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Atherosclerosis, C-Reactive Protein, and Risk for Open-Angle Glaucoma: The Rotterdam Study

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Purpose. To test the hypotheses that atherosclerosis and elevated serum C-reactive protein (CRP) levels are risk factors for open-angle glaucoma (OAG).

Methods. In a prospective, population-based cohort study, all participants 55 years and older and at risk for incident OAG underwent, at baseline (1990–1993) and at follow-up (1997–1999), the same ophthalmic examination, including visual field testing and optic disc photography. Baseline atherosclerosis was assessed by means of echography of the carotid arteries, abdominal x-ray examination, and ankle–arm index; baseline serum CRP levels were used in the analyses. The diagnosis of OAG was based on an algorithm using optic disc measures and visual field loss. Odds ratios of OAG were computed with logistic regression analyses. Risk factors were categorized in tertiles and according to standard deviation.

Results. After a mean follow-up of 6.5 years, incident OAG was diagnosed in 87 of 3842 (2.3%) participants at risk for OAG. Carotid artery plaques, carotid intima–media thickness, aortic calcifications, ankle–arm index, and CRP levels were not significant risk factors for OAG. The odds ratio, given for the highest and lowest tertiles, for carotid plaques was 1.43 (95% confidence interval [CI], 0.68–2.99), for carotid intima–media thickness 0.86 (95% CI, 0.47–1.57), for aortic calcifications 1.02 (95% CI, 0.60–1.75), for ankle–arm index 0.69 (95% CI, 0.38–1.25), and for CRP 1.19 (95% CI, 0.68–2.07).

Conclusions. In this prospective, population-based study, neither atherosclerosis nor serum CRP level was an important risk factor for OAG. (*Invest Ophthalmol Vis Sci.* 2006;47:3772–3776) DOI:10.1167/iovs.05-1278

Open-angle glaucoma (OAG) may be characterized as a retinal ganglion cell disorder leading to loss of nerve fibers and cupping of the optic disc, so-called glaucomatous optic neuropathy (GON), resulting in glaucomatous visual field loss (GVFL).[1,2] It is a progressive, blinding disease that has substantial impact on daily functioning. Because of aging populations, the burden of OAG on societies will increase.[3] The etiology of this process is still to be elucidated. One of many theories is impaired perfusion of the optic disc, possibly caused by autonomous vessel dysfunction or atherosclerosis.

Atherosclerosis is a systemic disease affecting arteries of all sizes, including small ocular ones.[4,5] Through thickening of the intima and development of plaques, the vessel lumen decreases, eventually leading to disturbed perfusion and ischemia.[6]

Noninvasive ways to measure atherosclerosis include echography of the carotid arteries for determining the intima–media thickness or the presence of plaques,[7] abdominal x-rays for quantifying the amount of calcification in the aorta,[8] and ankle–arm index.[9]

Inflammation appears to play a role in the process of atherosclerosis. Serum C-reactive protein (CRP), a general marker of inflammation, has been associated with the occurrence of atherosclerosis,[10,11] and CRP level gives an indication of its severity.[12] Whether CRP is only a proxy or is causally related to atherosclerosis has not been fully elucidated.[10,11,13] Limited information on the role of inflammatory factors as a cause for primary OAG is available in small case-control studies.[14,15] No population-based studies have looked into atherosclerosis or serum CRP as a risk factor for OAG, which is why we investigated whether atherosclerosis or inflammation is a risk factor for OAG in a general elderly white population.

Methods

Study Population

The ophthalmic part of the Rotterdam Study, a prospective, population-based cohort study of residents 55 years and older living in a district of Rotterdam, has been described.[16,17] In short, home interviews and examinations at the examination center were conducted after the appropriate medical ethics committees had approved the study protocol and all participants had given written informed consent, according to the Declaration of Helsinki. After the baseline examination, from 1990 through 1993, a follow-up examination to study incident OAG was performed from 1997 through 1999.[18]

Measures of Atherosclerosis and CRP

Intima–media thickness was ultrasonographically determined in both common carotid arteries, as was the presence of atherosclerotic

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plaques in these and in the internal carotid arteries and bifurcations with the use of a 7.5-MHz linear-array transducer and a duplex scanner (ATL UltraMark IV; Advanced Technology Laboratories, Bethel, WA).[7] We computed a weighted plaque score (range, 0–6) by adding the number of sites at which a plaque was detected, dividing by the total number of sites for which an ultrasonographic image was available, and multiplying by 6 (the maximum number of sites).[19] Maximum common carotid intima–media thickness was measured over a length of 10 mm, with the beginning of the dilatation of the distal common carotid artery as the reference point. We calculated the average of near- and far-wall measurements and of left and right common carotid arteries.[7]

We diagnosed abdominal atherosclerosis by radiographic detection of calcified deposits in the aorta on a lateral abdominal film.[8] The extent of aortic calcification was classified according to the length of the involved area (0 cm, ≤1.0 cm, 1.1–2.4 cm, 2.5–4.9 cm, 5.0–9.9, and ≥10 cm, respectively). This resulted in scores from 0 to 5.[20]

Lower extremity atherosclerosis was expressed as the ankle–arm index. Systolic blood pressure at the ankles (posterior tibial artery) was measured in the supine position with a random-zero sphygmomanometer and an 8-MHz continuous-wave Doppler probe (Huntleigh 500D; Huntleigh Technology, Bedfordshire, UK). The ratio of systolic blood pressure at the ankle and systolic blood pressure at the arm was the ankle–arm index. The lowest index of both sides was used in the analyses.[9] Because arterial rigidity prevents arterial compression and therefore may lead to spuriously high values of the ankle–arm index, an index greater than 1.50 was considered invalid.[21]

Nonfasting blood was collected at baseline, and all tubes were stored on ice before and after blood sampling. High-sensitivity CRP was determined in serum, which was stored at −20°C until performance of the CRP measurements in 2003 and 2004. We measured CRP using a rate near infrared particle immunoassay (Immage Immunochemistry System; Beckman Coulter, Fullerton, CA). Outliers (values >3 SD distribution) of logarithmically transformed CRP were excluded because they might indicate the presence of active inflammatory disease.

Assessment of Open-Angle Glaucoma

The procedure for assessing OAG has been described.[16,17] In short, ophthalmic examination included Goldmann applanation tonometry,[22] visual field screening, ophthalmoscopy, and stereoscopic fundus photography in pharmacologic mydriasis, with similar procedures at baseline and follow-up.[18,23]

For GON evaluation, simultaneous stereocolor transparencies were digitized and analyzed with a semiautomated image analyzer. If the transparencies were absent or of bad quality, ophthalmoscopic estimates were used. Possible GON was defined as vertical cup-to-disc ratio ≥0.7 or asymmetry between eyes of ≥0.2 or minimal rim width <0.1 and probable GON as vertical cup-to-disc ratio ≥0.8 or asymmetry between eyes of ≥0.3 or minimal rim width <0.05, based on the 97.5 and 99.5 percentiles in this population.[16] Visual fields were screened with automated suprathreshold perimetry. A defect in either eye, defined as nonresponse to a light stimulus in at least three contiguous tests points or in four contiguous test points when the blind spot was included, was checked by Goldmann perimetry on both eyes.[23] Visual field loss, compatible with OAG (thus excluding hemianopia, quadrantanopia, or isolated central defect) and not explained by other (neuro-) ophthalmic causes was defined as GVFL.[17,23]

The diagnosis OAG was based on an algorithm using GON and GVFL, independent of intraocular pressure, and could only be made in participants who had—in at least one and the same eye—an open anterior chamber angle and no history or sign of angle-closure or secondary glaucoma.[16,18] Definite OAG was defined as the presence of possible or probable GON *and* GVFL; probable OAG as probable GON *without* GVFL, or GVFL *without* GON. Possible OAG referred to possible GON only.[16] Incident OAG was defined as no or possible OAG in either eye at baseline and as probable or definite OAG in at least one eye at follow-up.[18] Excluded from this incidence definition were participants with possible GON at baseline and probable GON at follow-up as the only change, because a tiny increase in one of the GON criteria could lead to a change in this classification. We used this exclusion criterion primarily because we wanted to be as confident as possible that we really used cases with incident OAG in the risk analyses. We preferred to speak of OAG instead of primary OAG because at baseline we did not specifically exclude pseudoexfoliation glaucoma in all participants. This, however, was never encountered during subsequent examinations at baseline or follow-up.

Population for Analysis and Data Analysis

At baseline, 6780 participants (78% of those eligible) underwent ophthalmologic examination. After excluding persons with prevalent definite or probable OAG ($n = 221$) and those without data on perimetry and optic disc measures ($n = 7$), 6552 participants formed the cohort at risk for incident OAG.

Data on carotid plaques were available in 5385 persons, carotid intima–media thickness in 5417, aortic atherosclerosis in 5520, peripheral atherosclerosis in 5890, and serum CRP levels in 6111. Thirty-four participants were excluded because of ankle–arm index greater than 1.50, and 27 were excluded as CRP outliers.

We used univariate analyses of covariance to compare baseline characteristics of participants and nonparticipants in the follow-up examination, with appropriate adjustment for age and sex. Serum CRP was log transformed in the analyses with standard deviations because its distribution was skewed. Logistic regression analyses were used to calculate odds ratios with corresponding 95% CIs, which can be interpreted as relative risks. In further analyses we adjusted for age, sex, and follow-up time. Carotid intima–media thickness, ankle–arm index, and CRP were analyzed in tertiles and according to standard deviation. Carotid plaques and aortic calcifications were categorized in three groups and analyzed according to these groups or according to category increase. All analyses were performed with current software (SPSS for Windows, version 11; SPSS Inc., Chicago, IL).

Results

After a mean follow-up time of 6.5 years (range, 5.0–9.4 years), 1244 participants had died and 1466 declined or were unable to participate in the follow-up examination of the cohort at risk for incident OAG, leaving 3842 persons (participation rate, 72%). Baseline characteristics of the cohort at risk are provided in Table 1. Most variables were significantly different between participants and those who refused or died. This was not true of the OAG-related variables.

Incident OAG was diagnosed in 87 persons. Table 2 shows that baseline atherosclerosis—analyzed in tertiles, groups, and per SD or category—was not associated with incident OAG. There seemed to be a trend toward higher OAG incidence with increasing numbers of carotid plaques, but the 95% confidence intervals were too wide to draw a more definite conclusion. Table 3 shows that elevated baseline serum CRP levels, analyzed in tertiles and per SD, also constituted no risk for incident OAG.

We also analyzed incident OAG in those persons excluded for extreme CRP levels. At follow-up, 15 of the 27 persons were dead, four refused to participate, and eight participated in the follow-up examinations. No incident OAG was seen in these eight participants.

To look for bias from dropout, we calculated the prevalences of probable or definite OAG at baseline in persons who at follow-up had died, refused to participate, or participated. Adjusted for age and sex, no differences were observed between those who died (3.7%), refused (3.4%), or participated (3.1%).

TABLE 1. Baseline Characteristics of Study Population at Risk for Incident Open-Angle Glaucoma

Status at Follow-up	Participants (N = 3842)	Nonparticipants* (N = 1466)	Died† (N = 1244)
Age, y	65.7 ± 6.9	71.2 ± 8.7††	77.4 ± 9.1††
Female, %	57.8	68.6††	54.3††
Vertical cup-disc ratio‡	0.53 ± 0.13	0.50 ± 0.15††	0.48 ± 0.17††
Possible open-angle glaucoma, %	7.9	7.2	7.6
Intraocular pressure, mm Hg§	15.1 ± 3.1	15.2 ± 3.4	14.8 ± 3.4
Intraocular pressure treatment, %	1.8	2.7	2.3
Body mass index, kg/m^2	26.3 ± 3.5	26.7 ± 4.0††	25.8 ± 3.9††
Diabetes mellitus, %	6.9	10.6††	20.9††
Systemic hypertension, %	28.9	38.4††	45.5††
Total cholesterol, mmol/L	6.7 ± 1.2	6.7 ± 1.2	6.3 ± 1.3††
HDL cholesterol, mmol/L	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4††
History of stroke, %	1.3	3.5††	7.2††
Demented, %	0.2	3.4	15.2††
Intima–media thickness, mm	0.77 ± 0.14	0.81 ± 0.16††	0.89 ± 0.18††
Carotid plaques score¶	1.28 ± 1.56	1.68 ± 1.72††	2.40 ± 1.90††
Aortic calcification score#	1.47 ± 1.39	1.93 ± 1.48††	2.32 ± 1.48††
Ankle–arm index	1.11 ± 0.18	1.03 ± 0.23††	0.91 ± 0.29††
C-reactive protein, mg/L**	1.57 ± 2.65	1.90 ± 2.62††	2.74 ± 3.03††

Data are unadjusted mean ± SD for continuous variables and percentages for dichotomous variables.

* Unable or refused at follow-up.

† Persons who died before the follow-up examination.

‡ Measured as maximum vertical cup-to-disc ratio of both eyes.

§ Only presented here for persons without IOP-lowering treatment. Measured as maximum intraocular pressure in either eye.

¶ Score ranges from 0 through 6.

Score ranges from 0 through 5.

** Based on mean from the natural logarithm (back-transformed).

†† Significant ($P < 0.05$) compared with participants, after adjusting for age and sex if applicable.

TABLE 2. Relative Risks of Incident Open-Angle Glaucoma according to Level of Baseline Atherosclerosis

Atherosclerosis	Persons at Risk	OAG Cases	Relative Risk (95% CI)*		Relative Risk (95% CI)†	
Carotid plaques						
Low	1525	25	1.00	—	1.00	—
Intermediate	1315	38	1.79	(1.07–2.97)	1.55	(0.92–2.61)
High	389	11	1.75	(0.85–3.58)	1.43	(0.68–2.99)
Per category increase	3229	74	1.40	(1.02–1.93)	1.26	(0.90–1.75)
Carotid intima–media thickness						
Low	1080	23	1.00	—	1.00	—
Intermediate	1085	24	1.04	(0.58–1.85)	0.84	(0.47–1.53)
High	1082	29	1.27	(0.73–2.20)	0.86	(0.47–1.57)
Per SD increase	3247	76	1.11	(0.89–1.38)	0.95	(0.75–1.22)
Aortic calcification						
Low	1358	32	1.00	—	1.00	—
Intermediate	1263	23	0.77	(0.45–1.32)	0.63	(0.36–1.09)
High	874	29	1.42	(0.85–2.37)	1.02	(0.60–1.75)
Per category increase	3495	84	1.18	(0.90–1.55)	1.01	(0.75–1.34)
Ankle–arm index						
Low	1172	21	0.77	(0.43–1.37)	0.69	(0.38–1.25)
Intermediate	1171	27	1.00	(0.58–1.72)	0.98	(0.57–1.70)
High	1174	27	1.00	—	1.00	—
Per SD decrease	3517	75	0.90	(0.71–1.15)	0.86	(0.67–1.09)

Ranges (low, intermediate, high): carotid plaque score: 0, 1–3, 4–6; carotid intima–media thickness: 0.41–0.70, 0.70–0.81, 0.81–1.71; aortic calcification score: 0, 1–2, 3–5; ankle–arm index: 0–1.06, 1.06–1.19, 1.19–1.50.

* Unadjusted model.

† Adjusted for age, sex, and follow-up time.

TABLE 3. Relative Risks of Incident Open-Angle Glaucoma according to Baseline Serum C-Reactive Protein, in Tertiles and per Standard Deviation

C-Reactive Protein	Persons at Risk	OAG Cases	Relative Risk (95% CI)*		Relative Risk (95% CI)†	
Low	1205	23	1.00		1.00	
Intermediate	1205	33	1.45	(0.85–2.48)	1.40	(0.81–2.40)
High	1208	29	1.26	(0.73–2.20)	1.19	(0.68–2.07)
Per SD increase	3618	85	1.10	(0.88–1.38)	1.06	(0.85–1.34)

Ranges, C-reactive protein (low, intermediate, high): 0.20–1.03, 1.04–2.46, 2.47–41.0.
* Unadjusted model.
† Adjusted for age, sex, and follow-up time.

DISCUSSION

In our study we could not find an association between atherosclerosis or serum CRP levels at baseline and incident OAG. Impaired perfusion of the optic disc caused by atherosclerosis or inflammation is therefore not likely to be a major cause of OAG.

Earlier studies have measured atherosclerosis through echography or x-ray of the carotid arteries in clinic-based case series or within specific patients groups, such as those with low-tension OAG, high-tension OAG, or ocular hypertension or in healthy controls.[24–31] Despite some positive findings, no strong association could be found.[32–35] Another theory states that vascular dysregulation rather than chronically reduced blood flow by atherosclerosis may lead to local vasospasm and to systemic hypotension, which can lead to low perfusion pressure and insufficient autoregulation of the blood supply of the optic nerve head.[5,33,35–38] Similarly, vascular dysregulation of other areas, such as the brain and the cardiovascular system, have been described in glaucoma patients.[39,40]

The role of inflammation as a risk factor for primary OAG is not as clear as it is for secondary glaucoma. In secondary glaucoma, inflammatory proteins and cells may cause mechanical blockage or damage to the trabeculum, leading to increased intraocular pressure.[41] In what way could inflammation cause primary OAG? During inflammation, several acute-phase proteins are released, including CRP. In recent years it has become clear that CRP may be not only a biomarker but an active mediator in the pathogenesis of atherosclerosis. Atherosclerosis begins as a response to insults to the endothelium and smooth muscle cells of the arterial wall, and this process is accompanied by inflammatory processes in which CRP can take an early and active part. This can lead to impairment of the circulation with accompanying hypoperfusion or even nonperfusion of tissues. In this study, we could not demonstrate that this pathway works for OAG as it does for cardiovascular diseases.

In an old study,[14] no elevated serum CRP level was seen in eight OAG patients. A more recent case-control study found higher CRP levels in patients with normal-tension glaucoma than in healthy controls.[15] In separate analyses on incident normal-tension and incident high-tension glaucoma, we found no difference from the combined results presented in Table 3. Possible explanations are the differences in study design (cross-sectional vs. longitudinal), in population characteristics (CRP level in their controls[15] was lower than in our population), in laboratory assays, and in OAG definition.

Another optic nerve disease may show cupping similar to that seen in OAG. This is arteritic anterior ischemic optic neuropathy induced by giant cell arteritis.[42] In giant cell arteritis, the vessel walls become infiltrated with monocytes and macrophages, leading to intimal thickening. This can result in complications, such as permanent occlusion of posterior ciliary arteries with ischemia of the optic nerve head. The pathophysiology of optic disc cupping in arteritic anterior ischemic optic neuropathy, however, seems to be different from that in OAG because the former is usually associated with highly elevated levels of CRP and other acute-phase proteins,[43] shows profound disc pallor after a period of disc edema, and has a shorter time course.

We looked into the possible pathways of atherosclerosis and CRP for OAG. In spite of our large cohort, we had a limited number of incident OAG cases partially because of the prospective, population-based design. By using strict and, as much as possible, objective criteria to diagnose incident OAG, we tried to eliminate misclassification. Some incident OAG cases might have been missed because of these strict definitions. For risk analysis we considered it better to transfer a possible case into the large control group than to contaminate the case group with healthy persons. Our criteria led to high specificity but relatively low sensitivity. This underestimation of the cases was independent of CRP or atherosclerosis status; therefore, relative risk was unaffected. The limited number of cases did affect the precision of our estimates. Had we had more OAG cases, we still estimate that any effect of atherosclerosis or CRP on the incidence of OAG would have remained small.

A potential limitation of our study was the relatively large group of persons who were lost to follow-up. This can partially be explained by the number of deaths that occurred during follow-up in this elderly cohort. However, two studies show that patients with OAG are not at increased risk for death, making survival bias as an explanation for our negative findings less likely.[44,45] Furthermore, participants who refused the follow-up examination differed in several aspects, including atherosclerosis measures and CRP levels, compared with those who participated at follow-up. We have no reason to believe that the relation between CRP and OAG will be different among those who left the study and those who remained in the study. However, our risk estimates may be underestimated because the range of CRP levels in the upper tertile will be more limited in our study. Given that the risk estimate for this tertile was close to 1, we do not believe that an important effect of CRP on OAG, if present, was missed in our study. The age difference between participants and nonparticipants might have resulted in fewer incident cases, leading to larger confidence intervals in this study, because the incidence of OAG rises with age.[18]

All measures of atherosclerosis in this study reflected the amount of generalized atherosclerosis. They function as a proxy for atherosclerosis in the vessels and are important for OAG. We assumed there would be no difference between

generalized and localized atherosclerosis, but this also requires further exploration. In summary, we were unable to detect a significant association between atherosclerosis or serum CRP level and incident OAG in a relatively healthy population.

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