

Estimated Prevalence and Risk Factor for Age-related Maculopathy

Mi In Roh, Ji Hyun Kim, Suk Ho Byeon, Hyoung Jun Koh, Sung Chul Lee, and Oh Woong Kwon

Department of Ophthalmology, The Institute of Vision Research, Yonsei University College of Medicine, Seoul, Korea.

Purpose: To assess the estimate prevalence and risk factors for age-related maculopathy (ARM) in Seoul, Korea. **Patients and Methods:** We examined 9,530 subjects with, 40 years of age or older between January 2006 and December 2006 in Seoul, Korea. Subjects underwent fundus photography, clinical examinations (including blood analyses), and completed detailed questionnaires. Fundus images were graded according to definitions from the Wisconsin Age-Related Maculopathy Grading System. **Results:** ARM was present in 235 subjects, corresponding to an estimate prevalence of 2.46%. Hepatitis B infection (positive status for HBsAg and HBcAb), serum triglyceride levels and high density lipoprotein levels remained as significant risk factors after age-adjustment. Multivariate analyses showed that the prevalence of ARM was significantly higher in older subjects [odds ratio (OR) 1.134; 95% CI 1.114-1.154] and those who were seropositive for hepatitis B surface antigen (OR 2.566; 95% CI 1.519-4.335). **Conclusion:** The estimated prevalence of ARM was 2.46%. Age and hepatitis B infection may increase the risk of ARM.

Key Word: Age-related maculopathy, hepatitis B, triglyceride, high-density lipoprotein

INTRODUCTION

Age-related maculopathy (ARM) is the main cause of adult blindness in developed countries.¹ Although there is considerable information on the nature and prevalence of visual impairment and blindness in Western countries, only a few population-based articles have appeared, describing the prevalence of ARM and the association of ARM

with various patient characteristics in different racial and ethnic groups in Western countries.²⁻⁵ Only limited population-based data on the prevalence, characteristics, and risk factors for ARM in Asian populations are available.⁶⁻¹³

Studies from Western countries implicate lifestyle choices, nutritional parameters, and genetic risk factors in the pathogenesis of ARM.¹⁴ Known risk factors for developing ARM are age,¹⁴⁻¹⁸ smoking,^{14-17,19-21} and hypertension.²²⁻²⁴ Hyperlipidemia and fat intake are related to the presence of exudative ARM,²⁴ and obesity²⁵⁻²⁸ and atherosclerosis²⁴ contribute to ARM development in some studies. Asian lifestyles and nutritional choices are different, however, from those of Western populations. The purpose of this report is to provide an estimate of the prevalence of ARM in a large survey sample, and to evaluate possible risk factors for ARM in the South Korean population.

PATIENTS AND METHODS

The Yonsei Eye Study was carried out in Seoul, which is the largest city in South Korea. The Medical Ethics Committee of the Yonsei University medical center approved the study protocol, and all participants were well-briefed on the purposes of the study before giving written informed consent in accordance with the tenets of the Declaration of Helsinki. Baseline interviews and ophthalmic examinations, with concurrent general medical examinations, took place between January 2006 and December 2006. Of 13,016 participants who came in for a health check-up during that period, 9,530 subjects (73.2%) were ≥ 40 years old.

All examinations were carried out at the Yonsei

Received February 22, 2008
Accepted May 21, 2008

Reprint address: requests to Dr. Oh Woong Kwon, Department of Ophthalmology, Yonsei University College of Medicine, 250 Seongsanno, Seodaemun-gu, Seoul 120-752, Korea. Tel: 82-2-2228-3573, Fax: 82-2-312-0541, E-mail: owkwon0301@yuhs.ac

Medical Examination Center in Seoul, Korea. After measuring visual acuities and intraocular pressures (using a Type WT-200 instrument; Canon Inc, Tokyo, Japan), digital photographs of the maculae and optic discs were taken using a digital fundus camera (model TRC.NW 100; Topcon, Tokyo, Japan). Medical examinations were performed, which included blood analyses, urine analyses, and electrocardiograms. Additionally, the education level, income status, smoking habits, and illness history of each subject were assessed by questionnaire. Subjects were asked to report existing or previous diagnoses of diabetes mellitus, hypertension, cardiac disease, or hepatic disease.

Ophthalmic examination

For the assessment of ARM, the Wisconsin Age-Related Maculopathy Grading system was used, as described previously in detail.^{29,30} Fundus photographs were examined by ophthalmologists with special training in retinal diseases (MIR, JHK). Intergrader and intragrader agreement was assessed using the quadratic weighted kappa statistic on a random subset of 30 subjects. There was excellent inter- and intraobserver agreement ($\kappa = 0.82$) for the grading of fundus photographs. Senior investigators also reviewed all photographs graded as late ARM (ARM 4). Grading of the fundus photographs was based on the staging systems developed by the investigators of the Rotterdam Eye Study³¹: ARM 0, no feature characteristic of early ARM, or hard drusen only; ARM 1, either soft drusen or pigmentary irregularities only; ARM 2, either soft, indistinct ($\geq 125 \mu\text{m}$) or reticular drusen only, or soft, distinct, drusen with pigmentary irregularities; ARM 3, soft, indistinct, or reticular drusen with pigmentary irregularities; and ARM 4, neovascular ARM or geographic atrophy. Neovascular ARM was considered to be present if any of the following lesions were found: serous or hemorrhagic retinal pigment epithelial detachment, subretinal neovascular membrane, or subretinal hemorrhage. Geographic atrophy was considered to be present if preretinal fibrous scarring or retinal pigment atrophy with visible choroidal vessels was found. We defined ARM stage 2 and 3 as early ARM and stage 4 as late ARM. Subjects were excluded from the study whose fundi could not be

graded because of poor photograph quality or dense ocular media.

Data analysis

For smoking analysis, subjects were categorized as non-smokers (those who had never smoked), current smokers, and prior smokers (those who had smoked earlier but were not smoking for 6 months at the time of the study). Education level was graded on the basis of final education level attained, as follows: 0, no school education; 1, graduated from elementary school; 2, graduated from middle school; 3, graduated from high school; 4, bachelors degree from college and, 5; masters degree from college. Monthly income was divided into 6 categories: 1, monthly income less than 1.5 million won; 2, monthly income between 1.5 million and 2.5 million won; 3, monthly income between 2.5 million and 3.5 million won; 4, monthly income between 3.5 million and 4.5 million won; 5, monthly income between 5.5 million won and 6.5 million won, and; 6, monthly income more than 6.5 million won. Hypertension and hepatitis were considered to be present when subjects self-reported these conditions, and diabetes was considered to be present when subjects self-reported the condition and the self-report was confirmed by a measurement of fasting blood glucose level > 126 mg/dL.

Statistical analyses

Student t-test was used for analyses of continuous variables, and the Pearson χ^2 test was also employed for nominal variables. Age-adjusted logistic regression analysis was performed to determine risk factors for early and late ARM, using odds ratio calculations, and estimations of the 95% confidence intervals. We then developed multivariable models using the following procedure. The initial specification included independent variables consistently identified in previous research as risk factors for early and late ARM, or independent variables identified in univariate analyses as related to outcomes ($p > 0.10$). We then sequentially removed non-significant ($p > 0.15$) covariates, making it certain that these eliminations did not change estimated coefficients of the ex-

posure variable by more than 10%.³² Age and gender were adjusted regardless of association. Because our models might have been overspecified, given the limited number of ARM in the study group, we also constructed reduced form models by selecting covariates, based on their statistical significance in the adjusted models. SPSS version 12 (SPSS Inc, Chicago, IL, USA) was used to perform statistical analyses. A two sided *p* value < 0.05 was considered to be statistically significant.

RESULTS

Study population

A total of 13,016 potential participants (7,109 men and 5,770 women), who underwent examinations at the Yonsei Medical Examination Center between January 1, 2006 and December 31, 2006, were identified. Of the participants, 9,530 (73.2%) were aged ≥ 40 years, and underwent full clinical examinations. Of these, 9,468 (99.3%) completed all study procedures, including dilated fundus photo-

graphy. Fundus images were not available for 62 (0.7%) participants because subjects refused to be photographed, and poor-quality, unusable photographs were obtained from 151 (1.6%) subjects because of corneal opacities, phthisis bulbi, or small pupils. Table 1 shows the prevalence of ARM by gender and age. Percentages of the population in various age groups were 42.3% in the group aged 40 - 49 years, 36.0% in the group aged 50 - 59 years, 17.3% in the group aged 60 - 69 years, and 4.5% in the group aged ≥ 70 years. ARM was seen in 235 (2.46%) subjects. Estimated prevalence of early ARM (ARM 2 and ARM 3) and late ARM (ARM 4) increased from 0% and 0.1%, respectively, in the 40 - 49 year age group, to 2.0% and 0.1% in the group aged 50 - 59 years, to 6.7% and 0.2% in the group aged 60 - 69 years, and to 8.0% and 2.4% in subjects aged ≥ 70 years.

Mean age of the subjects with ARM was 63.17 ± 7.45 years [mean \pm standard deviation (SD)]. One hundred and twenty-six (53.6%) ARM patients were male and 109 (46.4%) were female, thus males showing a slight predominance. Early ARM and late ARM were present in 2.3% (215 subjects) and

Table 1. Numbers of Subjects over 40 Years of Age with ARM, and ARM Prevalence Rates (%)

	No pathology	ARM 1	ARM 2	ARM 3	ARM 4	Ungradable photograph	No photo
All ages							
Men (n = 5,425)	5,166 95.2%	13 0.2%	101 1.9%	14 0.3%	11 0.2%	82 1.5%	38 0.7%
Women (n = 4,105)	3,884 94.6%	19 0.5%	88 2.1%	12 0.3%	9 0.2%	69 1.7%	24 0.6%
Total (n = 9,530)	9,050 95.0%	32 0.3%	189 2.0%	26 0.3%	20 0.2%	151 1.6%	62 0.7%
Age group (yrs)							
40 - 49 (n = 4,026)	3,982 98.9%	2 0%	2 0%	1 0%	4 0.1%	14 0.3%	21 0.5%
50 - 59 (n = 3,429)	3,286 95.8%	18 0.5%	61 1.8%	7 0.2%	2 0.1%	37 1.1%	18 0.5%
60 - 69 (n = 1,651)	1,443 87.4%	12 0.7%	100 6.1%	10 0.6%	4 0.2%	69 4.2%	13 0.8%
≥ 70 (n = 424)	339 80.0%	0 0.0%	26 6.1%	8 1.9%	10 2.4%	31 7.3%	10 2.4%

ARM, age-related maculopathy.

0, no features of early ARM, or hard drusen only; 1, either soft drusen or pigmentary irregularities only; 2, either soft, indistinct ($\geq 125 \mu\text{m}$), or reticular drusen only, or soft, distinct, drusen with pigmentary irregularities; 3, soft, indistinct, or reticular drusen, with pigmentary irregularities; 4, neovascular ARM or geographic atrophy.

0.2% (20 subjects) of participants, respectively. Among these, ARM was bilateral in 123 subjects (52.3%) and unilateral in 112 subjects (47.7%). Among bilateral subjects, geographic atrophy was found in both eyes in a single subject, and 2 subjects each showed geographic atrophy in 1 eye and multiple drusens in the other eye. The remaining subjects showed multiple drusens in both eyes with or without pigment abnormalities. Among the unilateral ARM subjects, 17 (15.2%) eyes showed late ARM (neovascular AMD in 5 subjects and geographic atrophy in 12 subjects), and remaining 95 eyes showed early ARM. Among ARM subjects, there were no differences in distributions of ARM features between males and females (ARM 2, ARM 3, and ARM 4) (Pearson chi-square test, $p = 0.991$), or late ARM features (Pearson chi-square test, $p = 0.897$). Bilateral ARM was more prevalent in females (Pearson chi-square test, $p = 0.011$).

Neovascular AMD was found in 5 subjects. Among these, 2 patients showed subretinal hemorrhages with exudates, a single subject showed serous pigment epithelial detachment with hyperpigmentation, and 2 subjects had large subretinal hemorrhages with orange nodules.

Risk factors for ARM

When Student t-test and Pearson χ^2 test were used for analyses of variables, the following risk factors for early and late ARM (ARM 2, 3 and 4) were subjected to age-adjusted univariate analysis: gender, socioeconomic status (monthly income and education level), smoking history, self-reported diagnosis of hypertension, self-reported diagnosis of cerebral vascular accident, self-reported diagnosis of hepatitis, and body mass index. Serum levels of cholesterol, triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), lactate dehydrogenase (LDH) and C-reactive protein (CRP) were measured. In addition, serum hepatitis B surface antigen status (HBsAg), hepatitis B core antibody level (HBcAb), hepatitis B surface antibody level (HBsAb), and hepatitis C antibody level (HCVAb) were also assessed.

Subjects with ARM were significantly older ($p < 0.001$), and monthly income and final education level were lower than subjects without ARM. Also,

while 27% of the ARM subjects had hypertension, only 14.1% of the subjects without ARM had hypertension history ($p < 0.001$). As for blood sample analysis, significantly different platelet, LDH, and TG levels were found with ARM subjects (Table 2).

Therefore, estimated prevalence of ARM was strongly age-related (logistic regression; $p < 0.001$; OR 1.134; 95% CI; 1.114 - 1.154), as expected. The results of age-adjusted logistic regression analyses of risk factors for ARM are listed in Table 3. After adjusting for age, hepatitis B infection (positive status for HBsAg and HBcAb) and serum triglyceride levels and HDL levels remained as significant risk factors for ARM. Multivariate regression analysis indicated that serum HBsAg-positive status was significant and associated with a >2-fold increase in the risk of ARM, relative to normal macular subjects, in both the adjusted (OR 2.55; 95% CI 1.476 - 4.421) and reduced (OR 2.736; 95% CI 1.588 - 4.714) analyses (Table 4).

DISCUSSION

We estimated the prevalence and risk factors for ARM in Seoul, Korea. In our study population, 2.46% of participants had signs of early or late ARM in one or both eyes, suggesting that ARM is relatively rare among adult South Koreans in Seoul. A total of 2.26% of the study subjects showed early ARM, defined as soft indistinct drusen with or without pigmentation abnormalities. Late ARM (defined as neovascular AMD or geographic atrophy) was seen in 0.2% of the study population. Among those with late ARM, neovascular AMD in at least one eye was seen in 5 subjects and geographic atrophy in 15 subjects.

Although direct comparison is difficult due to the fact that our studies showed estimate prevalence of ARM, these estimates of early and late ARM are lower than the incidence rates observed in Western countries. In the Beaver Dam study,³³ the prevalence of indistinct soft drusen was 8.4% and patients with either pure geographic atrophy or exudative macular degeneration constituted 0.6% of the study population. The Framingham Eye Study³⁴ showed an incidence of 1.5% of exudative macular degeneration in people ≥ 52 years of age. In a population-based prevalence study (the

Table 2. Statistical Data on Risk Factors for Age-related Maculopathy

Variables	ARM	No-ARM	<i>p</i> value
Age, yrs (mean ± SD)	63.17 ± 7.45	52.14 ± 8.51	< 0.001
Gender, male/total (%)	126/235 (53.6)	5,205/9,126 (57)	0.296
Body mass index (kg/m ²)	24.26 ± 2.91	24.27 ± 2.81	0.986
Socioeconomic status			
Monthly income/month (million won)			
< 1.5	0/207 (0)	1/8,218 (0.0)	< 0.001
1.5 - 2.5	42/207 (20.3)	730/8,218 (8.9)	
2.5 - 3.5	40/207 (19.3)	951/8,218 (11.6)	
3.5 - 4.5	36/207 (17.4)	1,079/8,218 (13.1)	
4.5 - 5.5	16/207 (7.7)	1,213/8,218 (14.8)	
> 5.5	73/207 (35.3)	4,244/8,218 (51.6)	
Education level			
No school education	0/225 (0)	2/8,846 (0.0)	< 0.001
Graduated from elementary school	40/225 (17.8)	627/8,846 (7.1)	
Graduated from middle school	26/225 (11.6)	687/8,846 (7.8)	
Graduated from high school	62/225 (27.6)	2,299/8,846 (26)	
More than college education	97/225 (43.1)	5,231/8,846 (59.1)	
Cerebral vascular accident (%)	4/235 (1.7)	79/9,126 (0.9)	0.177
Hypertension (%)	65/235 (27.7)	1,285/9,126 (14.1)	< 0.001
Diabetes mellitus (%)	38/235 (16.2)	1,654/9,126 (18.1)	0.442
Hepatitis (%)	13/235 (5.5)	459/9,126 (5.0)	0.728
Current Smoking (%)	32/223 (14.3)	1,815/8,836 (20.5)	0.066
Blood sampling			
Hemoglobin (g/dL)	14.13 ± 1.31	14.25 ± 1.49	0.212
Platelets (k/μL)	240.89 ± 57.88	251.16 ± 56.43	0.006
White blood cell count (k/μL)	6.10 ± 1.67	5.94 ± 1.70	0.129
Cholesterol (mg/dL)	188.36 ± 31.67	188.24 ± 32.22	0.953
Triglycerides (mg/dL)	131.39 ± 66.83	142.51 ± 92.45	0.013
HDL (mg/dL)	56.64 ± 12.24	56.39 ± 13.04	0.755
LDL (mg/dL)	127.29 ± 29.80	126.51 ± 31.13	0.701
LDH (IU/L)	360.51 ± 58.40	341.03 ± 56.42	< 0.001
CRP quantitation (mg/dL)	0.19 ± 0.37	0.18 ± 0.39	0.785
HBsAg positivity	18/235 (7.7)	410/9,126 (4.5)	0.022
HBsAb positivity	155/235 (66)	6,518/9,126 (71.4)	0.068
HBcAb positivity	175/235 (73.2)	5,170/9,126 (56.7)	< 0.001
HCVAb positivity	1/235 (0.4)	78/9,126 (0.9)	0.478

ARM, age related maculopathy = ARM2 + ARM3 + ARM4; SD, standard deviation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDH, lactate dehydrogenase; CRP, C-reactive protein; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody; HCVAb, hepatitis C antibody.

Chi-square test was used for nominal variables.

Student's t test was used for continuous variables.

Beijing Eye Study), Li et al.¹³ found that the overall prevalence rates of early and late ARM were 1.4% and 0.2%, respectively, and these data are similar to our results. The prevalence of late ARM in the black population was 0.59% in a Barbados study,⁴

and was 0.5% in Hispanic individuals aged ≥ 50 years in Arizona.³⁵

The prevalence of early ARM obtained in the present study on South Koreans living in the Seoul area was slightly higher (2.46% vs. 1.4%) than in

Table 3. Age-adjusted Univariate Logistic Analyses to Find Associations of Prevalence Rates of ARM with Other Parameters

Variables	ARM	
	Age-adjusted	
	<i>p</i> value	OR (95% CI)
Sex	0.396	1.123 (0.859 - 1.468)
Body mass index (kg/m ²)	0.779	0.993 (0.947 - 1.042)
Socioeconomic status		
Monthly income/month	0.910	0.995 (0.917 - 1.081)
Education level	0.582	0.970 (0.868 - 1.083)
Self-reported diagnosis		
Cerebral vascular accident	0.277	1.803 (0.622 - 5.220)
Hypertension	0.437	1.131 (0.829 - 1.542)
Diabetes mellitus	0.978	1.005 (0.699 - 1.445)
Hepatitis	0.162	2.514 (0.691 - 9.148)
Current Smoking	0.866	1.034 (0.700 - 1.528)
Blood sampling		
Hemoglobin (g/dL)	0.709	1.019 (0.924 - 1.123)
Platelets (k/ μ L)	0.261	0.999 (0.996 - 1.001)
White blood cell count (k/ μ L)	0.678	1.013 (0.952 - 1.078)
Cholesterol (mg/dL)	0.459	0.998 (0.994 - 1.003)
Triglycerides (mg/dL)	0.017	0.998 (0.996 - 1.000)
HDL (mg/dL)	0.040	1.011 (1.000 - 1.021)
LDL (mg/dL)	0.570	0.999 (0.995 - 1.003)
LDH (IU/L)	0.820	1.000 (0.998 - 1.003)
CRP quantitation (mg/dL)	0.303	0.813 (0.548 - 1.205)
HBsAg positivity	<0.001	2.653 (1.591 - 4.425)
HBsAb positivity	0.547	0.916 (0.690 - 1.218)
HBcAb positivity	0.011	1.475 (1.092 - 1.992)
HCVAb positivity	0.103	0.187 (0.025 - 1.405)

ARM, age related maculopathy = ARM2 + ARM3 + ARM4; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDH, lactate dehydrogenase; CRP, C-reactive protein; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody; HCVAb, hepatitis C antibody; OR, odds ratio; 95% CI, 95% confidence interval.

Table 4. Multivariate Logistic Analysis of Risk Factors for ARM

Variables	ARM		
	Unadjusted model OR (95% CI)	Adjusted model* OR (95% CI)	Reduced form model† OR (95% CI)
Primary independent variable			
HBsAg positivity	1.763 (1.079 - 2.881)	2.555 (1.476 - 4.421)	2.736 (1.588 - 4.714)
Adjustment variable			
Age (yrs)	-	1.135 (1.115 - 1.156)	1.134 (1.114 - 1.154)
Sex	-	1.019 (0.716 - 1.449)	1.090 (0.772 - 1.538)
Monthly income/month	-	1.020 (0.925 - 1.125)	1.023 (0.928 - 1.128)
Education level	-	0.929 (0.800 - 1.078)	0.942 (0.812 - 1.092)
Body mass index (kg/m ²)	-	0.997 (0.942 - 1.055)	
Hypertension	-	1.305 (0.920 - 1.852)	1.239 (0.880 - 1.745)
Current smoking	-	1.172 (0.752 - 1.827)	1.104 (0.712 - 1.713)
CRP quantitation (mg/dL)	-	0.579 (0.302 - 1.113)	-
Triglycerides (mg/dL)	-	0.998 (0.996 - 1.001)	-
HDL (mg/dL)	-	1.005 (0.991 - 1.018)	-

ARM, age related maculopathy = ARM2 + ARM3 + ARM4; BMI, body mass index; HDL, high-density lipoprotein; CRP, C-reactive protein; OR, odds ratio; 95% CI, 95% confidence interval.

*Hosmer and Lemeshow Test: $p = 0.239$.

†Hosmer and Lemeshow Test: $p = 0.260$.

the Chinese population group of the Beijing Eye Study,¹³ nevertheless, the two studies yielded similar estimates of the prevalence of late ARM (0.2% vs. 0.2%). The prevalence rates of early ARM in the age groups of 40 - 49 years, 50 - 59 years, 60 - 69 years, and ≥ 70 years were 1.54%, 2.74%, 3.41%, and 6.31%, respectively, in the Beijing study. In the same study, prevalence rates of late ARM were 0.14%, 0.52%, 0.14% and 1.11%, respectively, in these age groups. These figures are similar to our data (Table 1). The slight between-study difference in prevalence of early ARM might have been due to a population difference, geographic difference (rural vs. urban), ethnic differences between Chinese and Koreans, differences in dietary or nutritional habits, environmental parameters, and difference in the study design.

Several studies^{14-19,22,23} have identified risk factors for ARM, and both population-based studies and case control studies have been carried out. Refractive error,³⁶⁻³⁸ iris color,^{39,40} hypertension and

cardiovascular disease,^{23,24,28,41} smoking,^{20,41-44} and alcohol consumption,⁴⁴⁻⁴⁶ are known risk factors for ARM. In our study, age was significantly associated with estimated early and late ARM prevalence, as expected. When adjustments were made for subject age in univariate analysis, seropositivity for HBsAg and HBcAb, indicating (past or present) infections with hepatitis B, serum levels of HDL and TG all remained significantly associated with ARM (Table 3).

Two previous studies^{47,48} have demonstrated statistically insignificant, but inverse associations between education levels attained and ARM. Although crude analysis showed significant relationships between education level and monthly income and ARM (Table 2), no significant inverse association was noted after age adjustment ($p = 0.582$, OR 0.970, 95% CI 0.868 - 1.083 for education, $p = 0.910$, OR 0.995, 95% CI 0.917 - 1.081 for monthly income).

Also, although smoking has been reported to be

one of risk factors for ARM, our study showed no definite association between smoking and ARM ($p = 0.866$, OR 1.034, 95% CI 0.700 - 1.528). This might have been due to relatively small number of late ARM in our study, which is more likely related with smoking.^{20,42}

One of the most distinct risk factors for ARM found in the present study is the association between hepatitis B and ARM in South Korea. Even after adjusted multivariate analysis for socioeconomic factors such as education level and monthly income in this study, HBsAg ($p < 0.001$; OR 2.736; 95% CI 1.588 - 4.714) and anti HbC antibody ($p < 0.05$; OR 1.475; 95% CI 1.092 - 1.992) were significantly associated with ARM, (Tables 3 and 4). The statistical significance of both HBs antigen and anti HbC antibody with ARM suggest that there is less opportunity than that this association is by chance alone ($1/20 \times 1/20 = 1/400$). The reason why there has been no epidemiologic study about Hepatitis B and ARM was that Hepatitis viral marker has not been included as covariates in previous epidemiologic studies. Since Hepatitis B infection is highly prevalent in South Korea, viral markers were checked in most examinees. Although the prevalence of hepatitis B surface antigenemia has declined because of an effective vaccination program, HBV remains endemic in South Korea. Seropositivity for HBsAg was estimated at 7 - 9% in the 1980s.⁴⁹ It was also reported in 1998 Korean National Health and Nutrition survey that prevalence of HBsAg was 5.1% in males and 4.1% in females, with low prevalence rates in individuals under 20 years old.⁵⁰ There is a biologic plausibility underlying this association. First, HBs Ag is found in subretinal fluids with increased detection rate of antibodies to S-antigen in healthy virus carriers, increasing risk for uveoretinal pathology.^{51,52} This inflammatory process may induce drusen formation. Secondly, molecular mimicry between retinal S-antigen and Hepatitis S antigen^{53,54} can induce cross reactivity which can predispose to uveoretinal inflammation. Furthermore, as viral hepatitis is associated with decreased level of complement C3, C4 and complement factor H related protein 1,⁵⁵ this may activate the alternative complement pathway, thereby increasing the risk of drusen formation.⁵⁶

Associations between ARM and hypertension,

cardiovascular disease,^{23,24,28} serum lipid level,^{14,41} obesity,^{24,27} cardiovascular biomarkers,^{28,57-59} and BMI²⁶ have previously been documented. In our subjects, no significant associations between ARM and hypertension, serum cholesterol level, or cardiovascular biomarker CRP were found after age-adjustment. The serum level of TG was inversely associated with the prevalence of ARM, whereas the serum level of HDL showed a significant positive association. However, the association between low TG level, high HDL level and ARM adjusted for age was not maintained in the adjusted model (Table 4), which was adjusted for age, HBs Ab positivity, gender and hypertension. This could be explained by the positive confounding by one or more of the above risk factors for ARM, although there are some reports to support the association between low TG, high HLD and ARM.^{28,57-59}

Strength of this study is the relatively large number of subjects examined. The protocol was standardized, thereby providing an accurate estimate of the prevalence, and risk factors for ARM in Seoul, Korea. Also, the strength of this study is that socioeconomic factors, cardiovascular risk factors, and hepatitis viral markers were considered for analysis. A limiting factor of the present study is that this is a cross-sectional design which cannot assess the causality. Therefore, prospective data are needed to confirm the issue of ARM causality. Although this data may not represent the general population of South Korea, subjects were those who visited the health examination center for regular check-ups, but not for the treatment of confirmed disease, which may lower the selection bias compared with previous hospital-based studies. Moreover, since there was only small number of subjects with ARM, the power of the study to identify all significant factors may be decreased. Therefore, the results of the present study may be taken as practical evidence for those associations that were statistically significant, but not as a proof for those associations which did not show statistical significance. Also, subjects, in whom a dense cataract or hazy cornea media were considered to be reasons for visual impairment, might additionally have had ARM. This fact might artificially reduce the prevalence figures for ARM.

In conclusion, the single most important risk

factor for ARM in our study, besides age, is seropositivity for HBsAg. However, factors such as current smoking, history of previous smoking, and the level of smoking, in addition to self-reported diagnoses of systemic diseases such as diabetes mellitus and cerebrovascular condition which had previously been reported as risk factors for ARM, did not show statistically significant influences on the prevalence of ARM in this study.

REFERENCES

- Thylefors B, Negrel AD, Pararajasegaram R, Dadzie KY. Global data on blindness. *Bull World Health Organ* 1995;73:115-21.
- Klein BE, Klein R. Cataracts and macular degeneration in older Americans. *Arch Ophthalmol* 1982;100:571-3.
- Klein R, Rowland ML, Harris MI. Racial/ethnic differences in age-related maculopathy. Third National Health and Nutrition Examination Survey. *Ophthalmology* 1995;102:371-81.
- Schachat AP, Hyman L, Leske MC, Connell AM, Wu SY. Features of age-related macular degeneration in a black population. The Barbados Eye Study Group. *Arch Ophthalmol* 1995;113:728-35.
- Cruickshanks KJ, Hamman RF, Klein R, Nondahl DM, Shetterly SM. The prevalence of age-related maculopathy by geographic region and ethnicity. The Colorado-Wisconsin Study of Age-Related Maculopathy. *Arch Ophthalmol* 1997;115:242-50.
- Lim JI, Kwok A, Wilson DK. Symptomatic age-related macular degeneration in Asian patients. *Retina* 1998; 18:435-8.
- Chang TS, Hay D, Courtright P. Age-related macular degeneration in Chinese-Canadians. *Can J Ophthalmol* 1999;34:266-71.
- Tsai SY, Hsu WM, Cheng CY, Liu JH, Chou P. Epidemiologic study of age-related cataracts among an elderly Chinese population in Shih-Pai, Taiwan. *Ophthalmology* 2003;110:1089-95.
- Saw SM, Foster PJ, Gazzard G, Seah S. Causes of blindness, low vision, and questionnaire-assessed poor visual function in Singaporean Chinese adults: The Tanjong Pagar Survey. *Ophthalmology* 2004;111:1161-8.
- Hsu WM, Cheng CY, Liu JH, Tsai SY, Chou P. Prevalence and causes of visual impairment in an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology* 2004;111:62-9.
- Tsai CY, Woung LC, Chou P, Yang CS, Sheu MM, Wu JR, et al. The current status of visual disability in the elderly population of Taiwan. *Jpn J Ophthalmol* 2005; 49:166-72.
- Sivaprasad S, Membrey WL, Sivagnanavel V, Gonzalez JG, Liu DT, Chan WM, et al. Second eye of patients with unilateral neovascular age-related macular degeneration: Caucasians vs Chinese. *Eye* 2006;20:923-6.
- Li Y, Xu L, Jonas JB, Yang H, Ma Y, Li J. Prevalence of age-related maculopathy in the adult population in China: the Beijing eye study. *Am J Ophthalmol* 2006; 142:788-93.
- Smith W, Assink J, Klein R, Mitchell P, Klaver CC, Klein BE, et al. Risk factors for age-related macular degeneration: Pooled findings from three continents. *Ophthalmology* 2001;108:697-704.
- Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. *Ophthalmology* 2000;107:2224-32.
- Miyazaki M, Kiyohara Y, Yoshida A, Iida M, Nose Y, Ishibashi T. The 5-year incidence and risk factors for age-related maculopathy in a general Japanese population: the Hisayama study. *Invest Ophthalmol Vis Sci* 2005;46:1907-10.
- McCarty CA, Mukesh BN, Fu CL, Mitchell P, Wang JJ, Taylor HR. Risk factors for age-related maculopathy: the Visual Impairment Project. *Arch Ophthalmol* 2001; 119:1455-62.
- Buch H, Vinding T, la Cour M, Jensen GB, Prause JU, Nielsen NV. Risk factors for age-related maculopathy in a 14-year follow-up study: the Copenhagen City Eye Study. *Acta Ophthalmol Scand* 2005;83:409-18.
- Clemons TE, Milton RC, Klein R, Seddon JM, Ferris FL 3rd. Risk factors for the incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no. 19. *Ophthalmology* 2005;112:533-9.
- Evans JR, Fletcher AE, Wormald RP. 28,000 Cases of age related macular degeneration causing visual loss in people aged 75 years and above in the United Kingdom may be attributable to smoking. *Br J Ophthalmol* 2005; 89:550-3.
- Tomany SC, Wang JJ, Van Leeuwen R, Klein R, Mitchell P, Vingerling JR, et al. Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. *Ophthalmology* 2004;111:1280-7.
- Chaine G, Hullo A, Sahel J, Soubrane G, Espinasse-Berrod MA, Schutz D, et al. Case-control study of the risk factors for age related macular degeneration. France-DMLA Study Group. *Br J Ophthalmol* 1998;82: 996-1002.
- Hyman L, Schachat AP, He Q, Leske MC. Hypertension, cardiovascular disease, and age-related macular degeneration. Age-Related Macular Degeneration Risk Factors Study Group. *Arch Ophthalmol* 2000;118:351-8.
- van Leeuwen R, Ikram MK, Vingerling JR, Witteman JC, Hofman A, de Jong PT. Blood pressure, atherosclerosis, and the incidence of age-related maculopathy: the Rotterdam Study. *Invest Ophthalmol Vis Sci* 2003; 44:3771-7.
- Schaumberg DA, Christen WG, Hankinson SE, Glynn RJ. Body mass index and the incidence of visually significant age-related maculopathy in men. *Arch*

- Ophthalmol 2001;119:1259-65.
26. Klein BE, Klein R, Lee KE, Jensen SC. Measures of obesity and age-related eye diseases. *Ophthalmic Epidemiol* 2001;8:251-62.
 27. Moeini HA, Masoudpour H, Ghanbari H. A study of the relation between body mass index and the incidence of age related macular degeneration. *Br J Ophthalmol* 2005;89:964-6.
 28. Delcourt C, Michel F, Colvez A, Lacroux A, Delage M, Vernet MH. Associations of cardiovascular disease and its risk factors with age-related macular degeneration: the POLA study. *Ophthalmic Epidemiol* 2001;8:237-49.
 29. Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L. The Wisconsin age-related maculopathy grading system. *Ophthalmology* 1991;98:1128-34.
 30. Klein R, Klein BE, Knudtson MD, Wong TY, Cotch MF, Liu K, et al. Prevalence of age-related macular degeneration in 4 racial/ethnic groups in the multi-ethnic study of atherosclerosis. *Ophthalmology* 2006;113:373-80.
 31. Klaver CC, Assink JJ, van Leeuwen R, Wolfs RC, Vingerling JR, Stijnen T, et al. Incidence and progression rates of age-related maculopathy: the Rotterdam Study. *Invest Ophthalmol Vis Sci* 2001;42:2237-41.
 32. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health* 1989;79:340-9.
 33. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology* 1992;99:933-43.
 34. Leibowitz HM, Krueger DE, Maunders LR, Milton RC, Kini MM, Kahn HA, et al. The Framingham Eye Study monograph: An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973-1975. *Surv Ophthalmol* 1980;24(Suppl):335-610.
 35. Muñoz B, West SK, Rubin GS, Schein OD, Quigley HA, Bressler SB, et al. Causes of blindness and visual impairment in a population of older Americans: The Salisbury Eye Evaluation Study. *Arch Ophthalmol* 2000;118:819-25.
 36. Sandberg MA, Tolentino MJ, Miller S, Berson EL, Gaudio AR. Hyperopia and neovascularization in age-related macular degeneration. *Ophthalmology* 1993;100:1009-13.
 37. Wang JJ, Mitchell P, Smith W. Refractive error and age-related maculopathy: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci* 1998;39:2167-71.
 38. Xu L, Li Y, Zheng Y, Jonas JB. Associated factors for age related maculopathy in the adult population in China: the Beijing eye study. *Br J Ophthalmol* 2006;90:1087-90.
 39. Khan JC, Shahid H, Thurlby DA, Bradley M, Clayton DG, Moore AT, et al. Age related macular degeneration and sun exposure, iris colour, and skin sensitivity to sunlight. *Br J Ophthalmol* 2006;90:29-32.
 40. Nicolas CM, Robman LD, Tikellis G, Dimitrov PN, Dowrick A, Guymer RH, et al. Iris colour, ethnic origin and progression of age-related macular degeneration. *Clin Experiment Ophthalmol* 2003;31:465-9.
 41. Tan JS, Mitchell P, Smith W, Wang JJ. Cardiovascular risk factors and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Ophthalmology* 2007;114:1143-50.
 42. Chakravarthy U, Augood C, Bentham GC, de Jong PT, Rahu M, Seland J, et al. Cigarette smoking and age-related macular degeneration in the EUREYE Study. *Ophthalmology* 2007;114:1157-63.
 43. Khan JC, Thurlby DA, Shahid H, Clayton DG, Yates JR, Bradley M, et al. Smoking and age related macular degeneration: the number of pack years of cigarette smoking is a major determinant of risk for both geographic atrophy and choroidal neovascularisation. *Br J Ophthalmol* 2006;90:75-80.
 44. Arnarsson A, Sverrisson T, Stefánsson E, Sigurdsson H, Sasaki H, Sasaki K, et al. Risk factors for five-year incident age-related macular degeneration: the Reykjavik Eye Study. *Am J Ophthalmol* 2006;142:419-28.
 45. Liu S, Lee IM, Linson P, Ajani U, Buring JE, Hennekens CH. A prospective study of physical activity and risk of prostate cancer in US physicians. *Int J Epidemiol* 2000;29:29-35.
 46. Moss SE, Klein R, Klein BE, Jensen SC, Meuer SM. Alcohol consumption and the 5-year incidence of age-related maculopathy: the Beaver Dam eye study. *Ophthalmology* 1998;105:789-94.
 47. Goldberg J, Flowerdew G, Smith E, Brody JA, Tso MO. Factors associated with age-related macular degeneration. An analysis of data from the first National Health and Nutrition Examination Survey. *Am J Epidemiol* 1988;128:700-10.
 48. The Eye Disease Case-Control Study Group. Risk factors for neovascular age-related macular degeneration. *Arch Ophthalmol* 1992;110:1701-8.
 49. Jang MK, Lee JY, Lee JH, Kim YB, Kim HY, Lee MS, et al. Seroepidemiology of HBV infection in South Korea, 1995 through 1999. *Korean J Intern Med* 2001;16:153-9.
 50. Lee DH, Kim JH, Nam JJ, Kim HR, Shin HR. Epidemiological findings of hepatitis B infection based on 1998 National Health and Nutrition Survey in Korea. *J Korean Med Sci* 2002;17:457-62.
 51. Friberg TR, Williamson D. Hepatitis B surface antigen in human subretinal fluid. *Am J Ophthalmol* 1983;95:712-3.
 52. Slepova OS, Kushnir VN, Zayseva NS, Titarenko ZD, Dumbrava VA. Clinical and immunological signs of retinal lesions and possibilities of their correction by drugs in patients with chronic diffuse liver diseases of viral etiology and carriers of Australia antigen. *Vestn Oftalmol* 1994;110:27-9.
 53. Singh VK, Kalra HK, Yamaki K, Abe T, Donoso LA, Shinohara T. Molecular mimicry between a uveitopathogenic site of S-antigen and viral peptides. Induction of experimental autoimmune uveitis in Lewis rats. *J Immunol* 1990;154:1282-7.

54. Shinohara T, Singh VK, Tsuda M, Yamaki K, Abe T, Suzuki S. S-antigen: from gene to autoimmune uveitis. *Exp Eye Res* 1990;50:751-7.
55. Gangadharan B, Antrobus R, Dwek RA, Zitzmann N. Novel serum biomarker candidates for liver fibrosis in hepatitis C patients. *Clin Chem* 2007;53:1792-9.
56. Yates JR, Sepp T, Matharu BK, Khan JC, Thurlby DA, Shahid H, et al. Complement C3 variant and the risk of age-related macular degeneration. *N Engl J Med* 2007;9;357:553-61.
57. Vine AK, Stader J, Branham K, Musch DC, Swaroop A. Biomarkers of cardiovascular disease as risk factors for age-related macular degeneration. *Ophthalmology* 2005; 11:2076-80.
58. Klein R, Klein BE, Jensen SC, Mares-Perlman JA, Cruickshanks KJ, Palta M. Age-related maculopathy in a multiracial United States population: the National Health and Nutrition Examination Survey III. *Ophthalmology* 1999;106:1056-65.
59. van Leeuwen R, Klaver CC, Vingerling JR, Hofman A, van Duijn CM, Stricker BH, et al. Cholesterol and age-related macular degeneration: is there a link? *Am J Ophthalmol* 2004;137:750-2.