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Age-Related Macular Degeneration and Coronary Artery Disease in a VA Population

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Abstract

Objectives—Age-related macular degeneration (AMD) is the leading cause of blindness in the United States. Although AMD shares multiple risk factors with coronary artery disease (CAD), the association between AMD and CAD has not been established. The objective of our study was to demonstrate an association between the diagnosis of AMD and CAD and/or major cardiovascular risk factors.

Methods—We performed a retrospective chart review of >13,000 patients at the Lexington Veterans Affairs Medical Center. Patients diagnosed as having AMD served as cases, and patients diagnosed with cataract and no AMD served as controls. We examined the prevalence of CAD and associated risk factors in both groups using univariate analysis followed by multivariate analyses to examine the association between AMD and CAD after adjusting for known common risk factors.

Results—We identified 3950 patients with AMD and 9166 controls. Patients with AMD were on average 6 years older than controls ($P < 0.001$) and had a significantly higher prevalence of CAD (39% vs 34%) and hypertension (88% vs 83%) but lower incidence of diabetes mellitus and smoking. Estimated odds ratio relating CAD to AMD was 1.22 (95% confidence interval 1.13–1.32; $P < 0.001$). The association between CAD and AMD remained significant in multivariate analyses in older individuals (76 years and older). When we conducted a secondary analysis and matched the AMD and non-AMD groups based on age, the association between CAD and AMD remained significant (39.4% in the AMD group vs 36.6% in the non-AMD group; $P = 0.011$).

Conclusions—These findings support the existence of an association between CAD and AMD, particularly in older adult patients in the predominantly male Veterans Affairs population. Such an association between AMD and systemic vascular disease justifies the potential coscreening for these conditions.

Keywords

age-related macular degeneration; coronary artery disease; Veterans Affairs patients

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Age-related macular degeneration (AMD) is the most common cause of blindness in the United States.[1] It is a degenerative disease of the central area of the retina known as the macula, which results primarily in loss of central vision. The etiology of AMD remains unclear; however, epidemiologic studies have demonstrated an association with cardiovascular risk factors such as hypertension,[2–4] smoking,[5] elevated serum cholesterol,[6] inflammatory state with elevated C-reactive protein,[7,8] genetic predispositions[9,10], and postmenopausal state.[6]

Coronary artery disease (CAD) is one of the leading causes of mortality in the United States.[11] The overlap of risk factors between AMD and CAD is remarkable because AMD may then be regarded as a predictor of CAD[12] and modifiable risk factors for CAD can be controlled to reduce the risk for both AMD and CAD. Although retrospective analyses have demonstrated the association between AMD and stroke[13] or CAD,[14] the association with CAD has been less defined and rather controversial.[15–19]

It has been proposed that the same pathological mechanisms that cause lipid deposition in the walls of systemic arteries in aging and atherosclerosis also lead to esterified lipid-rich deposition and apolipoprotein-B lipid deposition in the sclera and the Bruch membrane of the choroid[20] with AMD. This yields increased choroidal vascular resistance, resulting in elevated choriocapillary pressure, the development of subretinal deposits (drusen), and age-related maculopathy, as well as decreased choroidal blood flow.[21,22]

The aim of this retrospective study was to examine a potential association between AMD and CAD (or its risk factors), including hypertension, age, diabetes mellitus, hyperlipidemia, and tobacco abuse, in a large sample of Veterans Affairs (VA) patients.

Methods

Sample

We reviewed the electronic medical records of all patients at the Lexington Veterans Affairs Medical Center from 2000 to 2009. Based on *International Classification of Diseases* (ICD) codes, we identified 3950 patients with a diagnosis of AMD. This included early drusen pigmentary changes and advanced forms (geographic atrophy; choroidal neovascularization; retinal pigment epithelial detachment, subretinal; retinal pigment epithelium hemorrhage; and subretinal fibrous scar). The control group (9166 patients) included patients diagnosed as having cataract without AMD after formal ophthalmic examination. The diagnosis of cataract and the absence of AMD also were based on ICD codes. The rationale for using cataract patients as a control group was that both groups of patients were diagnosed using standard ophthalmological examination performed by similarly trained physicians in the same institution.

We identified the prevalence of CAD in both groups based on ICD codes for history of CAD, documented myocardial infarction, history of coronary artery bypass surgery, and history of coronary angioplasty. In addition, we collected data on the following risk factors of cardiovascular disease: age, sex, race, tobacco abuse, hypertension, diabetes mellitus, and

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hyperlipidemia. The study protocol was approved by the VA institutional review board and the VA research and development committees.

Data Analysis

Two-sample *t* tests and χ^2 tests were used to compare the AMD and control groups on means and proportions for CAD and the aforementioned risk factors of cardiovascular disease. Moreover, unadjusted odds ratios (ORs) describing the bivariate associations of AMD with these demographic and clinical characteristics were estimated via logistic regression. Age was chosen as a variable because of reports in the literature suggesting the importance of age as a risk factor for AMD. Furthermore, in our univariate analysis, age (76 years and older vs 75 years and younger; 75 was the median age) carried the highest estimated OR. We then conducted multivariate analyses in each of two age strata (76 and older vs 75 and younger) to assess the relation between AMD and CAD while controlling for possible confounding factors. More specifically, within each stratum a multivariate logistic regression model was fit with AMD as the outcome variable to estimate adjusted ORs, describing the multivariate associations of AMD with demographic and clinical characteristics (including CAD). This allowed us to identify which characteristics were associated with AMD among younger patients and which were associated with AMD among older patients. Given that the majority of patients were men, we did not include sex as a predictor in multivariate modeling. Also, because the number of Asian/Pacific Islanders in the sample was small (and because the "unknown" category could be rather heterogeneous), we excluded patients of races other than white and black. Because the AMD and non-AMD groups were imbalanced with respect to age, we next performed a secondary analysis in which we matched AMD and non-AMD subjects based on age, to seek assurance that the associations detected between AMD and CAD in the primary analyses were not spurious. All of the statistical analyses were performed using SPSS 16 (SPSS Inc, Chicago, IL) or SAS 9.3 (SAS Institute, Cary, NC) and the gmatch macro.[23] Statistical significance was defined by a P value < 0.05.

Results

The sample consisted of 13,116 patients: 3950 with AMD and 9166 with cataract(s) who served as controls. Table 1 compares these groups based on several demographic and clinical characteristics. Each group included approximately 98% men. The AMD group had a higher percentage of white patients than the control group (91% vs 85%; $P < 0.001$), whereas the control group had relatively more black patients (6.0% vs 3.4%; $P < 0.001$). Prevalence of CAD and hypertension was approximately 5% higher in the AMD group ($P < 0.001$), and the prevalence of diabetes mellitus and tobacco abuse was approximately 4% to 5% greater in the control group ($P < 0.001$). There was no significant difference between groups on hyperlipidemia. Mean age was approximately 6 years greater in the AMD group ($P < 0.001$). Correspondingly, confidence intervals (CIs) for unadjusted ORs describing the bivariate associations of AMD with demographic and clinical characteristics had a lower bound for the 95% CI that was >1 for white race, age, CAD, and hypertension (indicating positive associations of AMD with these characteristics) and had an upper bound for the

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95% CI that was <1 for black race, diabetes mellitus, and tobacco abuse (indicating negative associations).

Table 2 presents results for the multivariate logistic regression models in both age strata. Among patients 75 years old and younger, white patients were significantly more likely (estimated OR 1.582, 95% CI 1.188–2.106; $P = 0.002$) to have AMD compared with otherwise similar patients of black race. Conversely, diabetic patients are significantly less likely (estimated OR 0.859, 95% CI 0.754–0.979; $P = 0.02$) to have AMD compared with otherwise similar nondiabetic patients. We observed a weak positive association of AMD with hypertension in the multivariate model, but this did not attain statistical significance at the 0.05 level (estimated OR 1.183, 95% CI 0.984–1.422; $P = 0.07$). Notably, there was no significant association of AMD with CAD among patients 75 years old and younger. Among patients 76 years old and older, AMD had a significant positive association with white race (estimated OR 2.000, 95% CI 1.527–2.620; $P < 0.001$), and a significant negative association with diabetes mellitus (estimated OR 0.882, 95% CI 0.789–0.986; $P = 0.03$); both of these associations also were observed among patients 75 years old and younger. Among patients 76 years old and older, however, two additional associations were detected. Those with CAD were significantly more likely to have AMD (estimated OR 1.135, 95% CI 1.010–1.277; $P = 0.03$; controlling for all other predictors in the model), as were those with hypertension (estimated OR 1.469, 95% CI 1.224–1.763; $P < 0.001$). In neither age stratum was there a significant association of AMD with tobacco abuse. The majority of our patients included in our analysis were men (>97%); however, we conducted a separate analysis on women and did not observe the association between AMD and CAD in this group (data not shown). This lack of association in the female group could be related to the small sample size of women in our study.

We conducted an age-matched analysis to conform the association between AMD and CAD beyond the effect of age. Among the 3835 patients with AMD, 1511 (39.4%) had CAD; among the 3835 without AMD, 1402 (36.6%) had CAD; by the McNemar test the P value was 0.011. If we confined attention to those 2475 pairs in which both individuals with matched age were older than 75: 1059 (42.8%) with AMD had CAD; 929 (37.5%) without AMD had CAD; by the McNemar test the P value was < 0.001. If we confined attention to those 1360 pairs in which both individuals with matched age were not older than 75 years: 452 (33.2%) with AMD had CAD; 473 (34.8%) without AMD had CAD; by the McNemar test the P value was 0.396. As such, age-matched analysis accorded with our univariate and multivariate analyses results regarding the association between AMD and CAD, particularly in individuals older than 75 years.

Discussion

This is the first and largest study to date investigating the association between AMD and CAD among VA patients in the state of Kentucky. In addition, we examined the common risk factors of CAD and AMD in a large subset of patients from the VA healthcare system between 2000 and 2009. Our study confirms the associations of AMD with age, white race, CAD, hypertension, diabetes mellitus, and tobacco abuse in VA patients, similar to reports from multiple, community-based cohort and randomized studies.[2–6] In multivariate analyses,

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white race and diabetes also were associated with AMD in both age strata; however, history of CAD and hypertension were significantly associated with AMD in individuals 76 years old and older but not in individuals 75 years old and younger.

The association between AMD and CAD has been poorly defined and rather controversial despite the identification of risk factors common to both diseases.[15–19] Sun and colleagues demonstrated a strong association between CAD and different stages of AMD (except for late AMD) in the Cardiovascular Health Study; these associations persisted in their multivariate analysis.[15–19] Likewise, in a large case-control study with a cohort similar to ours, Chaine and colleagues demonstrated a strong association between CAD and AMD; this association persisted after adjustment for confounding variables.[19] Conversely, reports from some cross-sectional studies[17] failed to demonstrate similar findings. The VA patient population represents a unique cohort and our study included a large number of individuals to examine this question. In this study, we discovered a significant association between AMD and CAD (estimated OR 1.22, 95% CI 1.13–1.32; $P< 0.001$); however, after adjusting for potential confounding variables such as race, hypertension, diabetes mellitus, and tobacco abuse, this association persisted among individuals 76 years old and older (estimated OR 1.13, 95% CI 1.01–1.28; $P = 0.03$) but not among those 75 years and younger.

The importance of these findings has not been corroborated in randomized studies. Although it is logical to attempt reducing the incidence of AMD by modifying risk factors common to both AMD and CAD, randomized studies failed to demonstrate such a beneficial effect with statin therapy.[24] It is reasonable, however, to screen patients for AMD when diagnosed as having CAD and vice versa. In addition, it is important to note that patients with AMD experience higher mortality than age-matched patients without AMD because of the significantly higher incidence of comorbidities,[25] as well as greater cardiovascular mortality.[26] As such, the implications of our findings extend beyond coscreening for AMD and CAD to aggressive management of common risk factors.

Our cohort comprised a relatively old age group with a median age of 75 years. The patients with AMD were significantly older than controls; therefore, stratification by age was pursued to accommodate the possibility that age may confound or even modify the association between AMD and CAD. Several studies also have demonstrated an association between AMD and hypertension,[2–4] and the results from our analysis are consistent with those. More specifically, hypertension increased the estimated odds of AMD by 50% (without adjustment for other predictors of AMD) and 47%, with adjustment in the 76 years old and older stratum. The use of statin therapy as a marker of hyperlipidemia has yielded varied associations with AMD in the literature.[15,24,27] The different populations considered, as well as the wide definitions and indications of hypercholesteremia drugs, may explain these variations. In our study, history of hyperlipidemia was modestly associated with AMD (without adjustment for other predictors of AMD; OR 1.068, CI 0.986–1.157; $P = 0.1$) and was not included in the multivariate analysis model. Our age-matched secondary analysis confirmed the association between AMD and CAD. The association between AMD and CAD was significant in the entire age-matched cohort (39.4% vs 36.6%; $P = 0.011$); a

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significant association also was present in matched pairs older than 75 years of age but not in matched pairs 75 years or younger, in accordance with our primary multivariate analyses.

The negative association between diabetes mellitus and AMD in our study is counterintuitive but appeared consistently across our analyses (univariate, multivariate within the 75 years and younger age stratum, and multivariate within the 76 years and older age stratum). Conversely, the literature has not established a clear association between diabetes and AMD.[2,15,17] In our univariate analysis there was a negative association between AMD and tobacco abuse, but this did not persist in our multivariate analyses. Previous work has shown that the risk of AMD is significantly higher among current smokers but not in those with a history of smoking.[28] Our cohort contained a mix of current and past smokers and this could explain the discrepancy between our results and some of the available studies. In any event, our study involving a large number of VA patients has illuminated the association between AMD and CAD, particularly in those older than 75 years, as well as the associations between AMD and cardiovascular risk factors in this select patient population.

There are several limitations to this study. This is a retrospective chart review. The diagnoses of AMD and CAD were based on ICD codes and primary care physician records; therefore, there was no confirmation of the diagnoses by the authors. Similarly, our data are based on the VA medical records system, which should be inclusive of all chronic diagnoses, but it have missed some acute diagnoses if the veterans were admitted to outside facilities for acute care. Because our study is concerned only with chronic diagnoses, however, we believe that this limitation will not affect our study results and conclusions. The VA population is primarily white and male, which can explain some of the differences between our findings and other studies addressing similar associations as detailed above.

Conclusions

Our study demonstrates an association between AMD and CAD, particularly among those 76 years of age and older, in the predominantly white, male VA population. We also have confirmed the findings of others regarding the association between AMD and hypertension. Future studies examining the cost-effectiveness of applying routine screening for CAD among patients with AMD (and vice versa) as well as primary preventive measures for CAD in this population are warranted.

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Key Points

- Age-related macular degeneration (AMD) is a common finding in the veteran population.
- Patients with AMD are significantly older and have higher rates of coronary artery disease and its risk factors such as hypertension.
- In multivariate and age-matched analyses, the association between AMD and coronary artery disease persisted mainly in the older group of patients (older than 75 years).

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Table 1

Demographic and clinical characteristics of the sample

	AMD, N = 3950	Cataract (No AMD) (n = 9166)	*P*	Estimated OR (95% CI)
Demographic characteristics				
Male sex (%)	3867 (97.9)	8939 (97.5)	0.19	1.183 (0.918–1.526)
Race (%)	(n = 3948)	(n = 9153)		
White	3581 (90.7)	7789 (85.1)	<0.001	1.716 (1.519–1.937)
Black	135 (3.4)	551 (6.0)	<0.001	0.553 (0.457–0.670)
Asian or Pacific Islander	7 (0.2)	20 (0.2)	0.64	0.812 (0.343–1.921)
Unknown	225 (5.7)	793 (8.7)	<0.001	0.638 (0.547–0.743)
Age, y (median 75)	77.8 ± 9.9	71.9 ± 9.9	<0.001	2.864 (2.650–3.096)[a]
Clinical characteristics				
Coronary artery disease (%)	1553 (39.3)	3176 (34.6)	<0.001	1.222 (1.131–1.320)
History of hypertension (%)	3482 (88.2)	7630 (83.2)	<0.001	1.498 (1.340–1.674)
History of diabetes mellitus (%)	1704 (43.1)	4291 (46.8)	<0.001	0.862 (0.800–0.929)
History of tobacco smoking (%)	1217 (30.8)	3288 (35.9)	<0.001	0.796 (0.735–0.862)
History of hyperlipidemia (%)	2689 (68.1)	6107 (66.6)	0.105	1.068 (0.986–1.157)

Entries in the AMD and Cataract columns for categorical characteristics are numbers and percentages; entries for numeric characteristics are means and standard deviations. AMD, age-related macular degeneration; CI, confidence interval; OR odds ratio (more specifically the odds of having AMD [vs cataract], with the characteristic divided by the odds of having AMD without the characteristic [or in the case of age the factor by which the odds of AMD increase with increasing age]).

[a]Indicates the OR of developing AMD in patients above the median of 75 years compared to those ≤75 years.

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Table 2

Logistic regression results

Characteristics	Age ≤75 y		Age ≥76 y	
	Estimated OR (95% CI)	*P*	Estimated OR (95% CI)	*P*
White race	1.589 (1.194–2.116)	0.002	2.000 (1.527–2.619)	<0.001
History of coronary artery disease	0.949 (0.831–1.085)	0.45	1.1354 (1.016–1.267)	0.03
History of hypertension	1.200 (1.001–1.440)	0.049	1.467 (1.227–1.756)	<0.001
History of diabetes mellitus	0.871 (0.767–0.990)	0.04	0.882 (0.790–0.985)	0.03
History of tobacco smoking	0.938 (0.829–1.061)	0.31	1.021 (0.901–1.156)	0.75

AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio (more specifically the odds of having AMD [vs cataract], with the present characteristic divided by the odds of having AMD without the present characteristic, while controlling for all other characteristics in the model).