Age-Related Macular Degeneration in An Iranian Population

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Abstract

***Purpose*:** To determine the prevalence and determinants of age-related macular degeneration (AMD) in a 40-64 year old Iranian population

***Methods*:** In a cross-sectional study, 6,311 people were randomly selected from Shahroud. For all participants, visual acuity, refraction, slit-lamp examination and fundus photography were conducted under pupil dilation.

***Results*:** Results of this study are based on analysis of 4,387 high quality photographs. The prevalence of AMD in this study was 4.7% (95% confidence interval (CI): 4.1-5.4). Multiple logistic regression analysis revealed that only older age [odds ratio (OR)=1.07] and hyperopia (OR=1.12) significantly correlated with AMD. Associations with biometric components and spherical equivalent were studied in another model and older age (OR=1.08), male sex (OR=1.54), and ocular axial length (OR=0.66) significantly correlated with AMD.

***Conclusion*:** AMD prevalence in this population was lower compared to Western countries and higher in comparison to East Asian countries. In agreement with other studies, age strongly correlated with AMD. Regarding the correlation between AMD and ocular axial length; the incidence is more likely to occur in people with short axial lengths.

***Keywords*:** Age-related Macular Degeneration, Cross-Sectional Study, Middle East Region, Prevalence

Iranian Journal of Ophthalmology 2014;26(4):203-11 © 2014 by the Iranian Society of Ophthalmology

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Received: February 19, 2015
Accepted: April 9, 2015

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Introduction

According to the latest report by the World Health Organization, age-related macular degeneration (AMD) is responsible for 5% of global blindness and the third leading cause of blindness after cataract and glaucoma.[1] Reports in recent years indicate that AMD is the leading cause of visual impairment and blindness in developed countries.[2-5] In the past two decades, several studies have reported the prevalence and risk factors of AMD around the world.[6-30] Due to the high prevalence of this retinal conditionin in old ages, specially after the age of 60, more than half of the over 60-year-old population experience AMD in some countries.[8,25,31]

These patients tend to have a lower quality of life because AMD impairs distant and near vision, and thus affects their ability to read and perform daily tasks.[10,12] Most epidemiologic studies of AMD concern Western and East Asian countries and reports from the Middle East are scarce.[3-5,7-9,11,18,20,24-34] Iran is one of the densely populated countries in the Middle East, and the prevalence of AMD in the Tehran Eye Study has been reported.[35] However, other studies in Iran have shown that the prevalence of blindness and visual impairments are relatively high in some regions and certain age groups.[36-38] Failure to report the prevalence of AMD by age in the Tehran Eye Study limits our knowledge about AMD in older Iranians. Although AMD risk factors such as blood pressure, smoking, etc. are well known, no study has included these risk factors in Iran.

The population in Iran is aging, and the lack of information about AMD risk factors among middle-age Iranians tempted us to estimate the prevalence and determinants of AMD in such a population. Since information is generally rare for the Middle East Region, our results can be helpful in this regard as well.

Methods

The present report is part of the first phase of the Shahroud Eye Cohort Study which was conducted cross-sectionally in the urban population of Shahroud during 2009 and 2010.

The detailed methodology of the study has been published.[39] In brief, the target population of the study was 40 to 64 year old residents of the city. Using multistage cluster sampling, 6,311 people were selected from 300 randomly selected clusters in the nine zones of Shahroud. Then, study interviewers invited households to participate in the study. Upon enrollment, the study was explained to each respondent and all participants signed informed consent forms before commencing the interview. The study was approved by the Ethics Committee of Shahroud University of Medical Sciences. The interview questionnaire collected data on demographics, occupation, medical history, and history of medication and smoking. Then, optometry and ophthalmic exams were done in two stages before and after pupil dilation.

Examinations before inducing pupil dilation included the vision test and non-cycloplegic refraction. Uncorrected distance and near visual acuity were measured using logMAR charts, and autorefraction was done using the Topcon AR 8800 before testing corrected visual acuity. Cycloplegic refraction was performed for all those who had no contraindication for cycloplegic agents. As for ophthalmic exams, slit-lamp biomicroscopy and measurements of intraocular pressure were done before inducing pupil dilation, while clinical lens opacities grading, slit-lamp assessment of vitreous opacities, and fundus exams with direct and indirect ophthalmoscopy were done under pupil dilation.

Fundus photography

All participants with sufficient cooperation underwent fundus photography under pupil dilation using the NIDEK AFC-230 Fundus Camera according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol.[40] In non-diabetics, we acquired three standard photos of the first three ETDRS fields and two stereo photos of the first two ETDRS fields. The center of the first field was the examinee's disc, and focus is set on the peripapillary vessels. The center of the second field was the fovea, and the center of the third field was one disc diameter temporal to the macula focusing on the fine vessels around the macula. In diabetics, standard ETDRS 7-field photography was done for both eyes. Photos were reviewed by three retinal subspecialists who were given patients'

information regarding their blood pressure, history of diabetes, and blood glucose levels. In this study, AMD diagnosed based on clinical examination and cases of AMD were coded as 35.3 according to International Classification of Diseases (ICD) 10. Eventually, the presence of AMD was determined through two dimensional photographs and other findings, to the discretion of a retina subspecialist.

Exclusion criteria

For this report, we excluded subjects who had no fundus photo, had unclear photos due to cataracts, or lacked cooperation during the photography session.

Statistical analysis

In this study, we report the prevalence of AMD in percentages and 95% confidence intervals (CI). The effect of cluster sampling on the 95% CI was adjusted for. We used multiple logistic regression models to examine relationships. To compare biometric components between cases with and without AMD, we used the independent *t*-test, and eventually, we used a multiple logistic regression model to examine the association between AMD, as an outcome, and biometric components, as independent variables.

Ethical Issues

The Ethics Committee of Shahroud University of Medical Sciences approved the study protocol, which was conducted in accord with the tenets of the Helsinki Declaration. All participants signed a written informed consent.

Results

Of the 6,311 invitees, 5,190 participated in the study, 4,797 cooperated in taking fundus photos, and 4,387 who had high quality photos were used in the analyses. The mean age of the participants was 50.3±6.1 years (40 to 64) and 58.3% (2,559) were female. In the studied sample, 4.7% (95% CI: 4.1-5.4) had AMD in at least one eye. Table 1 presents the prevalence of AMD by gender and age groups. The prevalence of AMD was 4.2% in women and 5.5% in men; according to logistic regression, the prevalence of AMD was significantly higher in men (OR=1.34, 95% CI:1.007-1.78; p=0.045). As demonstrated in table 1, the prevalence of AMD significantly increases from 2.2% in the 40-44 year age group to 8.5% among 60-64 year olds; according to logistic regression, the odds of AMD increased by 1.07 for each year of aging. After the age of 60, however, the prevalence of AMD decreases in men while it continues to increase linearly in women. The prevalence of AMD in the over 50 year old population was 6.3% (95% CI: 5.3-7.3). In smokers and non-smokers, AMD prevalence rates were 6.3% (95% CI: 4.2-8.6) and 4.5% (95% CI: 3.8-5.2), respectively; the relation between AMD and smoking was not significant in the simple logistic regression model (OR=1.44, 95% CI: 0.97-2.15; p=0.071). The associations between AMD prevalence and systolic (p=0.112) or diastolic blood pressure (p=0.580) were not significant either. Logistic regression indicated that AMD prevalence decreased at higher body mss index (BMI) with borderline significance (OR=0.97, 95% CI 0.94-1.00; p=0.058). Examining AMD associations with age, sex, smoking, systolic blood pressure, diastolic blood pressure, BMI, spherical equivalent, and diabetes in a multiple regression model showed that only older age and hyperopic spherical equivalent correlated significantlywith the prevalence of AMD. Results of this model are summarized in Table 2.

Iris color had no significant impact on the prevalence of AMD (p=0.724). Table 3 shows the mean reading of ocular biometric components in cases with and without AMD. As demonstrated, all components, except the anterior chamber depth, significantly differed between these two groups.

AMD associations with ocular biometric components were studied in a multiple logistic regression model. In this model, the outcome variable was having or not having AMD, and we assessed its relation to the ocular axial length, vitreous chamber depth, lens thickness, keratometry, and spherical equivalent after adjusting for age and sex. This model showed that only older age (OR=1.08), male gender (OR=1.54) and axial length (OR=0.66) significantly correlated with AMD.

Table 1. The prevalence (95% confidence interval) of age-related macular degenerationin the 40-64 year old population of Shahroud, Iran

	Women	Men	Total
Age group	%(95%CI)	%(95%CI)	%(95%CI)
40-44	2.2 (1.0-3.3)	2.4 (0.6-4.2)	2.2 (1.3-3.2)
45-49	3.3 (1.9-4.6)	4.6 (2.7-6.6)	3.8 (2.6-5.0)
50-54	4.2 (2.5-5.8)	4.7 (2.8-6.5)	4.4 (3.2-5.6)
55-59	5.5 (3.3-7.7)	10.3 (7.1-13.6)	7.8 (5.9-9.7)
60-64	11.1 (6.7-15.5)	5.9 (2.8-9.0)	8.5 (5.8-11.3)
Total	4.2 (3.4-5.0)	5.5 (4.4-6.6)	4.7 (4.1-5.4)

CI: Confidence interval

Table 2. Association of age-related macular degeneration with studied variables according to the multiple logistic regression model

	OR (95%CI)	p-value
Age (year)	1.07 (1.04-1.11)	<0.001
Sex (men/women)	1.04 (0.69-1.55)	0.859
Smoking (yes/no)	1.27 (0.75-2.16)	0.374
Systolic blood pressure (mm/Hg)	1.01 (1.0-1.02)	0.196
Diastolic blood pressure (mm/Hg)	0.99 (0.97-1.01)	0.391
Body Mass Index	0.97 (0.94-1.01)	0.132
Spherical equivalent (diopter)	1.12 (1.03-1.21)	0.009
Diabetic (yes/no)	0.59 (0.31-1.13)	0.110

OR: Odds ratio, CI: Confidence interval

Table 3. The association between age-related macular degeneration and the studied biometric components

	Mean (95%CI) no-AMD	Mean (95%CI) AMD	p-value
Axial length (mm)	23.18 (23.15-23.21)	22.89 (22.75-23.03)	<0.001
Anterior chamber depth (mm)	2.63 (2.62-2.65)	2.59 (2.53-2.65)	0.116
Vitreous chamber depth (mm)	15.75 (15.72-15.78)	15.46 (15.34-15.58)	<0.001
Keratometry (diopter)	43.50 (43.45-43.56)	43.90 (43.66-44.15)	0.002
Lens thickness (mm)	4.27 (4.26-4.28)	4.32 (4.27-4.37)	0.033
Spherical equivalent (diopter)	-0.04 (-0.09-0.02)	0.33 (0.11-0.55)	<0.001

AMD: Age-related macular degeneration

Discussion

In this study, we demonstrated the prevalence of AMD in an Iranian population through a population-based study with a large sample size of 40-64 year old people. The study, however, had some limitations without which the report would be much more remarkable. Some of the important limitations include lack of 3-D images and OCT findings, angiography, and failure to determine the type of AMD and its degree of progression. Nonetheless, since there is no statistical information about AMD in the older age groups in Iran, our findings provide valuable information about this disorder. As demonstrated, the prevalence of AMD was 4.7%, ranging from 2.2% in the 40-44 year age group to 8.5% in the ≥60 year old age group. Results of different studies are summarized in table 4; AMD prevalence varies considerably from 2% to over 60%, and the prevalence in our study is in the mid-range. In comparing these studies, the most important factor is the age of participants. Compared to Asian countries,[18,20,30,41] AMD prevalence was higher in our study, while we saw a lower prevalence rate compared to studies such as the Beaver Dam Eye Study[34] and some European studies[29] (Table 4). Some studies have suggested that the prevalence of AMD is

generally lower in Asian countries and higher in Western countries, and table 4 appears to confirm these suggestions. Overall, although AMD rate is not high in the 40-50 year old population in Iran, it must be noted that over 6% of the over 50 year olds are affected by AMD; this group is at risk of visual impairment, and thus, preventive measures to stop the progression of AMD are of great importance for these patients. In the multivariable model, age was one of the variables that showed significant correlation with AMD. This was quite obvious,as all studies on AMD risk factors have found age to be the leading risk factor for this disorder.[9-11,18,20] In a study on population aged 90 years and older, the prevalence of AMD was more than 70%.[27] However, seeing an AMD rate of 2% among 40-44 year olds points to the fact that the elderlies are not the only ones at risk of AMD, and the middle aged might need to be screened for this disorder. AMD has been reported in other studies on the young as well.[16,20]

In our study, the prevalence of AMD was higher in men with borderline significance, and we found no significant inter-gender difference after adjusting for other variables. Other studies are inconclusive on the relationship between gender and AMD.[11,13,17,20,22,24,29,42-46] While some studies suggest there is no significant correlation, there seems to be stronger evidence in favor of higher AMD prevalence in men. For example, El Matri et al,[45] Nakata et al,[8] Varma et al,[24] Klein et al,[16] and Moon et al[13] have demonstrated a higher prevalence in men while few studies (Owen et al[47] and Pokharel et al[48]) suggest higher rates in women. Occupational exposures, specially exposure to sunlight, seem to be one of the main reasons for a higher rate of AMD in men.[49] Nonetheless, the correlation between AMD and sex needs further assessment.

Smoking has been found correlated with AMD in many studies.[10,11,13,16,18,20,47-50] In our study, the correlation between smoking and AMD showed borderline significance (p=0.071) and was insignificant after adjusting for confounding factors. Few studies agree with us that AMD and smoking are not significantly correlated like the one in Taiwan.[7] Willeford et al[50] have conducted a study on the effect of smoking in the development of AMD; they believe that in the extensive oxidative environment of the retina, smoke constituents act as strong pro-oxidants which can bring about changes in the retina. They have also discussed the important role of genetic polymorphic changes in regards to susceptibility to oxidative damage by cigarette smoke. Thus, the lack of association between AMD and smoking in our study could be due to genetic differences among people.

Blood pressure and AMD showed no significant correlation in our study. The relationship has been investigated by many studies. In agreement with our results, the study in India,[14] Korea,[51] Beaver Dam,[16] and Taiwan found correlation between AMD and blood pressure.[12,13] However, there are studies that suggest otherwise.[52-55] Hyman et al[55] demonstrated a correlation between AMD and systolic blood pressure and found a higher rate of AMD among patients consuming anti-hypertensive medication. Cougnard-Gregoire et al[56] has shown the long-term effect of high blood pressure on AMD. In a meta-analysis, Chakravarthy et al[57] examined results of five cohort studies, three case-control studies, and seven cross-sectional studies, and none of their analyses showed any correlation between AMD and blood pressure. However, according to three case-control studies, there was a weak correlation between late AMD and blood pressure. In this regard, there are more studies that confirm this observation, but unfortunately, we were not able to classify early and late AMD separately, and could not examine this correlation. While it is suggested that hypertensive vasoconstriction can interfere with blood delivery to the choroid and retina, and lead to AMD, further interventional studies are needed to determine the true relationship between AMD and blood pressure.

Iris color and AMD showed no correlation in our study, while some studies have found one. In the Blue Mountain Eye Study,[58] people with brighter iris had a greater chance of AMD. Bright eye colors were associated with AMD in studies by Hyman et al,[55] Weiter et al,[59] Frank et al[60] and Mitchell et al.[58] Although we found no significant correlation, it appears that less pigmentation in the iris can cause more sunlight passing onto the retina, and no pigmentation in the retina can make it more

susceptible to damage. This might explain the higher rate of AMD in western countries, where people have bright iris colors, compared to African and Asian countries.

Results of our study pointed to a higher chance of hyperopia among cases of AMD. Similarly, Lavanya et al[61] showed a higher rate of hyperopia among AMD patients; this has been confirmed by studies in Central India[62] and the study by You et al.[63] Where AMD appears to develop more commonly among hyperopic people. This relationship has been reported in a case-control study as well.[64] A recent review has examined the relationship between AMD and refractive errors. Results of this meta-analysis point to a correlation between hyperopia and AMD, and a reverse correlation between myopia and AMD.[65] However, this review article[65] and some other studies suggest that the axial length is shorter in cases of AMD. In our observations, the spherical equivalent did not correlate with AMD after adjusting for the axial length and the correlation between hyperopia and AMD was due to the relationship between axial length and AMD. This has been suggested in other studies as well.[12,61,66] Bokeret al attribute the correlation between AMD and hyperopia to reduced choroidal blood flow in eyes with shorter axial length, as an effect of a thicker sclera, which can progress the development of choroidal neovascularization.[67] Several explanations have been proposed in this regard. For example, reduced choroidal blood flow in shorter eyes reduces the exchange of nutrients and metabolic products across the retinal pigment epithelium which can appear as excess material such as Drusen. Further experimental studies are needed to examine this theory. Another possibility that needs investigation is a genetic link between AMD and hyperopia or short axial length.

Table 4. Prevalence of age-related macular degeneration in other studies worldwide

	Age (year)	Sample size	Early	Late	Overall
Japan[8]	50-59	5595	16.1	0.027	
Kenya[25]	≥50	3304	11.2	1.2	
India[10]	≥50	19140			1.38
Singapore[12]	≥40	3337	4.45	0.34	
India[12]		3422	5.80	0.16	
UK[47]	≥50			2.4	
Cologne[27]	≥90	150			59
China[41]	≥40	1910			7.3
Malaysia[41]	≥40	645			7.7
India[41]	≥40	617			5.7
China[20]	>30	6581	3.0	0.1	
China[20]	>50	4049	4.7	0.2	
Spain[29]	≥65	2132			3.4
Italy[23]	>60	885			62.7
United Kingdom[6]	65-83	934	9.2	0.5	
India (rural central)[28]	≥40	4542	6.1	0.2	
India (rural central)[28]	≥50		8.2	0.2	
India (rural central)[28]	≥60		8.3	0.6	
USA[32]	>40	5553		0.8	6.5
Iceland[26]	≥66	5272	12.4		3.3
Thailand[30]	>50	10788	2.7	0.3	3
USA (Oklahoma Indians)[14]	48-82	986	34.4	0.81	35.2
Beaver Dam[16]	21-34	168	2.4		
Beaver Dam[16]	65-84	174	9.8		
Sri Lanka[9]	≥40	1375	3.82	1.70	4.72
Japan[11]	≥35	1625	3.5	0.5	
Singapore (Malay)[18]	40-80	3265	4.9	0.70	
Taiwan[7]	≥65	1058	9.2	1.9	
Greenland[42]	≥60	695			52.3
Greece[22]	≥60	2554			2.5
USA (6 communities)[17]	45- to 85				2.4 (black), 4.2 (Hispanic), 4.6 (Chinese), 5.4 (white)
USA (Arizona)[19]	≥50	2780		0.5	
USA (Los Angeles Latino eye)[24]	≥80	5875			8.5
Australia[15]	50+	2522			13

Finally, one of the most important limitations of this study was lack of 3-dimensional photographs and retinal thickness data which can reduce the sensitivity of AMD diagnosis.

Conclusion

We demonstrated the prevalence of AMD in an Iranian population through a study with a considerable sample size. The prevalence rate of AMD in our study was lower compared to Western countries and relatively high compared to East Asian countries. In agreement with previous reports, age strongly correlated with AMD. We found that the association between hyperopia and AMD was due to the correlation between AMD and short axial length which continued to remain significant even after eliminating confounding factors. In this regard, preventive measures may help delay the development of AMD in people with short axial lengths.

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