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Age-related Macular Degeneration Is Associated with Atherosclerosis

The Rotterdam Study

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Age-related macular degeneration is the most frequent cause of blindness in the elderly. A vascular basis of the disease has been suggested, but not confirmed. The association between atherosclerosis and this type of macular degeneration was investigated in 104 subjects with and 1,324 subjects without macular degeneration as part of the population-based Rotterdam Study. The study was performed between March 1990 and July 1993 in a suburb of Rotterdam, the Netherlands. Macular degeneration was assessed on fundus photographs. Carotid atherosclerosis was ultrasonographically evaluated by measurement of the common carotid intima-media thickness and by assessment of the presence of atherosclerotic plaques. Atherosclerosis in arteries of the lower extremities was studied by determination of the ankle-arm systolic blood pressure ratio. In subjects younger than age 85 years, plaques in the carotid bifurcation were associated with a 4.7 times increased prevalence odds of macular degeneration (95% confidence interval (CI) 1.8–12.2); those with plaques in the common carotid artery showed an increased prevalence odds of 2.5 (95% CI 1.4–4.5). The intima-media thickness of the common carotid arteries was not significantly different. Lower extremity arterial disease (ankle-arm index less than 0.90 on at least one side) was associated with a 2.5 times increased prevalence odds (95% CI 1.4–4.5). These findings suggest that atherosclerosis may be involved in the etiology of age-related macular degeneration. *Am J Epidemiol* 1995;142:404–9.

adult; aged; atherosclerosis; cardiovascular diseases; macular degeneration; risk factors

Age-related macular degeneration is the most frequent cause of severe irreversible visual impairment in the elderly in industrialized countries (1–4). It affects the macula lutea of the retina, resulting in a central scotoma in the visual field in the late stages. The etiology of the disease is poorly understood. A vascular basis of macular degeneration was first suggested by Verhoeff and Grossman (5) and subsequently by others (6, 7). This hypothesis was never confirmed, however. With the availability of recent noninvasive techniques to assess vessel wall characteristics, it is possible to explore whether atherosclerosis plays a role in the pathogenesis of macular degeneration in populations at large. In this study, we evaluated the association between noninvasively assessed carotid atherosclerosis, lower extremity arterial disease, and macular degeneration in the population-based Rotterdam Study.

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Abbreviation: CI, confidence interval.

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MATERIALS AND METHODS

The Rotterdam Study is a single-center, prospective follow-up study of the total population aged 55 years and over of a city district in Rotterdam, the Netherlands. The study has been approved by the Medical Ethics Committee of the Erasmus University, Rotterdam. Rationale and design of the study have been described elsewhere (8). In brief, the objective of the study is to investigate prevalence, incidence, and determinants of chronic ophthalmologic, neurologic, cardiovascular, and locomotor diseases. Ophthalmologic diseases investigated in the Rotterdam Study are age-related maculopathy and glaucoma. The ophthalmologic examination was performed between March 1990 and July 1993. During this period, 10,191 persons were invited to participate in the study. Of these, 67 had died, and 350 could not be traced, resulting in 9,774 eligible participants. Of these, 7,599 persons (78 percent) were visited at home, and 6,781 (69 percent) participated in the ophthalmologic examination at the field center. All participants gave a written informed

consent. Baseline data were obtained in an initial home visit with interview, followed by a physical examination in the field center. Participants living in homes for the elderly were examined at the home for the elderly. This study included data of all study participants with macular degeneration (104 cases) and the first 1,324 participants without macular degeneration whose ultrasonography data were evaluated.

Eyes were dilated with tropicamide 0.5 percent and phenylephrine 5 percent. After 45 minutes, on average, two 35° color transparencies (Kodak Ektachrome 64 ASA (Eastman Kodak, Rochester, New York) and Topcon TRV-50VT fundus camera (Topcon Corporation, Tokyo, Japan)) centered on the macular area were taken of each eye. Photographs were graded by three trained graders using the definitions and grids of the Wisconsin Age-related Maculopathy Grading System (9). The graders were blinded to the results of other measurements. Gradable fundus photographs of at least one eye could be obtained in 6,251 participants (82 percent).

Macular degeneration was diagnosed if either geographic atrophy or neovascular macular degeneration was present in at least one eye. Geographic atrophy was defined as any well-demarcated area of retinal pigment epithelium atrophy with visible choroidal vessels without the presence of neovascular macular degeneration. Neovascular macular degeneration was defined as the presence of serous or hemorrhagic retinal pigment epithelial detachments, periretinal hemorrhages, subretinal neovascular membranes, or subretinal fibrous scars in the absence of generalized retinal vasculopathy. The reproducibility of the grading of macular degeneration was good (10).

Ultrasonography of both carotid arteries was performed using a 7.5-MHz linear-array transducer and a duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington) (11). In accordance with the Rotterdam Study ultrasound protocol, a careful search was performed for the lumen-intima interface and media-adventitia interface of the far wall of the distal common carotid artery (12, 13). When an optimal image was obtained, it was "frozen" on the R wave of the electrocardiogram and stored on videotape. This procedure was repeated three times for both sides. Subsequently, the common carotid artery and carotid bifurcation were evaluated on-line for the presence of atherosclerotic lesions, defined as focal widening relative to adjacent segments, with protrusion into the lumen. The entire ultrasound procedure was stored on videotape. Measurement of the intima-media thickness was performed off-line, as described in detail previously (14, 15). The presence of atherosclerotic plaques in the common carotid artery and in the carotid bifurcation was assessed from stored images on videotape. Wong et al. (16) and Bots et al. (17) have described good validity and reproducibility of carotid atherosclerosis measurements. Atherosclerosis in the arteries of the lower extremities was studied by the ratio of the systolic blood pressure at the ankle to the systolic pressure at the arm (11). The systolic pressure level of the posterior tibial artery was measured at both sides using an 8-MHz continuous wave Doppler probe (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, United Kingdom) and a random-zero sphygmomanometer (Hawksley, Lansing, Sussex, England). For each leg, the ankle-arm index was calculated, and the lowest index was used in the analysis (11, 18, 19). In conformity with criteria proposed by Fowkes et al. (19) and Schroll and Munck (20), an ankle-arm index of less than 0.90 on at least one side was used to select a group with a high probability of having lower extremity arterial disease. The ankle-arm index reflects atherosclerosis of the arteries of the lower extremities and is a strong predictor of future atherosclerotic cardiovascular disease (21, 22).

During two visits to the research center, several cardiovascular risk factors were measured. Sitting blood pressure was measured on the right upper arm using a random-zero sphygmomanometer. The average of two measurements obtained on one occasion, separated by a count of pulse rate, was used in the analysis. Hypertension was defined as a systolic pressure level of 160 mmHg or more and/or a diastolic blood pressure level of 95 mmHg or more and/or current use of antihypertensive drugs.

A venipuncture was performed, applying minimal stasis, using a 21-gauge butterfly needle with tube (Surflo winged infusion set (Terumo Europe NV, Leuven, Belgium)). Serum total cholesterol was determined by means of an automated enzymatic procedure (23). High density lipoprotein cholesterol was measured similarly, after precipitation of the non-high density lipoprotein fraction with phosphotungstate-magnesium.

The prevalences of characteristics in subjects with and those without macular degeneration and differences between these groups were calculated with adjustment for age and sex by using logistic regression analysis. Continuous variables were adjusted for age and sex by using analysis of covariance. Age was entered in the model as a continuous variable. The prevalence odds ratio of macular degeneration according to presence or absence of atherosclerosis was estimated by logistic regression analysis with adjustment for age and sex, and corresponding 95 percent confidence intervals were calculated. To assess whether the magnitude of the associations was modi-

fied by age, we initially performed the analyses in four 10-year age strata with adjustment for confounding by age within these strata. Age strata, within which the directions of the associations were similar, were grouped into one age category to obtain sufficient numbers of cases. This strategy resulted in two age strata of 55–84 years and 85 years and over, respectively.

RESULTS

Macular degeneration was diagnosed in 104 participants in the Rotterdam Study (1.7 percent, 95 percent confidence interval (CI) 1.3–2.0). The prevalence of macular degeneration was 1.1 percent (68 cases/5,925 participants) in those below age 85 years (95 percent CI 0.9–1.4) and 11.0 percent (36 cases/326 participants) in subjects aged 85 years and over (95 percent CI 7.6–14.4). Age- and sex-specific data on the prevalence of macular degeneration in the Rotterdam Study are shown in table 1 (10). Data on atherosclerosis were available from 96 subjects with macular degeneration. General characteristics of the study population and of subjects with and those without macular degeneration are shown in table 2. Subjects with macular degeneration were older and more likely to be current smokers. Diastolic pressure was marginally higher in cases with macular degeneration; other cardiovascular risk factors were not significantly different.

In table 3, age- and sex-adjusted indicators of atherosclerosis according to presence or absence of macular degeneration are given. Plaques in the carotid bifurcation and common carotid artery were more frequently observed in subjects with macular degeneration than in controls. No differences were observed in intima-media thickness of the common carotid artery in the total group or within the two age categories. Subjects with macular degeneration had a lower mean ankle-arm index and presented more frequently with lower extremity arterial disease than did controls.

Table 4 shows the associations between indicators of atherosclerosis and macular degeneration. Plaques in the carotid bifurcation were associated with a 4.5 times increased prevalence odds of macular degeneration (95 percent CI 1.9–10.7). Subjects with plaques in the common carotid artery and those with lower extremity arterial disease had a 2.0 times increased prevalence odds of macular degeneration (95 percent CI 1.2–3.2). The associations were notably present in subjects younger than age 85 years. In persons aged 85 years and over, only those with plaques in the carotid bifurcation appeared to have an increased risk, but this was not statistically significant.

All observed associations were similar in men and women and for atrophic and neovascular macular degeneration. Additional analyses with adjustment for the possible confounding effect of smoking, hypertension, and cholesterol did not change the magnitude of the associations.

DISCUSSION

These findings suggest that macular degeneration may be associated with atherosclerosis in an older population. This association appears to be particularly pronounced in subjects between ages 55 and 85 years. Before we accept these findings, some methodological issues have to be discussed. First, caution is needed regarding a causal interpretation of the results. The data were obtained in a cross-sectional study, and indicators of atherosclerosis and macular degeneration were measured simultaneously. Yet, it seems highly unlikely that macular degeneration leads to atheroscle-

TABLE 1. Age- and sex-specific prevalence (number) of atrophic and neovascular age-related macular degeneration in the Rotterdam Study, 1990–1993

Sex and age (years)	Macular degeneration					
	Atrophic		Neovascular		All	
	Prevalence	No.	Prevalence	No.	Prevalence	No.
Men						
55–84	0.5	13	0.6	15	1.1	28
≥85	2.7	2	6.8	5	9.6	7
Women						
55–84	0.4	13	0.8	27	1.2	40
≥85	4.0	10	7.5	19	11.5	29
All						
55–84	0.4	26	0.7	42	1.1	68
≥85	3.6	12	7.4	24	11.0	36

TABLE 2. General characteristics of the study population,* Rotterdam Study, 1990–1993

Macular degeneration	Age (years)	(SD)†	Sex (% women)	BMI† (kg/m²)	(SD)	Cigarette smoking			Systolic blood pressure (mmHg)	(SD)	Diastolic blood pressure (mmHg)	(SD)	Hypertension‡ (%)	Total cholesterol (mmol/liter)	(SD)	HDL cholesterol (mmol/liter)	(SD)
						Current (%)	Former (%)	Never (%)									
Present (n = 96)	81.2	(0.8)	62	26.5	(0.4)	30	39	31	135.8	(2.2)	73.5	(1.2)	30	6.5	0.1	1.4	0.04
Absent (n = 1,324)	70.3	(0.2)	63	26.7	(0.1)	20	40	40	137.9	(0.5)	71.1	(0.3)	33	6.6	0.3	1.3	0.01
p value§	<0.01		0.88	0.61		0.01	0.83	0.04	0.32		0.07		0.47	0.29		0.16	

* Values are means with standard deviation in parentheses or percentages, adjusted for age and, when appropriate, for sex.
† BMI, body mass index; SD, standard deviation.
‡ Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg and/or current use of antihypertensive drugs for the indication of hypertension.
§ p value for the difference between subjects with and those without macular degeneration, adjusted for age and sex.

rosis rather than the reverse. Second, nonparticipation may have affected our findings. The response rate in the Rotterdam Study is relatively high; still, nonresponders to the study are likely to have more disease, which could have resulted in an underestimation of the prevalence of both macular degeneration and atherosclerosis. We consider it unlikely, however, that the association between the two is due to nonresponse.

Previous studies have reported contradictory results on the association between a history of cardiovascular disease and macular degeneration as an approximation of atherosclerosis, some showing positive associations (24–26) and others not (27–30). In one study, hypertension as determined 25 years before eye examination was associated with macular degeneration (31). Other studies used blood pressure levels taken at the time of eye examination and observed a positive association with increased systolic pressure (30, 32), although not uniformly (29). Increased total serum cholesterol was associated with an increased risk of neovascular macular degeneration in a one study (30), but could not be confirmed in another (29). The assessment of atherosclerosis directly with noninvasive techniques in our study may have resulted in more specific data.

It is conceivable that atherosclerosis plays a direct role in the development of macular degeneration by affecting the flow and permeability of choroidal vessels. A prolonged filling of the choroidal capillaries has been described in patients with macular degeneration (33). This phenomenon can be explained by thickening of Bruch's membrane, but also by a decreased perfusion of the choroidal capillaries (33). In histologic studies of macular degeneration, choroidal capillaries show a decreased density (34) and thickening of the intercapillary pillars (34–36), but the etiology of these changes is unclear. There is evidence that the choroidal capillaries are regulated by the retinal pigment epithelium (37, 38). Decreased functioning of the retinal pigment epithelium, which is seen in macular degeneration, could therefore cause atrophy of the choroidal capillaries. Exposure to light was suggested to be a factor in the pathogenesis of macular degeneration (39, 40) since it has a damaging effect on photoreceptors and retinal pigment epithelium (41, 42). In epidemiologic studies, however, the relation between exposure to light and macular degeneration is weak (24, 30, 43, 44).

Alternatively, there may also be a systemic basis for the capillary alterations, which in turn cause damage to the retinal pigment epithelium (34). Possibly, these capillary changes are caused by atherosclerosis. The exact mechanism remains to be clarified, however.

The association could have occurred indirectly through a risk factor involved in the pathogenesis of

TABLE 3. Indicators of atherosclerosis in subjects with and those without macular degeneration, Rotterdam Study, 1990–1993*

Macular degeneration	Carotid arteries			Lower extremities	
	Plaques in carotid bifurcation (%)	Plaques in common carotid artery (%)	Carotid intima-media thickness (mm) (mean ± SE†)	Ankle-arm index (mean ± SE)	Lower-extremity arterial disease
Present	87	30	1.01 ± 3.3	0.99 ± 0.02	26
Absent	59	18	1.03 ± 0.8	1.07 ± 0.01	15
p value‡	0.0004	0.005	0.62	15	0.006

* Adjusted for age and sex.
† SE, standard error.
‡ *p* value for the difference between groups, adjusted for age and sex.

TABLE 4. Prevalence odds ratio of macular degeneration according to indicators of atherosclerosis in two age groups, Rotterdam Study, 1990–1993

	Prevalence odds ratio of macular degeneration					
	55–84 years		≥85 years		Total	
	Prevalence OR*,†	95% CI†	Prevalence OR*	95% CI	Prevalence OR*	95% CI
Plaques in carotid arteries						
Carotid bifurcation	4.7	1.8–12.2	3.5	0.4–32.9	4.5	1.9–10.7
Common carotid artery	2.5	1.4–4.5	0.9	0.4–2.3	2.0	1.2–3.2
Lower-extremity arterial disease‡	2.5	1.4–4.5	1.1	0.5–2.6	2.0	1.2–3.2

* Adjusted for age and sex.
† OR, odds ratio; CI, confidence interval.
‡ Ankle-arm index less than 0.90 on at least one side.

both atherosclerosis and macular degeneration. However, adjustments for such possibly shared risk factors, such as smoking, hypertension, and cholesterol, did not alter the magnitude of the association. A deficiency of antioxidants could be an interesting candidate as a shared risk factor since this has been reported to be involved in both atherosclerosis (45) and macular degeneration (30).

Indicators of atherosclerosis measured in the Rotterdam Study were associated with macular degeneration only in cases below age 85 years. One explanation for the modifying effect of age could be a higher mortality among subjects with macular degeneration and atherosclerosis compared with those with atherosclerosis alone. We did not find an increased intima-media thickness of the common carotid artery in cases with macular degeneration. Carotid plaques are an indicator of more advanced atherosclerotic process compared with common carotid intima-media thickness, which represents an earlier sign of atherosclerosis. The association with macular degeneration may therefore differ.

In conclusion, these results suggest that atherosclerosis may be implicated in the etiology of macular degeneration. Further studies may reveal whether the association is based on a direct causal effect or on shared risk factors.

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