–204	204–276	81–150	150–159	159–169	169–221
Demographics & Behaviors[a]								
Age, years	60.7 ± 5.6	59.7 ± 5.7	59.3 ± 5.5	58.8 ± 5.5	60.4 ± 5.6	59.8 ± 5.6	59.5 ± 5.5	58.8 ± 5.6
Male, N (%)	1088 (39.9)	1213 (44.5)	1214 (44.3)	1311 (48.2)	1360 (49.9)	1243 (45.3)	1140 (41.9)	1083 (39.8)
Black, N (%)	304 (11.2)	486 (17.8)	653 (23.9)	876 (32.2)	487 (17.9)	596 (21.7)	599 (22.0)	637 (23.4)
Smoking status, N (%)								
Current	220 (8.1)	348 (12.8)	502 (18.4)	847 (31.2)	317 (11.7)	415 (15.2)	474 (17.5)	711 (26.2)
Former	1115 (41.0)	1188 (43.7)	1174 (42.9)	1029 (37.8)	1222 (44.9)	1137 (41.5)	1132 (41.7)	1015 (37.4)
Never	1386 (50.9)	1180 (43.5)	1058 (38.7)	843 (31.0)	1182 (43.4)	1186 (43.3)	1109 (40.9)	990 (36.5)
Physiologic Characteristics[a]								
Height, inches	167 ± 9	168 ± 9	168 ± 9	169 ± 9	169 ± 9	168 ± 9	168 ± 9	167 ± 9
Weight, lbs	173 ± 37	176 ± 37	179 ± 39	181 ± 38	180 ± 38	178 ± 38	178 ± 38	173 ± 38
Total cholesterol, mg/dL	207 ± 37	207 ± 38	207 ± 38	209 ± 38	208 ± 38	206 ± 37	209 ± 38	208 ± 38
HDL cholesterol, mg/dL	54.0 ± 18.7	52.6 ± 18.2	51.9 ± 18.0	50.1 ± 17.5	52.6 ± 18.7	52.2 ± 18.0	51.8 ± 17.9	52.0 ± 18.0
Systolic blood pressure, mm Hg	125 ± 19	124 ± 19	123 ± 18	123 ± 19	130 ± 19	125 ± 18	123 ± 18	118 ± 18
Diabetes, N (%)	337 (12.4)	347 (12.8)	350 (12.9)	518 (19.1)	354 (13.1)	388 (14.2)	414 (15.3)	396 (14.6)
Blood pressure medication, N (%)	988 (36.3)	994 (36.5)	970 (35.4)	1027 (37.7)	1135 (41.6)	1020 (37.2)	969 (35.6)	855 (31.4)
Lipid lowering medication, N (%)	273 (10.0)	288 (10.6)	253 (9.3)	232 (8.5)	259 (9.5)	267 (9.7)	266 (9.8)	254 (9.3)

ARIC, Atherosclerosis Risk in Communities; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent.

[a]Mean ± SD unless otherwise noted.

Table 2.

Associations of venular diameters, arterial diameters, and retinopathy with risk of incident abdominal aortic aneurysm (AAA): ARIC Study, 1993–2011

Venular diameters (CRVE), μm	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**
Range	127–182	182–193	193–204	204–276
AAA events (*n*)	83	92	97	106
Incidence rate[a]	1.98	2.19	2.29	2.60
Hazard ratio (95% CI)				
Model 1	(ref)	1.17 (0.87, 1.58)	1.31 (0.97, 1.75)	1.61 (1.20, 2.16)
Model 2	(ref)	1.04 (0.77, 1.40)	1.03 (0.76, 1.38)	1.02 (0.75, 1.38)
Model 3	(ref)	1.03 (0.76, 1.39)	1.04 (0.77, 1.41)	1.00 (0.74, 1.36)
Arterial diameters (CRAE), μm	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Range	81–150	150–159	159–169	169–220
AAA events (*n*)	92	104	99	83
Incidence rate[a]	2.24	2.48	2.37	1.97
Hazard ratio (95% CI)				
Model 1	0.88 (0.65, 1.18)	1.07 (0.80, 1.43)	1.12 (0.84, 1.50)	(ref)
Model 2	1.13 (0.83, 1.52)	1.30 (0.97, 1.73)	1.24 (0.93, 1.66)	(ref)
Model 3	1.07 (0.78, 1.46)	1.25 (0.93, 1.69)	1.24 (0.93, 1.67)	(ref)
Retinopathy	No	Yes		
AAA events (*n*)	353	22		
Incidence rate[a]	2.24	2.65		
Hazard ratio (95% CI)				
Model 1	(ref)	1.23 (0.80, 1.89)		
Model 2	(ref)	1.33 (0.86, 2.04)		
Model 3	(ref)	1.23 (0.79, 1.93)		

AAA, abdominal aortic aneurysm; ARIC, Atherosclerosis Risk in Communities; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; CI, confidence interval.

[a]Incidence rate per 1,000 person-years.

Model 1: Adjusted for age, sex and race/center.

Model 2: Adjusted for model 1 variables plus height, weight, and smoking status.

Model 3: Adjusted for model 2 + total cholesterol, HDL cholesterol, diabetes, systolic blood pressure, blood pressure medication and lipid lowering medication.