SCIENTIFIC REPORT

Is early age-related macular degeneration related to carotid artery stiffness? The Atherosclerosis Risk in Communities Study

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Background/Purpose: Atherosclerosis and vascular stiffness have been implicated in the pathogenesis of age-related macular degeneration (AMD). The association of carotid artery stiffness, a measure of arterial elasticity reflecting early atherosclerosis, with early AMD, was examined in this study.
Methods: A population-based, cross-sectional study of 9954 middle-aged people (age range 51–72 years). The presence of AMD signs was determined from fundus photographs according to the Wisconsin grading protocol. Carotid arterial stiffness was measured from high-resolution ultrasonic echo tracking of the left common carotid artery, and was defined as an adjusted arterial diameter change (AADCμ). A smaller AADC reflects greater carotid artery stiffness. The associations of pulse pressure and carotid artery intima–media thickness (IMT) with early AMD signs were also analysed.
Results: In the study population, 454 (4.6%) had early AMD. The mean (SD) AADC was 403 (127) μ. After adjusting for age, sex, race/centre, education, cigarette smoking, fasting glucose, lipid profile and inflammatory markers, a smaller AADC was found to be not associated with early AMD (odds ratio 0.94; 95% confidence interval, 0.71 to 1.25) or its component lesions. Other measures of arterial stiffness (pulse pressure) and atherosclerosis (carotid IMT) were also not associated with early AMD.
Conclusions: Carotid artery stiffness was not associated with signs of early AMD in this middle-aged population. These data provide no evidence of a link between age-related elastoid changes and early atherosclerotic processes in the carotid arteries and early AMD.

Age-related macular degeneration (AMD) is a leading cause of blindness,[1] but its pathogenesis remains poorly understood. Understanding the risk factors for the development of early signs of AMD may facilitate new preventive and treatment strategies.

Atherosclerosis has long been hypothesised as a possible risk factor for development of AMD, principally via processes involving lipid deposition and its effects on the choroidal vasculature.[2–5] Data from some,[6–8] but not all,[9 10] epidemiological studies support this hypothesis. The Beaver Dam Eye Study, for example, has reported an association between higher pulse pressure, an indirect measure of arterial stiffness, and the 10-year incidence of late AMD (risk ratio 1.34; 95% confidence interval (CI), 1.14 to 1.60, per 10 mm Hg increase in pulse pressure).[8 11] Carotid atherosclerotic markers (eg, carotid plaque) have also been linked with AMD in the Rotterdam Study (odds ratio (OR) 1.49; 95% CI, 1.03–2.17, comparing the presence *v* absence of carotid plaque).[7 8] However, not all studies have found consistent associations of atherosclerosis with AMD.[9 10]

Carotid artery stiffness (CAS) is a direct measure of large artery elasticity. Increasing carotid stiffness reflects early atherosclerotic processes, is strongly associated with hypertension and cigarette smoking, and predicts clinical cardiovascular events.[12] We previously reported in the Atherosclerosis Risk in Communities (ARIC) study that CAS is associated with generalised retinal arteriolar narrowing, a sign of chronic hypertension.[13] In the current study, we examined the relationship of CAS, pulse pressure and carotid intima–media thickness (IMT) with early AMD.

METHODS

Study population

The ARIC study is a population-based study of 15 792 people aged 45–64 years residing in four US communities.[14] Population samples were selected from four US communities: Forsyth County, North Carolina; Jackson, Mississippi (only black patients); the suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Initial participation rates at baseline were 46% in Jackson and approximately 65% in the other three communities. Of these, 14 346 returned for a second examination in 1990–92 when CAS was measured,[13] and 12 887 returned for a third in 1993–5 when retinal photography was performed.[15]

Of the 12 887 participants who returned for the third examination, we excluded 2933 who had no CAS measurement, who had ungradable retinal photographs, whose ethnicity was neither white nor African–American (owing to small numbers in other racial groups), and 12 people who had late AMD, leaving 9954 for the current study. Table 1 shows the characteristics of the excluded (2933) and included (9954) participants, stratified by early AMD status and by quartile extremes of CAS.

Retinal photography and AMD grading

The assessment of AMD has been reported previously.[16] In brief, a 45° non-mydriatic retinal photograph centred in the region of the optic disc and the macula of a randomly selected eye was taken after 5 min of dark adaptation. Trained graders, blinded to the subject's identity, evaluated the photographs for AMD using the Wisconsin grading system.[16] Early AMD was defined as the presence of either soft drusen alone, retinal pigment epithelium depigmentation alone, or a combination of soft drusen with increased retinal pigment and/or retinal pigment epithelium depigmentation in the absence of late AMD.[16]

Measurement of carotid arterial stiffness

The procedures for measuring CAS were based on the functional data from the common carotid arterial diameter, and have been described elsewhere.[17 18] The arterial diameter

Abbreviations: AADC, adjusted arterial diameter change; AMD, age-related macular degeneration; ARIC, Atherosclerosis Risk in Communities study; CAS, carotid artery stiffness; IMT, intima–media thickness

Table 1 Participant characteristics, by early age-related macular degeneration and carotid artery stiffness

	Excluded participants	Early AMD			CAS, AADC		
	Without CAS data (n = 2933)	Yes* (n = 454)	No* (n = 9500)	p†	Q1, <314 μm (n = 2487)	Q4, ⩾477 μm (n = 2488)	p†
Men, %	44.8	49.1	43.9	0.03	44.2	48.5	<0.001
African-Americans, %	27.8	14.5	21.3	0.001	21.4	21.7	0.68
High-school graduates, %	81.8	81.5	81.8	0.86	79.5	84.0	<0.001
Cigarette smokers, current, %	22.2	15.9	17.1	0.51	13.6	23.3	<0.001
Alcohol users, current, %	48.9	54.1	53.4	0.78	50.5	57.4	<0.001
Participants with hypertension, %	44.8	37.4	38.2	0.75	41.3	35.3	<0.001
Patients with diabetes, %	17	13.9	12.9	0.53	14.6	11.9	0.003
Mean (SD)							
Age, years	57 (5.9)	61.6 (5.6)	59.7 (5.7)	<0.001	61 (5.5)	58.7 (5.6)	<0.001
Body mass index, kg/m^2	27.6 (5.3)	27.7 (4.6)	28 (5.1)	0.24	28.3 (5.1)	27.6 (4.9)	<0.001
Fasting glucose, mg/dl	120.6 (55.4)	108.1 (35.9)	109 (39.5)	0.65	111.1 (44)	107.5 (37.2)	0.001
Total cholesterol, mg/dl	208.1 (38.9)	206 (37.8)	207.5 (37.3)	0.4	210 (37.8)	204.7 (36.2)	<0.001
Serum triglyceride, mg/dl	139.1 (124.2)	137.2 (82.2)	141 (90.3)	0.39	145.8 (81)	134 (93.7)	<0.001
Systolic BP, mm Hg	125.2 (21.1)	123.7 (17.6)	123.7 (18.6)	0.97	124 (18.5)	124.2 (18.9)	0.72
Diastolic BP, mm Hg	73.1 (11.6)	70.5 (9.7)	71.8 (10.3)	0.41	73.4 (10.4)	70.3 (10.1)	<0.001
WBC count, 10^9 cells/l	6.2 (1.9)	6.0 (2.3)	6 (1.8)	0.76	5.9 (1.7)	6.2 (2.1)	<0.001
Fibrinogen level, mg/dl	308.1 (67.2)	297 (66)	296.5 (60.6)	0.67	299 (61.4)	297 (63.9)	0.19

AADC, adjusted arterial diameter change; AMD, age-related macular degeneration; BP, blood pressure; CAS, carotid artery stiffness; WBC, white blood cell.
*Crude means or proportions, †p value represents difference in means or proportions, adjusted for age, sex, race and field centre (except for age, men and African–Americans, which are not adjusted for age, sex and race, respectively).

data of the left common carotid artery collected during B-mode ultrasound examination were used to calculate CAS. The primary measure of stiffness was the blood pressure-adjusted arterial diameter change (AADC, μ) between the systole and diastole from the left carotid artery during cardiac cycles, treating arterial diameter change (strain) as a dependent variable, and other blood pressure-related variables (diastolic blood pressure, pulse pressure, pulse pressure squared, height and diastolic arterial diameter) as covariates for adjustment.[13 17] Smaller AADC values represent reduced arterial elasticity and therefore increased arterial stiffness. Details regarding the rationale for this adjustment—that is, how AADC compares with other conventional methods of estimating arterial stiffness—and the reproducibility of these measurements, have been presented elsewhere.[17] Intergrader and intragrader reliability coefficients ranged from 0.6 to 0.8.[18]

Measurements of other risk factors

Information on educational levels, cigarette smoking status, alcohol intake, blood pressure measurements and body mass index was obtained using standardised questionnaires and examinations.[19] Pulse pressure was defined as the difference in measurement between systolic and diastolic blood pressure. Blood collection provided data on the serum lipid profile, fasting glucose, white blood cell (WBC) count and plasma fibrinogen levels. The carotid artery IMT was measured using high-resolution B-mode ultrasound scanning as described previously.[20]

Statistical analysis

AADC was analysed in quartiles. Participant characteristics were compared by early AMD status (present *v* absent) and AADC (lowest *v* highest quartile). Logistic regression was used to determine the odds ratio and 95% CI for early AMD lesions by AADC quartiles, adjusting initially for age, sex, race and field centre (model 1), and then for education, smoking, fasting glucose, total cholesterol, triglyceride level, WBC count and fibrinogen levels (model 2). Additional adjustment for body mass index was performed for assessing the association of pulse pressure (model 3) and for systolic blood pressure for assessing the association with carotid artery IMT (model 4). Stratified analyses were performed to assess potential effect modification by sex, race, hypertension, smoking status and carotid artery IMT. Analyses were performed using SPSS V.12.0.1.

RESULTS

Baseline characteristics of the study population are listed in table 1. There were 454 (4.6%) participants who had early AMD. These participants were generally older, more likely to be men, but less likely to be African-Americans. The mean (SD) AADC was 403 (127) μ in the entire population. Compared with participants with the highest AADC quartile (least CAS), individuals with the lowest AADC quartile (greatest CAS) had a higher prevalence of cardiovascular risk factors.

Table 2 shows that the prevalence of early AMD was similar among participants with the lowest AADC quartile (4.9%) and those with the highest (4.4%). In logistic regression models, AADC was not associated with early AMD or its component lesions after adjustment for age, sex, race, and centre (model 1) or other factors (model 2). Similarly, pulse pressure and carotid artery IMT were not associated with early AMD. In a supplementary analysis excluding cigarette smokers, results were largely similar (data not shown). Stratification by sex, race, smoking status, hypertension and carotid IMT did not show any significant interactions (table 3).

DISCUSSION

Our study shows that CAS, a measure of vascular elasticity and early atherosclerosis, was not associated with soft drusen or other signs of early AMD in this middle-aged cohort. Early AMD signs were also not associated with the two other measures of atherosclerosis (pulse pressure and carotid artery IMT). Whether CAS and carotid IMT are associated with late AMD cannot be determined from our study, as we had insufficient late AMD cases in our cohort.

Atherosclerosis has long been hypothesised as a key pathogenic factor for AMD.[7 8] Several investigators have suggested that increased blood pressure and atherosclerosis, by virtue of their effects on the choroidal circulation and lipid deposition in Bruch's membrane, may be related to the pathogenesis of AMD.[2–5] Prospective data from the Beaver Dam Eye Study supported this hypothesis and showed that higher pulse pressure was significantly associated with an increased risk of exudative AMD but not geographical

Table 2 Relationship of carotid artery stiffness, pulse pressure and intima–media thickness with early age-related macular degeneration

	Early AMD				Soft drusen			Any pigmentary abnormality		
	n	%	OR (95% CI)*	OR (95% CI)	%	OR (95% CI)*	OR (95% CI)†	%	OR (95% CI)*	OR (95% CI)†
Quartiles of AADC, (μ)										
1st, <314	2487	4.9	0.93 (0.7 to 1.24)	0.84 (0.62 to 1.13)	4.3	0.98 (0.72 to 1.33)	0.89 (0.64 to 1.23)	2.6	1.07 (0.73 to 1.58)	1.04 (0.69 to 1.57)
2nd, 314–390	2495	4.2	0.86 (0.65 to 1.14)	0.78 (0.58 to 1.06)	3.6	0.87 (0.64 to 1.19)	0.79 (0.57 to 1.1)	2.0	0.88 (0.59 to 1.31)	0.87 (0.57 to 1.31)
3rd, 390–477	2484	4.7	1.01 (0.77 to 1.33)	0.94 (0.71 to 1.25)	4.0	1.02 (0.76 to 1.37)	0.95 (0.69 to 1.29)	2.1	0.89 (0.61 to 1.31)	0.83 (0.55 to 1.26)
4th, ⩾477	2488	4.4	1	1†	3.7	1†	1†	2.3	1†	1†
Quartiles of pulse pressure, (mm Hg)										
1st, <41	2504	3.6	1	1‡	3.2	1	1‡	2	1	1‡
2nd,41–50	2736	5.0	1.26 (0.96 to 1.66)	1.32 (1 to 1.75)	4.2	1.19 (0.89 to 1.61)	1.23 (0.91 to 1.66)	2.3	1.09 (0.75 to 1.60)	1.17 (0.8 to 1.72)
3rd, 50–60	2342	4.4	0.98 (0.72 to 1.32)	1.01 (0.75 to 1.37)	3.8	0.98 (0.71 to 1.34)	0.99 (0.72 to 1.37)	2.0	0.89 (0.59 to 1.34)	0.94 (0.61 to 1.44)
4th, ⩾60	2369	5.2	1.05 (0.78 to 1.42)	1.11 (0.81 to 1.51)	4.3	0.97 (0.71 to 1.35)	0.99 (0.71 to 1.38)	2.6	1.1 (0.73 to 1.65)	1.21 (0.8 to 1.85)
Quartiles of carotid IMT, (mm)										
1st, <0.61	2436	4.1	1	1§	3.6	1.00	1.00§	2.0	1.00	1.00§
2nd,0.61–0.70	2433	4.4	0.99 (0.75 to 1.31)	1 (0.75 to 1.33)	3.9	1 (0.74 to 1.36)	1.01 (0.75 to 1.37)	1.9	0.9 (0.6 to 1.35)	0.9 (0.6 to 1.36)
3rd, 0.70–0.81	2434	4.3	0.88 (0.66 to 1.18)	0.9 (0.67 to 1.20)	3.6	0.85 (0.62 to 1.16)	0.86 (0.63 to 1.18)	2.4	1.04 (0.7 to 1.55)	1.06 (0.71 to 1.58)
4th, ⩾0.81	2431	5.5	1.03 (0.77 to 1.36)	1.05 (0.79 to 1.41)	4.4	0.94 (0.69 to 1.29)	0.96 (0.7 to 1.32)	2.7	1.05 (0.7 to 1.57)	1.09 (0.72 to 1.64)

AADC, adjusted arterial diameter change; AMD age-related macular degeneration.
*Model 1: Adjusted for age, sex, race/centre; †model 2: model 1 with additional adjustment for education, smoking, fasting glucose, total cholesterol, triglyceride level, white cell count and fibrinogen level; ‡model 3: model 2 with body mass index; §model 4: model 3 with systolic blood pressure

atrophy.[11] Increased pulse pressure reflects age-related elastoid tissue and collagen degeneration seen in the Bruch's membrane,[11] but is a crude indicator of arterial elasticity. The Rotterdam Eye Study reported associations between late AMD and carotid artery atherosclerosis (eg, carotid plaque, increased carotid wall thickness) in both cross-sectional[7] and longitudinal data analyses.[8] In our current study, CAS, a more specific and direct measure of arterial elasticity, was not found to be associated with early AMD signs. We also found no association of pulse pressure and carotid IMT with early AMD signs. Our finding is consistent with the lack of association of carotid IMT and plaque with early AMD signs in the Cardiovascular Health Study.[9] Thus, these data provide little evidence to support an association between measures of atherosclerosis and early AMD.

The strengths of our study include a large and representative population-based sample, quantitative and blinded evaluation of CAS and AMD, and standardised ascertainment of blood pressure and other risk factors. However, the limitations also merit consideration. Firstly, the method of AMD assessment in the ARIC study might result in misclassification, because of the use of a single 45° non-stereoscopic fundus photograph taken through non-pharmacologically dilated pupils in only one eye. The lack of association found in this study could be due to

Table 3 Relationship of carotid artery stiffness (per standard deviation [12 7μ] decrease in adjusted arterial diameter change) and early age-related macular degeneration, stratified by sex, race, hypertension and smoking status

	OR (95% CI)*		
	Early AMD	Soft drusen	Any pigmentary abnormality
All	0.94 (0.85 to 1.04)	0.98 (0.87 to 1.09)	0.92 (0.80 to 1.06)
Sex			
Female	1.09 (0.93 to 1.27)	1.15 (0.97 to 1.36)	0.85 (0.68 to 1.06)
Male	0.84 (0.73 to 0.97)	0.84 (0.71 to 0.98)	0.97 (0.80 to 1.18)
Race			
African-American	0.97 (0.73 to 1.28)	0.96 (0.72 to 1.28)	1.09 (0.62 to 1.91)
White	0.95 (0.84 to 1.06)	0.98 (0.87 to 1.12)	0.91 (0.78 to 1.05)
Hypertension			
Absent	0.96 (0.84 to 1.10)	1.00 (0.86 to 1.16)	0.95 (0.79 to 1.14)
Present	0.93 (0.79 to 1.11)	0.95 (0.79 to 1.14)	0.90 (0.71 to 1.15)
Smoking			
Non-smoker	0.96 (0.85 to 1.08)	0.98 (0.86 to 1.12)	0.97 (0.83to 1.15)
Current/past smoker	0.88 (0.69 to 1.12)	0.94 (0.72 to 1.22)	0.72 (0.51 to 1)
IMT			
Below median, <0.7	1.08 (0.91 to 1.27)	1.16 (0.97 to 1.39)	1.03 (0.82 to 1.30)
Above median, >=0.7	0.88 (0.77 to 1.01)	0.88 (0.76 to 1.02)	0.89 (0.74 to 1.07)

AADC, adjusted arterial diameter change; AMD, age-related macular degeneration; IMT, intima–media thickness.
*OR (95% CI) of early age-related macular degeneration signs per standard deviation decrease in AADC (127 μ decrease), adjusted for age, sex (except for sex strata), race/center (except for race strata), education, cigarette smoking (except for cigarette smoking strata), fasting glucose, total cholesterol, triglyceride level, white cell count and fibrinogen level.

non-differential misclassification, which tends to bias true associations towards the null. Secondly, because this was a cross-sectional study, with AMD assessed (1993–5) soon after CAS measurement (1990–2), we were unable to determine cause (CAS) and effect (AMD). Finally, CAS is thought to be a less sensitive marker of early atherosclerosis in people with multiple cardiovascular risk factors, such as those with hypertension and diabetes. In high-risk people, atherosclerosis development in the aorta may occur earlier than in the carotid vessels. Thus, the lack of association of AMD with CAS may not imply a lack of association with generalised atherosclerosis.

In summary, our population-based study found no association of CAS and other atherosclerotic measures with early AMD signs in middle-aged people. Our data therefore do not support a substantial role of age-related elastoid degeneration or subclinical atherosclerotic processes in the pathogenesis of early AMD.

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