Hypertension, Cardiovascular Disease, and Age-Related Macular Degeneration

Leslie Hyman, PhD; Andrew P. Schachat, MD; Qimei He, PhD; M. Cristina Leske, MD, MPH; for the Age-Related Macular Degeneration Risk Factors Study Group

Objectives: To describe a case-control study of risk factors for neovascular and non-neovascular age-related macular degeneration (AMD) and to present findings on associations with systemic hypertension and cardiovascular disease.

Methods: Participants with and without neovascular and non-neovascular AMD were recruited from 11 ophthalmology practices in the New York, NY, metropolitan area. Comprehensive data collection included (1) a standardized interview, (2) blood pressure measurements, and (3) blood samples. Cases and controls were classified from fundus photograph gradings. Polychotomous logistic regression analyses were used to evaluate associations.

Results: Classification of 1222 sets of available photographs resulted in the inclusion of a neovascular case group (n = 182), a non-neovascular case group (n = 227), and a control group (n = 235). Neovascular AMD was positively associated with diastolic blood pressure greater than 95 mm Hg (odds ratio [OR] = 4.4), self-reported use of potent antihypertensive medication (OR = 2.1), physician-reported history of hypertension (OR = 1.8), use of antihypertensive medication (OR = 2.5), combinations of self-reported and physician-reported data on hypertension and its treatment (OR = 1.7), high-density lipoprotein level (OR = 2.3), and dietary cholesterol level (OR = 2.2). Non-neovascular AMD was unrelated to hypertension or cholesterol level. No associations were found between either AMD type and other definitions of hypertension or other cardiovascular disease.

Conclusions: These findings suggest that neovascular AMD is associated with moderate to severe hypertension, particularly among patients receiving antihypertensive treatment. They also support the hypotheses that neovascular and non-neovascular AMD may have a different pathogenesis and that neovascular AMD and hypertensive disease may have a similar underlying systemic process.


Between 4 and 10 million people in the United States, aged 45 to 75 years, are estimated to have age-related macular degeneration (AMD), a leading cause of vision impairment. The disease is thought to be non-neovascular (non–NV) to begin, and to progress to a neovascular (NV) form in some patients. Although an estimated 80% of AMD patients have the non-NV form, the NV form may account for almost 90% of the severe visual loss (20/200 OU or worse) due to AMD.

Most studies have evaluated risk factors for AMD alone or for both forms combined. These studies have suggested associations with AMD that include systemic hypertension, other cardiovascular disease, plasma fibrinogen levels, nutritional and antioxidant status, light or medium eye color, hyperopia, lens opacities, dermal elastic degeneration, cigarette smoking, and a family history of AMD. Other than age and cigarette smoking, however, these associations have not been consistent across the different studies. To address the possibility that the 2 AMD forms have different risk factors, this study evaluated these factors separately for NV and non-NV AMD. Risk factors under study were (1) systemic hypertension, cardiovascular disease, and cardiovascular risk factors (eg, cholesterol); (2) nutrients, particularly those with antioxidant potential (eg, vitamins E, C, and beta carotene); (3) personal characteristics (eg, eye color, refractive error, smoking, and family AMD history); and (4) environmental exposures (ie, sunlight and occupational exposures). This report will describe the study design and findings related to systemic hypertension, cardiovascular disease, and selected cardiovascular risk factors; other results will be reported separately.

From the Department of Preventive Medicine, Division of Epidemiology, University Medical Center, Stony Brook, NY (Drs Hyman, He, and Leske); and the Retinal Vascular Center, The Johns Hopkins Hospital, Baltimore, Md (Dr Schachat). Members of the Age-Related Macular Degeneration Risk Factors Study Group are listed on page 357.
PATIENTS AND METHODS

STUDY POPULATION

The Age-Related Macular Degeneration Risk Factors Study was a case-control study designed to have 2 distinct case groups (NV and non-NV AMD) and 1 control group (no AMD). Participants were recruited from 11 ophthalmology practices in the New York, NY, metropolitan area (listed on p 357) according to a standard protocol that involved initial screening for eligibility criteria through a review of the medical records and an ophthalmologic evaluation. Inclusion criteria for the case and control groups were (1) white persons between the age of 50 and 79 years; (2) residence in the greater New York, NY, metropolitan area; (3) no physical or mental disabilities that would preclude participation; (4) no contraindications for pupillary dilation in either eye; (5) clear media on fundus photograph evaluation in both eyes; and (6) examination between September 1986 and September 1989 at a participating ophthalmology practice. All participants in the case groups were diagnosed within 3 years of referral to the study. In addition, participants in the NV case group had to demonstrate evidence of choroidal neovascular membranes or pigment epithelial detachments without other known causes (eg, angiod streaks, Fuchs spots, or histoplasmosis scars) and drusen consistent with standard photographs (minimum of approximately 30 small drusen) in at least 1 eye. Those in the non-NV case group also had drusen with or without pigmentedary changes or other changes, consistent with standard photographs (minimum of approximately 30 small drusen) in at least 1 eye, and loss of visual acuity of at least 20/23 attributable to macular disease or drusen and not other ophthalmic conditions. Those in the control group demonstrated no NV and/or non-NV manifestation of AMD in either eye and were seen for a routine eye examination or other ocular diagnosis (eg, prebyopia, posterior vitreous detachment, or mild lens opacities). Eligibility forms were reviewed further at the Age-Related Macular Degeneration Risk Factors Study Group Coordinating Center, Stony Brook, NY; patients confirmed as eligible were invited by letter and telephone to participate in the study.

RESULTS

Two thousand sixty-seven eligible persons (463 NV cases, 513 non-NV cases, and 1091 controls) were referred to the study by the recruiting ophthalmologists. Of these, 1235 (60%) completed study visits, with participation rates of 66% for non-NV cases, 63% for NV cases, and 55% for controls. These rates were similar in most clinical sites, with lack of interest or time reported as the main reasons for refusals. Participation rates were higher in men than in women (65% vs 56%, respectively, P<.001) and in younger persons (mean age, 70 vs 71 years). While NV participants were older and more likely to be male than NV nonparticipants, no such differences were seen in the non-NV cases. Control participants were more likely to be male than control nonparticipants, but these groups were similar in age.

DATA COLLECTION

Data were collected by trained study personnel according to a standardized protocol; the interviewers were masked as to case or control status of the participants. The variables relevant to this report are as follows:

- Measurements of blood pressure (average of 2 measurements using a Baum sphygmomanometer), visual acuity (using the Early Treatment Diabetic Retinopathy Study protocol), and iris color (using photographic standards such as light, medium, and dark).
- Dietary history, assessed by an interviewer-administered food frequency questionnaire that was developed, described, and evaluated by Block et al and Cummings et al.
- An extensive interview to assess demographics; possible angina, myocardial infarction, and intermittent claudication (using the Rose questionnaire); medical history (eg, hypertension or other cardiovascular diseases) and medication use (at least once a week for more than a month); vitamin supplement use; alcohol intake; and smoking duration and frequency.
- Blood samples taken after fasting (for at least 12 hours) for biochemical determinations of cholesterol, triglycerides, high-density and low-density lipoproteins (HDL and LDL); and vitamins A, E, and C, beta carotene, selenium, and glutathione peroxidase.
- Mailed questionnaires to the patient’s primary physician to validate medical history.
- Bilateral color iris and stereo fundus photographs.

BIOCHEMICAL DETERMINATIONS

At Roche Biomedical Laboratories, Raritan, NJ, serum cholesterol was analyzed by colorimetric procedures and triglycerides were measured enzymatically; HDL levels were determined by precipitation and LDL levels by calculations based on levels of HDL, cholesterol, and triglycerides. At Our Lady of Mercy Medical Center, Bronx, NY, plasma beta carotene and vitamins A, C, and E were analyzed by spectrophotometric, spectrophuorometric, and colorimetric procedures, respectively. At the Department of Chemistry, Montana State University, Bozeman, selenium and glutathione peroxidase analyses were performed using both wet ashing high-pressure liquid chromatography and a spectrophotometric
method monitoring nicotinamide adenine dinucleotide phosphate, coupled through glutathione reductase. The reproducibility of the biochemical analyses was evaluated throughout the study period by a detailed protocol that included drawing a duplicate sample on 10% of the participants.

**STUDY GROUPS**

Final classification into study groups was based on standardized evaluations of bilateral stereo fundus photographs of the macula and disc by 2 masked, independent graders at the Reading Center. Discrepancies not resolved by consensus were adjudicated by a retinal specialist (A.P.S.). Drusen size was evaluated using circles 63 µm, 125 µm, and 250 µm in diameter on a clear acetate overlay. Using standard photographs, patients were classified into a definite control group (≤7 small [<63 µm] drusen and no medium or large drusen in both eyes) or a case group (a minimum of 30 small drusen in at least 1 eye). Cases were classified further as NV (subretinal blood, lipid or fluid, or serous pigment epithelial detachments in at least 1 eye) or non-NV (≥30 small drusen with or without solid elevation of the pigment epithelium secondary to confluent drusen). Therefore, the criteria for case classification did not include medium or large drusen. Fluorescein angiograms were requested only to clarify designation of case status as NV or non-NV.

The same 2 graders reevaluated photographs of 400 eyes from 200 patients to assess their intragrader and intergrader agreement, as well as their overall consensus at 2 different times. Agreement in diagnostic category and each nonordinal AMD characteristic (eg, presence or absence of fluid) was measured by percentage agreement and by unweighted $\kappa$, while weighted $\kappa$ was used for ordinal characteristics (eg, drusen number). $\kappa$ is a measure of chance-corrected agreement, which is interpreted as follows: less than 0.4 indicates poor agreement; 0.40 to 0.75, fair to good agreement; and more than 0.75, excellent agreement. Intrgrater, intrarater, and consensus reproducibilities were good to excellent, with $\kappa$ ranging from 0.66 to 0.79 for drusen smaller than 63 µm; 0.84 to 0.88 for drusen 64 µm to 125 µm; 0.85 to 0.92 for drusen 126 µm to 250 µm; 0.63 to 0.77 for confluence; and 0.68 to 0.70 for pigment. Reproducibility was also good to excellent for grading of fluid ($\kappa$ = 0.70-0.81), hemorrhage ($\kappa$ = 0.80-0.86), lipid ($\kappa$ = 0.76-0.88), disciform scar ($\kappa$ = 0.82-0.86), geographic atrophy ($\kappa$ = 0.71-0.93), and retinal pigment epithelium hypopigmentation ($\kappa$ = 0.59-0.66). In addition, the reproducibility for study group classification into NV AMD, non-NV AMD, and control groups was excellent for cases ($\kappa$ = 0.76-0.85) and fairly good to excellent for controls ($\kappa$ = 0.62-0.78).

**DEMOGRAPHIC CHARACTERISTICS**

As seen in Table 2, those in the NV case group were the oldest. Approximately 60% of the study population was female and the distribution by sex was similar among the 3 groups. The years of education, occupation, and religious preference varied among the study groups (Table 2).

**HYPERTENSION-RELATED VARIABLES**

Systolic/diastolic blood pressure measurements (mean [±SD]) were similar among the NV case group (137.7 [18.9]/80.0 [9.4] mm Hg), the non-NV case group (136.6 [16.9]/79.1 [8.2] mm Hg), and the control group (134.9 [17.2]/79.0 [7.7] mm Hg). However, significant associations were found between NV AMD and several hypertension-related variables by Mantel-Haenszel analysis (data not shown), which remained significantly associated with NV AMD in PLR analyses, with similar ORs (Table 3).

First, NV AMD cases were more likely than controls to have a diastolic pressure greater than 95 mm Hg (7.2% vs 2.1%; OR = 4.4, 95% confidence interval [CI], 1.4-14.2) (Table 4). This association with elevated diastolic pressure became stronger when the...
analyses were limited to the subgroup of persons (n = 148) who were taking antihypertensive medication (OR = 18.0; 95% CI, 2.0-164.8) (Table 3). Although the CIs are wide, reflecting small numbers in these categories, the results suggest an association between elevated diastolic pressure and NV AMD, particularly among persons who are receiving treatment. Of the patients in the NV case group with elevated diastolic blood pressure (n = 12), all were using antihypertensive medications, as compared with less than half of the patients in the control group with the same blood pressure level.

Second, when considering types of antihypertensive treatment, NV AMD was related to self-reported use of antihypertensive medications more potent than diuretics (OR = 2.1; 95% CI, 1.2-3.6) (Table 3); no association was found with use of diuretics alone.

Third, data reported by physicians also support the association of NV AMD with hypertension and use of antihypertensive medication. Odds ratios ranged from 1.8 for a physician-reported hypertension history to 2.8 for use of more potent antihypertensive medication (Table 3).

None of these variables were related to non-NV AMD. In addition, no associations were identified between either AMD type and other definitions of hypertension or any other cardiovascular diseases.

A positive association was found between NV AMD and higher cholesterol intake (P = .04) by logistic regression analysis, adjusting for age, sex, and energy intake. This observation was of borderline significance (P = .05) in the presence of additional covariates using PLR (Table 4). Although serum HDL and the total serum cholesterol–HDL cholesterol ratio were similarly associated with both AMD types by Mantel-Haenszel analyses, when analyzed with other variables, this association remained significant only between NV AMD and elevated serum HDL cholesterol (OR = 2.3; 95% CI, 1.1-4.7) (Table 4). Neither AMD type was related to serum cholesterol, triglycerides, or LDL.

COMPARISON OF NV AND NON-NV CASE GROUPS

Comparisons between the 2 case groups, using non-NV cases as the reference group, were also made (data not shown). These comparisons identified associations with NV AMD that were of similar or lower magnitude for all factors presented in Tables 3 and 4, other than HDL, which was no longer a significant variable.
The fundus photograph classification system resulted in the exclusion of 591 participants who were initially classified in the case and control groups (Figure). Additional analyses, similar to those presented in Tables 3 and 4, were performed that included these participants, based on their classifications by the referring ophthalmologists (n = 1235). Results were in a similar direction, but associations were of lower magnitude (ORs closer to 1) than those based on the fundus photograph classifications. For example, the PLR model evaluating the association of the use of antihypertensive medication (self-reported or physician-reported) with NV AMD in these analyses yielded an OR of 1.8 (95% CI 1.2-2.7) vs 1.1 (0.7-1.6), based on the fundus photograph classification system. This observation demonstrates the importance of having a standardized fundus photograph classification system.

**Comparison of Results Based on Photographic and Clinical Classifications of AMD**

This case-control study found associations between NV AMD and moderate to severe hypertension, particularly among patients being treated with antihypertensive medication, as defined by several different self-reported and physician-reported variables. All of the positive findings relating hypertension to AMD were with NV disease only. Neovascular AMD cases were more than 4 times as likely to have elevated diastolic blood pressure (>95 mm Hg) than controls, and the OR was much higher among persons with these pressure levels who were also using antihypertensive medication (Table 3). Other results were also consistent with the relationship between NV AMD and more severe hypertension, because the association with self-reported antihypertensive treatment was limited to the use of medications more potent than diuretics. Additional physician-reported variables also associated with NV AMD were hypertension, use of antihypertensive medication, and use of more potent antihypertensive medications (Table 3).

Results from various studies have differed regarding an association between hypertension, cardiovascular disease, and AMD, but no prior study has identified a specific link with more severe hypertension. In the previous study by Hyman et al, AMD was related to a history of cardiovascular disease, but not to hypertension. Results of the present study, in comparison, suggest an association with more severe hypertension, but not with specific cardiovascular diseases. While the Framingham Eye Study, National Health and Nutrition Examination Survey, another smaller case-control study, and this study found associations between AMD and hypertension variables, the Beaver Dam Eye Study, Eye Disease Case-Control Study, and others did not. In a study specifically evaluating the relationship between hypertension and AMD, the OR was 1.2 (95% CI 0.8-1.8) for persons with hypertension, but the association was not statistically significant.
recent study from the Netherlands, macular degeneration was associated with atherosclerosis (as determined by plaques in the carotid bifurcation and common carotid artery, lower mean ankle-arm index, and lower extremity arterial disease), but only in persons aged 55 to 84 years. More than 60% of those with AMD in that study had the NV form. The Blue Mountains Eye Study recently reported an association between late AMD (which included geographic atrophy) and increasing plasma fibrinogen levels, a possible predictor of subsequent cardiovascular events. All these findings are consistent with the possibility of an underlying systemic disease process associated with AMD, particularly the NV form, and cardiovascular disease. Hypertension and NV AMD are chronic conditions that probably begin years before they are diagnosed. Given the case-control study design, it is difficult to determine whether one condition causes the other or whether they are both caused by another factor. An underlying atherosclerotic process could play a role in AMD development by affecting the flow and permeability of choroidal vessels, as has been proposed, but a specific mechanism for this process remains unclear. While some of the differences in results among the various studies may be due to differences in the study populations, sample sizes, or other methodological issues, no studies have identified a specific relationship between hypertension and non-NV AMD.

The Macular Photocoagulation Study found that a select group of patients with NV AMD who had highly elevated blood pressure and/or were taking antihypertensive medication received no apparent benefit of krypton laser treatment, as compared with patients without hypertension. These results also lend further support to a correlation between the severity of both conditions. If such an association is confirmed, persons with severe hypertension can be identified as being at high risk for NV AMD and can then be followed closely for signs requiring early treatment.

**CHOLESTEROL**

After adjustment for other covariates, positive associations with dietary cholesterol and high levels of HDL cholesterol remained for NV AMD (Table 4). No associations with either AMD type were identified for total serum cholesterol, triglycerides, LDL, or low total cholesterol/HDL cholesterol ratio.

A relationship between cholesterol and AMD would suggest the presence of shared risk factors for AMD and cardiovascular disease, and may support the hypothesis of a similar pathogenesis. However, findings on cholesterol and AMD have been inconsistent across studies. In the Beaver Dam Eye Study, a high intake of saturated fat and cholesterol was related to early, but not late, AMD. Additionally, a positive relationship was found with HDL cholesterol and an inverse relationship with total cholesterol/HDL cholesterol ratio, but only in men, while total serum cholesterol was inversely related to early AMD in women. In contrast, the Eye Disease Case-Control Study found a positive relationship between total serum cholesterol and NV AMD, although the National Health and Nutrition Examination Survey and the Framingham Eye Study did not. A possible link with high levels of HDL is inconsistent with the hypothesized connection of AMD to cardiovascular disease and its interpretation is unclear, but the positive results of 2 studies raise the possibility of a true relationship.

**POSSIBLE EFFECT OF BIAS**

In interpreting the findings of this study, one must consider several possible biases. Selection biases could occur if patients from specialty and general practices differ in socioeconomic, demographic, and other factors. To reduce this possibility, cases and controls were identified from ophthalmologic practices according to a similar protocol; furthermore, cases and controls were referred similarly to the study, as determined by the distribution of county of residence and adjacency of their ZIP codes to the ophthalmologic referral practices.

The response rate of 60% (66% for the non-NV case group, 63% for the NV case group, and 55% for the control group) was not surprising for a study involving an older population, although offers of transportation and evening or weekend appointments were made equally among all study groups. Motivation may have accounted for the higher participation of those in the case groups than in the control group. An extensive comparison of respondents and nonrespondents showed that the former were more likely to be younger and male. Although this fact must be considered when interpreting the generalizability of the study findings, it should not affect the validity of the results unless response is related to exposure status, eg, if nonrespondents were more or less likely to be hypertensive than participants. Because of observed differences in the distributions of demographic characteristics of occupation, religion, and age among the 3 study groups (Table 2), these factors were included in the final PLR model to control for possible confounding effects.

Misclassification of cases and controls was addressed by incorporating a standardized classification system to separate the study groups clearly. As a result, a large group of participants could not be classified because they had too few drusen to be a definite case or too many drusen to be a definite control. Our main analyses were based on the 644 patients who were classified as cases or controls from their fundus photographs. In the additional analyses that included all 1235 participants classified by their clinical referral diagnoses, ORs were all in the same direction, but weaker (ie, closer to 1). This suggests that the clinical diagnoses were less specific, and the photocard classification system met its goal of creating study groups with a more clear distinction between cases and controls. As a result, misclassification is reduced, increasing the likelihood of identifying associations.

Observation bias was minimized because the interviewers were trained to collect data according to a standard protocol and were masked as to study group status and the specific hypotheses under study. The likelihood
of observation biases was reduced further because some risk factors, such as dietary intake of specific nutrients, were quantified after the study visit.

While all cases were diagnosed within 3 years of entry into the study, the true duration of disease is unknown, given the difficulty in determining the date of AMD onset. While patients may have changed their habits, such as diet, once AMD was diagnosed, such change is not likely to affect the study's findings on hypertension.

The interpretation of findings of a study requiring multiple comparisons of various risk factors is always a concern. For this study, analyses were based on specific hypotheses, there was consistency of findings among different subgroups, and the findings are consistent with those from other studies. Thus, while it is always possible, it is unlikely that chance alone accounted for the significant associations identified. In addition, PLR was used to minimize the effects of potentially confounding variables.

The purpose of this study was to investigate hypertension and cardiovascular disease as possible risk factors for NV and non-NV AMD and to determine whether the associations are similar or different for each type. A relationship was demonstrated between NV AMD and moderate to severe hypertension, use of antihypertensive medication, and dietary cholesterol. Therefore, patients with NV AMD with moderate to severe hypertension who are receiving treatment may warrant careful follow-up. The lack of positive findings for non-NV AMD also suggests possible differences in the pathogenesis of the 2 AMD types. Because the associations of AMD with cardiovascular disease, hypertension, and use of antihypertensive medication are consistent with those of other studies, such risk factors seem highly likely. However, they should be investigated further in longitudinal studies.