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Original Research Article

Prevalence and Predictors of Age Related Macular Degeneration in the Population of Punjab: North Indian Age Related Macular Degeneration Epidemiology and Molecular Genetic Study (NI-ARMEMS)

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ABSTRACT

Background: Age related macular degeneration (AMD) is an ocular disease that is threatening elderly population of Punjab for vision impairment and blindness. Comprehensive understanding of the susceptible factors still remains to be explored in this region.
Objective: To examine the risk variables which are independently associated with the risk of AMD along with the investigation of its prevalence in the population of Punjab.
Methods: A case-control study by design involved 416 subjects (cases; 219, controls; 197) of age ranging from 45 to 75 years. Various risk factors were investigated for their role in consenting and confirmed AMD subjects along with controls.
Results: In the univariate full factorial regression analysis, advancing age (≥66years), being a woman, diastolic blood pressure (DBP) (>80mmHg), cigarette smoking, alcohol drinking, body mass index (BMI) (23-29.9Kgm^{-2} and ≥30Kgm^{-2}), sedentary life style, total cholesterol (>200mg/dl), low density lipoproteins (>100mg/dl), high density lipoproteins (≥40mg/dl), non-vegetarian diet and positive family history were found to be risky determinants. Multivariable stepwise regression analysis revealed age ≥66 years, DBP > 80mmHg, alcohol drinking and smoking as independent predictors for the risk of AMD.
Conclusion: Considerable prevalence of dry AMD (20.5%) is evident in the population of Punjab which is mediated independently by age (≥66 years), DBP (>80 mmHg), alcohol drinking and smoking.

Key Words: Prevalence of Age related macular degeneration, Independent predictors, Punjab, North India

INTRODUCTION

Age-related macular degeneration (AMD) is a spectrum of age related changes of macula which starts with the presence of few small drusen (subretinal lipid and protein containing deposits) to the most advanced stages with abnormal neovascularization accompanied by vision loss. [1] AMD is recognized by two forms. Dry or atrophic macular degeneration, in which atrophy of retinal pigment epithelium (RPE) results in untreatable progressive vision loss. Wet or neovascular macular degeneration is characterized by intra retinal invasion of blood vessels from the choroid, which causes retinal bleeding and dense macular scars. The most prevalent form of AMD in India is dry or atrophic AMD. [2]

WHO estimated that 20-25 million people are suffering from AMD, out of which 8 million people have severe visual impairment. [3] According to the projections

by WHO, 196 million people will have AMD in 2020, which will rise to 288 million by 2040, if remains untreated and unmanaged. [4] This dreadful disease alone is responsible for 8.7 percent of global blindness and its impact is severe in the developing countries, especially in India. According to three significant reports by Aravind Comprehensive Eye Study, [5] Andhra Pradesh Eye Study [6] and India Eye Study, [7] prevalence of AMD ranges between 1.4 to 1.8 percent within India.

India has the second highest population of the world accounting for 23.5 percent of global blindness [8] which suggests that effective risk factor surveillance and preventive policies are required. Moreover, these risk factors may vary according to diverse eating patterns, dissimilar ethnicities, different environments and heterogeneous work cultures. In depth understanding of significant risk factors and their *modus operandii* will usher us to develop efficient strategies for its better care and management. Albeit, scientists are mulling over the pathological causes and consequences of AMD, investigation of region specific risk correlates are still inadequate to draw some conclusions. The information on the prevalence of AMD and its affiliated predictors has not been examined hitherto in Northwest region of India which has been hypothesized to investigate in the present cross sectional study.

MATERIALS AND METHODS

The present case control study comprised of 416 subjects who had come for regular eye checkups in the ophthalmology outpatient departments (OPDs) of various hospitals of Punjab including Rajindra Government Medical College and Hospital (GMCH), Patiala, G.S Randhawa Eye Hospital and Lasik Centre, Patiala, Hans Eye Hospital, Patiala, J.P Eye Hospital, Zirakpur, Dhami Eye Hospital, Ludhiana and Kalia Eye Hospital, Ferozepur. These hospitals provide specialized state of the art facilities to referral cases and cater to almost entire region of Punjab. Total 1135 subjects were screened out of which, 119 subjects were excluded because they refused to participate in the study. Subjects (n= 105) who were aged less than 45 years, non-residents of Punjab, were also excluded from the study. Also, subjects (n=495) suffering from other associated diseases such as cataract, glaucoma, wet AMD, central serous chorioretinopathy, retinal detachment, cardiovascular disease, renal disease and diabetes were found to be ineligible for the participation in study. The final representative data included 416 participants who underwent detailed fundus examination (Fundoscopy) by the vitreo-retinal specialist. 219 subjects were included as cases who were diagnosed positive for AMD on the basis of drusen size (≥63 micron) and 197 subjects were diagnosed free from AMD, thus taken as controls. A written consent was obtained from all the subjects prior to the participation in the study. The study was approved by the institutional ethical committee and strictly followed the rules of Helsinki declaration.

Statistical Analysis

Data values are indicated as absolute numbers, mean±SD and percentages in the parenthesis. Statistical difference between groups was examined using chi-square for categorical variables and student's *t*-test for continuous variables. A linear regression analysis was applied (JLM procedure) to determine the association between risk variables and AMD (dependent variable). Variables which showed linear relationship ($P<0.05$) with the dependent variable were further incorporated in multivariate backward stepwise regression analysis to identify the independent predictors. Insignificant variables were excluded to avoid any noise in the data and linearity diagnostic was done to determine variance inflation factor (VIF). The significance was checked at 5 percent level however, for multiple comparisons, Bonferroni correction was applied.

RESULTS

Table 1. General characteristics of study participants

VARIABLES	Subjects with AMD (n=219)	Subjects without AMD (n=197)	Total (n=416)	P value
AGE (years)				
45-55	31 (14.16)	47 (23.86)	78 (18.75)	0.04
56-65	68 (31.05)	56 (28.43)	124 (29.81)	
66-75	120 (54.79)	94 (47.72)	214 (51.44)	
MEAN AGE(years)	58.74± 8.76	55.91±8.11	57.40±8.57	<0.001
GENDER				
Men	147 (67.12)	101 (51.27)	248 (59.62)	0.05
Women	72 (32.88)	96 (48.73)	168 (40.38)	
BLOOD PRESSURE (mmHg)				
Systolic	139.54±34.61	118.75±23.46	131.67±28.52	<0.001
Diastolic	75.21±20.61	72.36±26.45	73.58±23.52	0.22
EDUCATION LEVEL				
Matriculation	86(39.27)	75 (38.07)	161 (38.70)	0.97
Secondary	91 (41.55)	83 (42.13)	174 (41.83)	
Graduation or Above	42 (19.18)	39 (19.80)	81 (19.47)	
SOCIOECONOMIC STATUS				
High income	51 (23.29)	46 (23.35)	97 (23.32)	0.90
Middle income	97 (44.29)	91 (46.19)	188 (45.19)	
Low income	71 (32.42)	60 (30.46)	131 (31.49)	
SMOKING STATUS				
Non-smokers	65 (29.68)	100 (50.76)	195 (46.88)	<0.001
Smokers	116 (52.97)	51 (25.89)	144 (34.62)	
Ex-smokers	38 (17.35)	46 (23.35)	77 (18.51)	
ALCOHOL DRINKING				
Non-drinkers	69 (31.51)	106 (53.81)	205 (49.28)	<0.001
Drinkers	106 (48.40)	44 (22.34)	130 (31.25)	
Ex-drinkers	44 (20.09)	47 (23.86)	81 (19.47)	
BODY MASS INDEX(Kgm^{-2})	28.56±3.64	26.75±4.35	27.41±3.42	<0.001
PHYSICAL ACTIVITY				
Active	87 (39.73)	119 (60.41)	206 (49.52)	<0.001
Sedentary	132 (60.27)	78 (39.59)	210 (50.48)	
LIPID LEVELS (mg/dl)				
Total cholesterol	188.34±31.13	180.11±30.22	184.26±30.65	0.01
Low density lipoproteins	149.12±46.7	147.52±45.9	148.37±46.7	0.66
Triglycerides	151.19±72.9	145.65±71.4	148.41±71.8	0.40
High density lipoproteins	47.21±45.2	43.26±33.9	45.23±4.1	<0.001
IRIS COLOR				
Dark	211 (96.35)	187 (94.92)	398 (95.67)	0.48
Light	8 (3.65)	10 (5.08)	18 (4.33)	
EATING HABITS				
Vegetarian	63 (28.77)	76 (38.58)	139 (33.41)	0.03
Non-vegetarian	156 (71.23)	121 (61.42)	277 (66.59)	
FAMILY HISTORY				
Yes	76 (34.70)	19 (9.64)	95 (22.84)	<0.001
No	60 (27.40)	82 (41.62)	142 (34.13)	
Unknown	83 (37.90)	96 (48.73)	179 (43.03)	
SUNLIGHT EXPOSURE				
<4 hour/day	59 (26.94)	78 (39.59)	137 (32.93)	0.01
4-8 hour/day	56 (25.57)	43 (21.83)	106 (25.48)	
>8 hour/day	104 (47.49)	76 (38.58)	173 (41.59)	

AMD: Age related macular degeneration, Significance level P<0.05

The present study involved 219 subjects with AMD and 197 subjects without AMD confirmed on the basis of dilated pupil fundoscopy (size of drusen). 248 subjects (59.62percent) were men and 168 (40.38percent) were women. Mean age of the AMD subjects was 58.74±8.76 and 55.91±8.11 for subjects without AMD. Prevalence of AMD in the subjects ranging in age from 45-75 years was observed to be 20.5percent. Number of AMD patients increased substantially from 45 years onwards and maximum number of subjects with AMD fall in the 66-75 years age group. Higher levels of systolic blood pressure (SBP) (139.54±34.61) were observed in AMD subjects in comparison to controls (118.75±23.46) and the differences were found to be statistically significant (P<0.001) however, no differences were observed for diastolic blood pressure (DBP) between cases and controls. There were no

significant differences for education level and socio-economic status between both the groups. It was observed that higher number of smokers and alcohol drinkers suffered from AMD in comparison to controls (P<0.001). Significant dissimilarities (P<0.001) were evident for body mass index (BMI) between both the groups, whereby AMD subjects were obese (28.56±3.64 Kgm^{-2}) in comparison to controls (26.75±4.35 Kgm^{-2}). Considerable differences (P<0.001) were observed in relation to physical activity. More subjects having sedentary life style (60.27percent) were present in AMD group in comparison to lesser subjects having sedentary life style (39.59percent) in control group. Levels of total cholesterol (TC) were observed to be higher in cases (188.34±31.13) in comparison to controls (180.11±30.22) whereas higher levels of high density lipoproteins (HDLs) (47.21±45.2) were observed in cases with respect to lower levels in controls (43.26±33.9). These differences were found to be significant statistically (P<0.001). Iris color did not show any differences between cases and controls however, eating habits showed considerable differences (P=0.03). It is noticeable that those subjects who suffered from AMD had positive family history in comparison to those where no family history was found (P<0.001). It is clearly discernable that those subjects had more chances of having AMD who were exposed for more than 8 hours of sunlight per day than those subjects who had experienced lesser sunlight exposure (P=0.01) (Table 1).

Univariate regression analysis with full factorial model showed that subjects >56 years of age were at higher risk of macular degeneration (OR 1.84, 95%CI 1.04-3.27, P=0.05) which increased in the subjects having age group 66-75 years (OR 1.94, 95%CI 1.14-3.28, P=0.01). Being a woman was observed to be doubly susceptible for the risk of AMD (OR 2.54, 95%CI 1.67-3.86, P<0.001). Some variables such as systolic blood pressure, education level and socio-economic status did not impact the AMD pathology. Diastolic blood pressure augmented 2 fold higher risk of AMD (OR 2.04, 95%CI 1.24-3.35, P=0.006), smoking increases the risk by 3.5 fold (P<0.001) and drinking alcohol increased the risk by 3.7 times (P<0.001). Univariate analysis suggested obesity to be a risky proposition whereby, BMI>23Kgm^{-2} enhanced the risk of AMD substantially (OR 1.99, 95%CI 1.30-3.04, P=0.002) which increased further in the subjects having BMI ≥30Kgm^{-2} (OR 2.51, 95%CI 1.38-4.55, P=0.004). Subjects having sedentary lifestyle were at 2.31 times higher risk of AMD (OR 2.31, 95%CI 1.56-3.43, P<0.001). Higher levels of total cholesterol (>200mg/dl), low density lipoproteins (LDLs) (>100mg/dl) and high density lipoproteins (≥40mg/dl) enhanced the AMD risk substantially (P<0.05). Higher triglyceride levels and light iris color failed to show any significant effect for AMD however, higher sunlight exposure (>4 hours/day) and non-vegetarian diet conferred considerable risk for AMD (P<0.05) (Table 2).

Collinearity statistics revealed variance inflation factor (VIF) less than three (VIF=1.80) which showed that there was no significant interaction between independent variable and the analysis is free from multicollinearity. All the univariate risk variables were analyzed by multivariable logistic regression analysis in the backward stepwise pattern to identify those variables which are independently predicting the risk of AMD (Table 3). In this analysis, age ≥66 years emerged as an independent risk predictor which increased the risk by 5 times (OR 5.34, 95%CI 1.87-7.05, P=0.009). It was observed that every unit increase of age increased the risk of dependent variable (AMD risk) by 1.76±0.53 times (β±SE). Diastolic blood pressure >80mmHg appeared to be risky variable which augmented approximately 6 fold higher risk of AMD (OR 6.42, 95%CI 2.17-8.12, P=0.002). Those subjects who drank alcohol were observed to be at approximately 8 times higher risk of AMD

(OR 7.88, 95%CI 2.15-7.86, P=0.005) than those individuals who were non-drinkers. Cigarette smoking appeared to be the strongest independent risk factor which increased the risk of AMD by 8 times (OR 8.11, 95%CI 1.03-8.11, P<0.001) than those who did not smoke. β value suggested that every unit increase of smoking enhanced the AMD risk by 2.57±0.23 times (β±SE).

Table 2. Disease association analysis for the risk of age related macular degeneration

VARIABLES	Subjects with AMD (n=219)	Subjects without AMD (n=197)	OR (95% CI), P value
AGE (years)			
45-55	31 (14.16)	47 (23.86)	Referent
56-65	68 (31.05)	56 (28.43)	1.84 (1.04-3.27), P=0.05
66-75	120 (54.79)	94 (47.72)	1.94 (1.14-3.28), P=0.01
GENDER			
Men	147 (67.12)	101 (51.27)	Referent
Women	72 (32.88)	96 (48.73)	2.54 (1.67-3.86), P<0.001
BLOOD PRESSURE: SBP			
≤120mmHg	131 (59.82)	112 (56.85)	Referent
>120mmHg	88 (40.18)	85 (43.15)	0.89 (0.60-1.31), P=0.61
BLOOD PRESSURE: DBP			
≤80mmHg	162 (73.97)	168 (85.28)	Referent
>80mmHg	57 (26.03)	29 (14.72)	2.04 (1.24-3.35), P=0.006
EDUCATION LEVEL			
Matriculation	86 (39.27)	75 (38.07)	Referent
Secondary	91 (41.55)	83 (42.13)	0.96 (0.62-1.47), P=0.92
Graduation or above	42 (19.18)	39 (19.80)	0.94 (0.55-1.60), P=0.92
SOCIECONOMIC STATUS			
High income	51 (23.29)	46 (23.35)	Referent
Middle income	97 (44.29)	91(46.19)	0.96 (0.59-1.57), P=0.97
Low income	71 (32.42)	60 (30.46)	1.07 (0.63-1.81), P=0.91
SMOKING STATUS			
Non-smokers	65 (29.68)	100 (50.76)	Referent
Smokers	116 (52.97)	51 (25.89)	3.50 (2.22-5.51),P<0.001
Ex-smokers	38 (17.35)	46 (23.35)	1.27 (0.75-2.16), P=0.45
ALCOHOL DRINKING			
Non-drinkers	69 (31.51)	106 (53.81)	Referent
Drinkers	106 (48.40)	44 (22.34)	3.70 (2.33-5.89), P<0.001
Ex-drinkers	44 (20.09)	47 (23.86)	1.44 (0.86-2.40), P=0.21
BMI (Kg/m^2)			
<23	69 (31.51)	97 (49.24)	Referent
23-29.9	109 (49.77)	77 (39.09)	1.99 (1.30-3.04), P=0.002
≥30	41 (18.72)	23 (11.67)	2.51 (1.38-4.55), P=0.004
PHYSICAL ACTIVITY			
Active	87 (39.73)	119 (60.41)	Referent
Sedentary	132 (60.27)	78 (39.59)	2.31 (1.56-3.43), P<0.001
LIPID LEVELS (mg/dl)			
Total cholesterol			
≤200mg/dl	147 (67.12)	161 (81.73)	Referent
>200mg/dl	72 (32.88)	36 (18.27)	2.19 (1.39-3.46), P=0.001
Low density lipoproteins			
≤100mg/dl	44 (20.09)	55 (27.92)	Referent
>100mg/dl	175 (79.91)	142 (72.08)	1.54 (0.98-2.43), P=0.008
Triglycerides			
≤150mg/dl	74 (33.79)	80 (40.61)	Referent
>150mg/dl	145 (66.21)	117 (59.39)	1.34 (0.90-2.00), P=0.18
High density lipoproteins			
<40mg/dl	91 (41.55)	143 (72.59)	Referent
≥40mg/dl	128 (58.45)	54 (27.41)	1.88 (1.25-2.84), P=0.004
IRIS COLOR			
Dark	211 (96.35)	187 (94.92)	Referent
Light	8 (3.65)	10 (5.08)	0.71 (0.27-1.83), P=0.64
EATING HABITS			
Vegetarian	63 (28.77)	76 (38.58)	Referent
Non-vegetarian	156 (71.23)	121 (61.42)	1.56 (1.03-2.34), P=0.04
FAMILY HISTORY			
No	76 (34.70)	19 (9.64)	Referent
Yes	60 (27.40)	82 (41.62)	5.47 (2.99-9.99), P<0.001
Unknown	83 (37.90)	96 (48.73)	1.18 (0.76-1.84), P=0.53
SUNLIGHT EXPOSURE			
<4 hour/day	59 (26.94)	78 (39.59)	Referent
4-8 hour/day	56 (25.57)	43 (21.83)	1.72 (1.02-2.90), P=0.05
>8 hour/day	104 (47.49)	76 (38.58)	1.81 (1.15-2.84), P=0.01

Table 3. Multivariable backward stepwise regression analysis to determine factors independently associated with AMD.

Variables	β ± SE	OR	95% CI	P
Age ≥ 66 years	1.76±0.53	5.34	1.87-7.05	0.009
DBP > 80mmHg	1.90±0.75	6.42	2.17-8.12	0.002
Alcohol drinking	2.38±0.82	7.88	2.15-7.86	0.005
Smoking	2.57±0.23	8.11	1.03-8.11	<0.001

DBP: diastolic blood pressure, AMD: Age related macular degeneration, Significance level P<0.05

DISCUSSION

The present study has revealed that the prevalence of AMD is 20.5 percent in the population of Punjab. Almost 12 studies have been conducted to deduce the prevalence of AMD in different regions of India whereby, the range of AMD prevalence is observed to be from 1.8 percent in Karnataka to 47.8 percent in Maharashtra. Out of these 12 studies, 10 studies have depicted the prevalence of AMD in South Indian population, [9-18] whereas 2 studies are conducted in the population of North India. [18,19] This wide range of heterogeneity in the prevalence of AMD prompts that different sampling methods, diverse diagnostic criteria and several associated risk factors are responsible.

With the advancing age, there is an attenuation of functional retinal pigment epithelium (RPE) and melanin content in retina. Heavy degradation of the RPE cells is evident in septuagenarians and octogenarians. [20] Degradation and death of these RPEs begin to accumulate as lipofuscin and drusen. Hence, it is clearly believed that vision impairment in AMD progressively worsens with advancing age. [21] According to National Eye Institute (NEI), Maryland, USA, the prevalence of AMD is 2.1 percent in age group 40-49 years, whereas, it increases significantly to 35 percent in the subjects over 80 years of age. [22] It has been confirmed that age specific prevalence of AMD in quinquagenarians is 0.4 percent, which increases to 0.7 percent in sexagenarians, 2.3 percent in septuagenarians and further to 12 percent in octogenarians. [23] The present study in conformity with the above mentioned reports has revealed that advancing age is a significant risk factor for AMD which increases after every decade.

There are conflicting reports regarding female gender to be more susceptible for the risk of AMD. According to National Institute of Health (NIH), USA, two third of the worst affected AMD patients are women. [24] The present study has also revealed that females are at 2.5 times higher risk of AMD than males which is endorsed by the results of Age Related Macular Degeneration Study (AREDS), which has demonstrated that females are doubly vulnerable than males. [24]

It is consensus among scientists that smoking is very risky for the propagation of all ocular diseases especially glaucoma and AMD. The Rotterdam study has observed that smokers are at 6.6 fold higher risk of AMD than non-smokers and this number increases further with a number of pack years smoked. [25] Some other studies have also confirmed that relative risk of developing AMD is 5 times higher in subjects consuming 20-39 pack years. [26,27] Present study has revealed that it increases the risk of AMD by 3.5 percent in smokers than non-smokers and ex-smokers.

Several studies have documented that BMI > 30Kgm^{-2} is associated with early and neovascular AMD. [28-30] Primarily, excessive body fat adversely affects transport and deposition of carotenoids from blood to macula, which eventually reduces the level of macular pigments in retina. This reduction of pigments cannot prevent retina from oxidation hence, causes disruption of macula. In the present study, BMI levels > 23Kgm^{-2} upto 29Kgm^{-2} and even higher levels (≥30Kgm^{-2}) are significantly associated with the risk of AMD which justifies the fat related worst outcome of retinal degeneration.

It is controversial that whether alcohol drinking is associated with AMD risk or not. Reykjavik Eye Study (RES) [31]

has suggested protective role of alcohol but when consumed in moderate amount, whereas, another study has observed higher AMD risk in subjects who consume higher amount of both beer and alcohol. [32] Present study has also observed that alcohol drinkers are at higher risk of AMD (OR 3.7, P<0.001).

Although there are several factors found to be univariately associated with the risk of AMD but after adjusting the effects of confounders, present study has revealed that advancing age (≥66 years), diastolic blood pressure (>80mmHg), smoking and alcohol drinking are independent predictors for the risk of AMD in the population of Punjab.

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