AGE RELATED MACULAR DEGENERATION IN PATIENTS ATTENDING AMERICAN EYE AND RETINA CENTER IN Erbil GOVERNORATE FROM DECEMBER 2015 TO DECEMBER 2016.

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ABSTRACT

Background: Age-related macular degeneration (AMD) is the cause of sever vision loss and legal blindness in adult over 60 years. It's rate increases with age. It affects 14%-24% of the U.S. population at aged 65-74 years. Age-related macular degeneration causes 5% of global blindness and 1% of visual impairment.

purposes: To assess the prevalence , vision status, and risk factors of age-related macular degeneration in Erbil Governorate, IRAQ .

Patients and methods: A population–based cross sectional study carried out in American eye and retina center in Erbil Governorate, IRAQ from December 2015 to December 2016. A total of 1100 participants aged 60 years and above participated in health interviews, physical examinations and comprehensive ophthalmologic assessment including ocular cohorant tomography and fundus photography. There were 185 patients diagnosed with Age-related macular degeneration, of whom 113 (61%) were female. Surveys were used for patients age, gender, race, smoking, sunlight exposure, body mass index, hypertension, hyperlipidemia, diabetes mellitus (and type of treatment), and family history of AMD. Results: From the total 1100 participants, there were 185 patients aged 60 years and above with a mean age of 69.5 years diagnosed with AMD, of whom 113 (61%) were female. The overall prevalence of AMD from a total was 16.8%.The prevalence of early AMD among the one hundred eighty five AMD patients was estimated at 72 (38.9%), and the prevalence of late AMD was estimated at 113 (61.1%), including a prevalence of 65 (35.1%) for dry AMD type and 48 (25.9%) for wet AMD type. 99 (53.5%) had AMD in their right eyes, 80 (43.2%) in their left eyes, and 6 (3.2%) in both eyes; among them 4 (2.1%) had bilateral early AMD and 2 (1.1%) had bilateral late AMD. The prevalence of early AMD increased with age, from 15 (8.1%) in patients aged 60-64 years to 22 (11.9%) among patients aged 75-79 ($p<0.05$), the prevalence rates of late AMD, dry and wet AMD followed a similar trend. When analyzed by sex, the prevalence rates of early AMD was estimated at 32 (17.3%) in male patients and 40 (21.6%) in female patients while late AMD was 41 (22.2%) in male patients and 72 (38.9%) in female patients. The prevalence rate of blindness was 29 (15.7%) and the prevalence rate of vision impairment was 71 (38.4%). The prevalence of blindness was 0 among patients with early AMD and 29 (15.7%) among those with late AMD ($P=0.05$ and $p <0.05$, respectively). The prevalence of vision impairment was 10 (5.4%) among patients with early AMD and 61 (33.0%) among

those with late AMD (P <0.05 and p <0.05, respectively). Age was strongly associated with the prevalence of early and late AMD (P <0.05). Risk factors with a p value < 0.1 for the presence of early and late AMD included female sex, Caucasian race, hypertension, increased BMI, smoking, sunlight light exposure and positive family history. While those with p value > 0.1 included diabetes mellitus and hyperlipidemia.

Conclusion: The prevalence of early AMD in Erbil population was similar to the prevalence of pooled Asian and Western populations. The risk factors in the present study are older age, female sex, Caucasian race, smoking, sunlight exposure, increased BMI, hypertension and family history. Diabetes mellitus and hyperlipidemia were not significant risk factors and there may be other variables. A larger sample size may produce different and better results.

Keywords: Age-related macular degeneration; Risk factors; Sunlight exposure; Family history; ERBIL ; Cross- sectional study.

INTRODUCTION

Age related macular degeneration (AMD) is a progressive eye condition affecting as many as 15 million Americans and millions more around the world. The disease attacks the macula of the eye, where our sharpest central vision occurs. This is the vision we use to drive, read, recognize faces and perform daily tasks. AMD does not cause complete blindness, only central blindness. It spares the peripheral vision (around the edges), leaving only dim images or black holes at the center of vision. AMD is the number one leading cause of sever vision loss and legal blindness in adult over 60 years in the U.S. It escalates with age. It affects 14%-24% of the U.S. population aged 65-74 years and 35-40% of people aged 74 years or more have the disease. In other words, more than one person in three can develop signs of age related macular degeneration, with over 200,000 new cases diagnosed every year [1].

Age-related macular degeneration (AMD) causes 5% of global blindness and 1% of visual impairment [2, 3]. The prevalence of AMD has been estimated at 3.5% to 13.2% for early AMD and 0.3% to 1.9% for late AMD [4, 5]. Several risk factors have been associated with AMD including age, smoking, and hyperopia [6, 7]. In the early stages of AMD, deposits of drusen are observed in the retina between the retinal pigment epithelium and choroid in the macular region [8]. The disease progresses to more advanced stages, leading to 2 types of late AMD: geographic atrophy of the retinal pigment epithelium and photoreceptor cells (dry AMD) and aberrant choroidal neovascularization (wet AMD), which leads to central vision loss [8]. AMD is the leading cause of blindness among the elderly in developed countries with prevalence of late AMD at 1.2-1.7% [9, 10]. While AMD has generally been a greater issue in developed countries, studies from India suggest prevalence (1.4-1.8%) for late AMD as the population continues to age in developing countries [11, 12]. China, on the other hand, has a considerably lower prevalence as confirmed by the Beijing Eye Study [13].

AMD was considered untreatable until argon laser treatment and, later, photodynamic therapy was applied [14]. Today, intravitreal anti-vascular endothelial growth factor (VEGF)

therapy is the preferred treatment, which has decreased the annual incidence of visual impairment due to AMD by 32-50% in some developed countries [14, 15]. Anti-VEGF therapy is effective, although it does not restore vision to previous levels in the majority of subjects treated, and it requires multiple injections that are very costly [16].

Over the past 2 decades, efforts have been made to identify the associations between AMD and risk factors with varied results, but it is generally agreed that older age, female gender, Caucasian race, and family history of AMD are significant unmodifiable risk factors to developing the disease and/or progressing to late AMD and smoking might be a modifiable risk factor. An algorithm was developed to predict which subjects with early/intermediate AMD are most likely to progress to late dry/wet AMD, by assessing the following variables:6 genetic variants, age, sex, education, baseline AMD grade, smoking, Body Mass Index (BMI), and nutritional supplement use [17]. Multivariate risk models were next modified to additionally include time varying rates of progression of up to 12 years and macular drusen size in both eyes at baseline to follow the disease progression in the Age-Related Eye Disease Study [18]. Of the 2,937 patients who participated in study, 819 progressed to late AMD during the 12-year follow-up period. Age, smoking, BMI, genetic variants, advanced AMD in one eye and drusen size in both were independently associated with progression [18]. In Latin America, AMD treatment is very costly, and little research has been done on the disease, approximately 8.3% of the population of Latin America and the Caribbean is 65 years or older [19, 20]. The objectives of this study , to assess prevalence, vision status, risk factors and protective factors for the development and progression of AMD in Kurdistan of Iraq –Erbil governorate.

PATIENTS AND METHODS

A population based cross-sectional study carried out in American eye and retina center in Erbil Governorate, IRAQ during the period from December 2015 to December 2016. From the total 1100 participants participated in this study there were 185 patients aged 60 years and above with the mean age of 69.5 years diagnosed with AMD. In the survey, patients answered questions, when applicable, on their age, gender, race, systemic hypertension (defined as systolic blood pressure $\geq$130), cholesterol, diabetes (Type I or Type II and type of treatment), smoking, sunlight exposure and family history of AMD. Weight, height, and abdominal diameter were measured at the time of the survey to calculate body mass index (BMI). The comprehensive ophthalmologic examination was conducted after the interview which include visual acuity testing using the Snellen chart, automatic refractometry, Goldmann applanation tonometry, slit-lamp biomicroscopy and retinal examinations. The retinal examinations were performed by direct and indirect ophthalmoscope, ocular coherent tomography, nonmydriatic fundus photograph of each eye. The photographs were taken with a digital fundus camera in a dark room to allow for physiological dilation of pupils. In cases where the nonmydriatic photograph was of insufficient quality for grading due to media opacity or a small pupil, a mydriatic fundus photograph was taken after achieving maximal pupillary dilation, using 1.0% tropicamide and 10% phenylephrine.

The classification of AMD in each eye based on the standard classification of the disease, and also performed an Amsler grid test on each eye. Early AMD if they met one of the following criteria :

(1) the presence of soft , indistinct drusen or reticular drusen (2) the presence of hard or soft distinct drusen with pigmentary abnormalities in the absence of signs of late AMD [21]. Retinal pigmentary abnormalities were graded as depigmentation or hyperpigmentation. Advanced non-neovascular AMD was classified as presence of drusen and geographic atrophy extending to the center of the macula. Advanced neovascular AMD was classified as presence of choroidal neovascularization and any of its potential sequelae, including subretinal fluid, lipid deposition, hemorrhage, retinal pigment epithelium detachment, and a fibrotic scar [21].

Risk analysis was performed .Race was categorized as Caucasian, black and others. BMI was calculated by dividing weight in kilograms by the square of height in meters and categorized as being normal/slightly underweight (>18.5 kg/m2 and <25 kg/m2), overweight (25-29.9 kg/m2), and obese or morbidly obese (≥30 kg/m2) [23]. Systemic hypertension was categorized as present or not. Diabetes was categorized as present (Type I or Type II) or not. Smoking was categorized as current smoker or not. Sunlight exposure was classified as an ordinal 2-level factor (light to moderate: 0-2 hours per day of sunlight exposure and moderate to heavy: +6 hours per day). AMD was categorized as present or not for each eye. AMD type was categorized as none, early ,late Dry and late Wet.

RESULTS

A total of 1100 participants aged 60 years and above participated in this study, there were 185 patients aged 60 years and above with a mean age of 69.5 years diagnosed with AMD, of whom 113 (61%) were female. The overall prevalence of AMD from a total was 16.8%. The prevalence of early AMD among the one hundred eighty five AMD patients was estimated at 72 (38.9%), and the prevalence of late AMD was estimated at 113 (61.1%), including a prevalence of 65 (35.1%) for dry AMD type and 48 (25.9%) for wet AMD type. fig 1

99 (53.5%) had AMD in their right eyes, 80 (43.2%) in their left eyes, and 6 (3.2%) in both eyes. Of the patients with AMD in their right eyes, 42 (22.7%) had early AMD type, 44 (23.8%) had late dry AMD type, and in 13 (7.1%), had late wet AMD type. The comparable figures for left eyes were: 26 (14.1%), 19 (10.3%), 35 (18.9%), respectively. Both eyes were: 4 (2.2%), 2 (1.1%), and 0, respectively. fig 2

The prevalence of blindness was 29 (15.7%) and the prevalence of vision impairment was 71 (38.4%). All blind patients had late AMD in either eye, 17 (9.2%) had dry AMD type and 12 (6.5%) had wet AMD type, among patients with vision impairment, 10 (5.4%) had early AMD in one or both eyes, 48 (25.9%) had late dry AMD and 13 (7.1%) had late wet AMD type in one or both eyes. fig3

Aging is the greatest risk factor; Therefore, the prevalence rates of early , dry and wet AMD were 15 (8.1%), 14 (7.6%) and 7 (3.8%) among patients aged 60-64 years, the prevalence rates increased to 22 (11.9%), 18 (9.7%) , and 17 (9.2%) among patients aged 75-79 years. Therefore, the prevalence rates of early AMD increased with age and the prevalence rates of late AMD followed a similar trend. fig 4

When analyzed by gender, the prevalence rates of early AMD was estimated at 40 (21.6%) in female patients and 32 (17.3%) in male patients .The prevalence rates of late

AMD was 72 (38.9%) in female patients and 41 (22.2%) in male patients. fig 5

With regard to demographics of all patients, 133 were Caucasian (71.9%), 38 black (20.5%), and 14 of other races (7.56%). Among 133 Caucasian patients 45 (24.3%) had early AMD and 88 (47.6%) had late AMD. Therefore, Caucasian race represent a significant risk factor. fig 6

149 patients (80.5 %) currently smoked, among them 58 (31.3%) had early AMD and 91 (49.2%) had late AMD, therefore smoking considered a potential risk factor for AMD progression particularly with late AMD type. fig 7

The majority of patients received moderate-to-heavy sunlight exposure 148 (80%), while only 37 (20%) of patients had light-to-moderate sunlight exposure. table 1

BMI that indicated they were slightly underweight or of normal weight 45 (24.3%), 50 (27%) were overweight, and 90 (48.6%) were obese or morbidly obese, the majority of patients 140 (75.7%) were overweight and obese while 45 (24.3%) were slightly underweight or of normal weight this indicated that increase BMI considered a strong risk factor for progression of AMD. table 2

Seventy percent reported on the surveys that they had systemic hypertension (n=130). 28 (15%) was early AMD while 102(55%) was late AMD. Therefore, systemic hypertention considered a significant risk factor for AMD progression particularly with late AMD. table 3

Fourty six percent reported on the surveys that they had hyperlipidemia (n=86), among them 33 (17.8%) associated with early AMD and 53 (28.6%) associated with late AMD. Therefore, no significant association between hyperlipidemia and AMD except, wet type in which 29 (15.7%) associated with hyperlipidemia and 19 (10.3%) not associated. table 4

89 patients reported to have diabetes (48.1%), of whom 15 controlled their diabetes through diet (8.10%), 44 through oral drugs (23.78%), and 30 with insulin (16.21%),among them 37 (18%) associated with early AMD and 52 (28%) associated with late AMD, therefore diabetes mellitus in this study not represent a significant risk factor. table 5

122 patients (65.9%) had a family history of AMD, among them 54 (29%) had early AMD and 68 (36.8%) had late AMD, while those that had no family history or did not know 63 (43 %), therefore positive family history considered a potential risk factor particularly with late AMD. table 6

Interpretation of the main risk factors shows that it is dominated by higher sunlight exposure and a family history of AMD. Other risk factors include systemic hypertension and smoking. Black race lowers the risk of getting AMD. As expected, aging shows relationship with progression to more severe AMD. Higher BMI, however, appears to be a significant risk factor in AMD progression.

DISCUSSION

The estimated prevalence rates of early and late AMD from a total 1100 participants were 6.5% and 10.3%, respectively. The prevalence rates of early AMD were consisted with those estimated for the United States population in 2005 to

2008 (6.5%) [22], and the pooled Indian population (6.3%) [23], as well as those for pooled Asian population (6.8%) [24]. While the prevalence rates of late AMD were higher than those estimated for United States population in 2005 to 2008 (0.8%) [22], and the pooled Asian population (0.56%) [24]. These indicated that a similar prevalence rates of early AMD are observed across different ethnic groups, including the Asian, and Western populations while our estimates for late AMD were higher than previous studies. The higher prevalence rates of late AMD in this study in comparative to previous studies might be related to life span of participants as well as increase risk factors.

Blindness is defined as visual acuity of less than 3/60 (20/400, 1.3 log Mar) in the better eye with best possible correction. Vision impairment is defined as visual acuity of less than 6/18 (20/60, 0.5 Log Mar) and higher than 3/60 (20/400, 1.3) in the better eye with best possible correction [3]. In this study the prevalence of blindness and visual impairment were 15.7% and 38.4% respectively, the prevalence of blindness was higher than the study held in Iran 7.3% % [25]. And lower than Rotterdam study 37% [26]. While the prevalence of visual impairment was higher than Beijing eye study 2% [27]. And lower than the Rotterdam study 48% [26]. The visual acuity was normal in 62 (33.5%) patients with early AMD and 38 (20.5%) patients with late wet AMD, these patients with late wet AMD was on intravitreal injection of anti VEGF and regular follow-up.

The prevalence of all forms of AMD increased significantly with age. The prevalence of early and late AMD increased steadily from the age of 60 years, approaching a peak ≥ 75 years as observed in other studies [5, 24]. The prevalence rates of late AMD were higher than early AMD among all age groups , this might suggest that cumulative senile changes are associated with development of late AMD includes a progressive degeneration of photoreceptors and underling retinal pigmented epithelium (RPE) in the macula region of the retina. An older age was the significant risk factor for progression to more sever AMD.

This study correlated with several studies has shown that women have a higher prevalence rate than men for late AMD [4, 28]. Whereas other studies reported no significant association between sex and early or late AMD [13, 29, 30]. The higher prevalence rates of AMD in women related to longer female life span as well as hormonal or cerebrovascular changes [28]. But the sex differences in AMD have not been clearly elucidated.

In this study we find a significantly increased prevalence of AMD in Caucasian patients compared with black patients, in agreement with some previous studies [31, 32]. But not others [33, 34].

Cigarette smoking in our study represent a significant risk factor, this consisted with the Beaver Dam Eye Study in which smoking considered the single most important modifiable environmental risk factor for development of all forms of AMD.(36) Cigarette smoking has been considered a strong risk factor for the development of late AMD in many large studies [6, 29, 30, 35]. While some studies have observed an association between smoking and early AMD [30]. In this study smoking were associated more with late AMD. This might imply a cumulative effects of smoking for the development of late AMD. These effects included cigarette smoke tar contains

numerous pro-oxidant compounds within the quinone family leads to sub-RPE deposit formation [37]. Nicotine is an attractive candidate molecule to explain an association of smoking with wet AMD. It has been shown to be mitogenic for vascular endothelial cells and smooth muscle pericytes, to reduce apoptosis of vascular endothelial cells, and to induce the formation of capillary tubes [39]. The immediate clinical implications of these findings are that we must continue to impress upon our patients that smoking is not only a significant risk factor for cancer ,heart disease and pulmonary disease, but that it is the leading modifiable risk factor for the leading cause of blindness in patients older than 50 years of age .

Sunlight exposure considered a significant risk factor in this study. This consisted with a Canadian study that considered sunlight exposure to be a possible risk factor [10]. While a study carried out in the South of France, which used ambient solar radiation to test for an association of more sunlight exposure with AMD, did not conclude that there was an effect [40]. It has been demonstrated that retinal lipofuscin is a photo–inducible generator of reactive oxygen species and this may translate into cell damage via several mechanisms. The position of lipofuscin in the retinal pigmented epithelium within the lysosome implies that irradiated lipofuscin is liable to cause oxidative damage to either the lysosomal membrane or the lysosomal enzymes [45].

Higher BMI seemed to increase the risk. Another study found that a greater BMI, waste circumference, and waist to hip ratio increased the risk for progression to late AMD [41].

The association between hypertension and AMD was observed in some study [23]. But not in others [42]. The Rotterdam study suggested elevated SBP is a risk factor for AMD [43]. In the current study, SBP was associated with late AMD. Several hypotheses suggesting that atherosclerosis causes accumulation of lipids and an increase in choroidal vascular resistance as well as the functional impairment of the retinal pigment epithelium have been proposed for this association [43].

In our study high serum HDL not represent a significant risk factor unlike others studies that
associated with the presence of any AMD type [16, 17, 18].

Our study indicates no significant relationship between diabetes and late AMD , this not agreed with cross sectional study that suggested hyperglycemia probably affects the function and structure of the retinal pigmented epithelium, Bruchs membrane and choroidal circulation thus increase the risk of AMD [44].

For family history, the results are significant and suggest that many of these patients may indeed have a family history of AMD. It is, therefore, very important that greater attention in ERBIL Governorate be given to raising awareness of AMD and its risks not only with patients, but with their families, who should be informed of the association between family history and AMD. These results and recommendations were confirmed by a case-control study in the UK, which found that family history was associated with a 12-fold increase in the odds for disease [8]. The previously mentioned Canadian study determined that family history, obesity, and smoking were significant risk factors, and a lighter colored

iris (and sun exposure) was a possible factor [10].

In conclusion, this is the first study of the prevalence and significant risk factors of each AMD type in Erbil Governorate, IRAQ. The prevalence of early AMD in Erbil population was similar to the prevalence of pooled Asian and Western populations. The risk factors in the present study are older age, female sex, Caucasian race, smoking, sunlight exposure, increased BMI, hypertension and family history. The sample size was small; a larger sample size with more participating regional eye care programs would perhaps provide a broader perspective to the risk factors of AMD in Erbil. A future study in ERBIL or other governorate that uses a larger sample may produce different, stronger, and/or better results.Also, the present study recommended stop smoking, reduce body weight, wear sunglass, and control blood pressure and serum cholesterol by exercise and diet restriction, eat a lot of omega three fatty acid.

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Sunlight exposure	Early AMD %	Late AMD		Total
		Dry AMD %	Wet AMD %	
Light to moderate	9(4.9)	12(6.5)	16(8.6)	37(20.0)
Moderate to heavy	63(34.0)	53(28.6)	32(17.3)	148(80.0)
Total	72(38.9)	65(35.1)	48(25.9)	185

BMI Kg/m2	Early AMD %	Late AMD		Total
		Dry AMD %	Wet AMD %	
Normal	39(21.1)	5(2.7)	1(0.5)	45(24.3)
Overweight	13(7.0)	23(12.4)	14(7.6)	50(27.0)

Table 1 The relationship between sunlight exposure and AMD severity

Obese	20(10.8)	37(20.0)	33(17.8)	90(48.6)
Total	72(38.9)	65(35.1)	48(25.9)	185

Hypertension	Early AMD %	Late AMD		Total
		Dry AMD %	Wet AMD %	
Yes	28(15.1)	54(29.2)	48(25.9)	130(70.3)
No	44(23.8)	11(5.9)	0(0.0)	55(29.7)
Total	72(38.9)	65(35.1)	48(25.9)	185

Table 2 The relationship between BMI and AMD severity

Table 3 The relationship between hypertension and AMD severity

Diabetes mellitus	Early AMD %	Late AMD		Total
		Dry AMD %	Wet AMD %	

Table 4 The relationship between hyperlipidemia and AMD severity

Hyperlipidemia	Early AMD %	Late AMD		Total
		Dry AMD %	Wet AMD %	
Yes	33(17.8)	24(13.0)	29(15.7)	86(46.5)
No	39(21.1)	41(22.2)	19(10.3)	99(53.5)
Total	72(38.9)	65(35.1)	48(25.9)	185

Yes	37(20)	27(14.6)	25(13.5)	89(48.1)
No	35(18.9)	38(20.5)	23(12.4)	96(51.9)
Total	72(38.9)	65(35.1)	48(25.9)	185

Table 5 The relationship between diabetes mellitus and AMD severity

Table 6 The relationship between family history and AMD severity

Family history	Early AMD %	Late AMD		Total
		Dry AMD %	Wet AMD %	
Yes	54(29.2)	40(21.6)	28(15.1)	122(65.9)
No	18(9.7)	25(13.5)	20(10.8)	63(34.0)
Total	72(38.9)	65(35.1)	48(25.9)	185

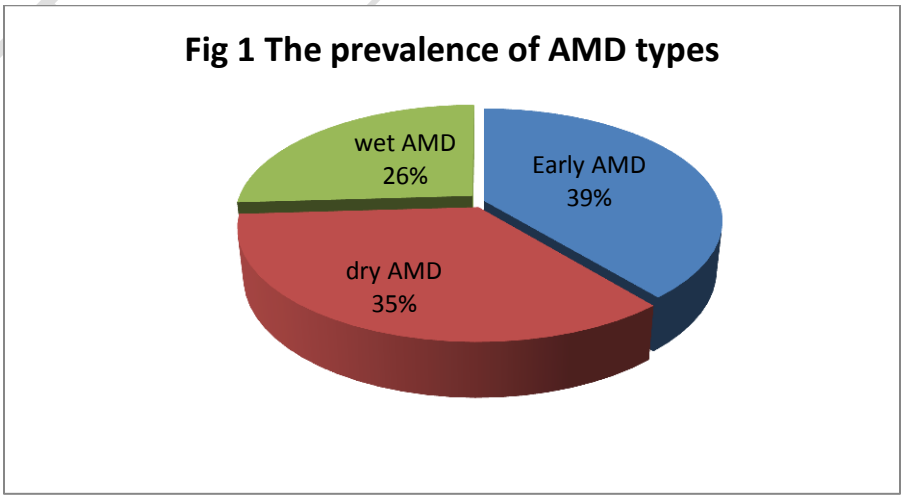
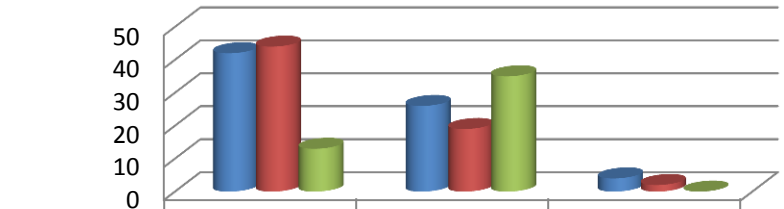
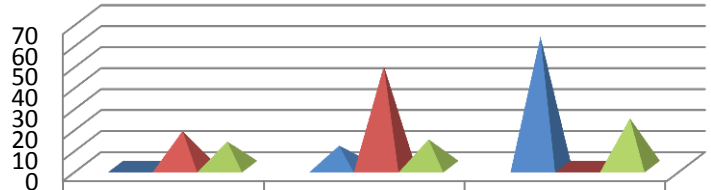


Fig 2 The prevalence of AMD types in each eye



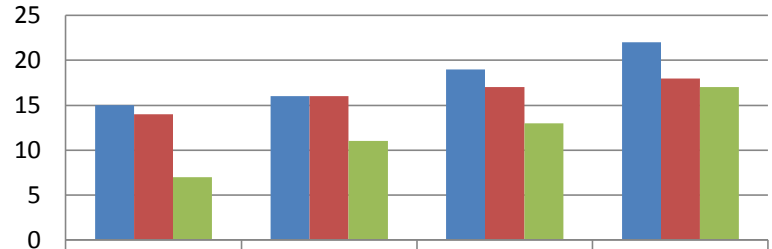
	Right eye	left eye	bilateral
Early AMD	42	26	4
dry AMD	44	19	2
wet AMD	13	35	0

Fig 3 The relationship between vision status and AMD severity



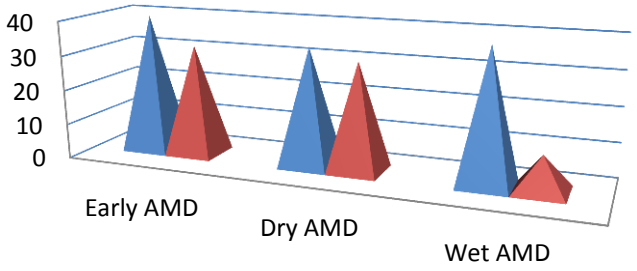
	Blindness	visual impairement	without visual impairement
Early AMD	0	10	62
dry AMD	17	48	0
wet AMD	12	13	23

Fig 4 the relationship between aging and AMD severity



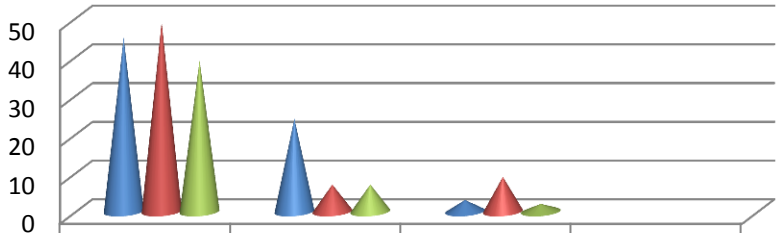
	60-64	65-69	70-74	75-79
Early AMD	15	16	19	22
Dry AMD	14	16	17	18
Wet AMD	7	11	13	17

Fig 5 the relationship between gender and AMD severity



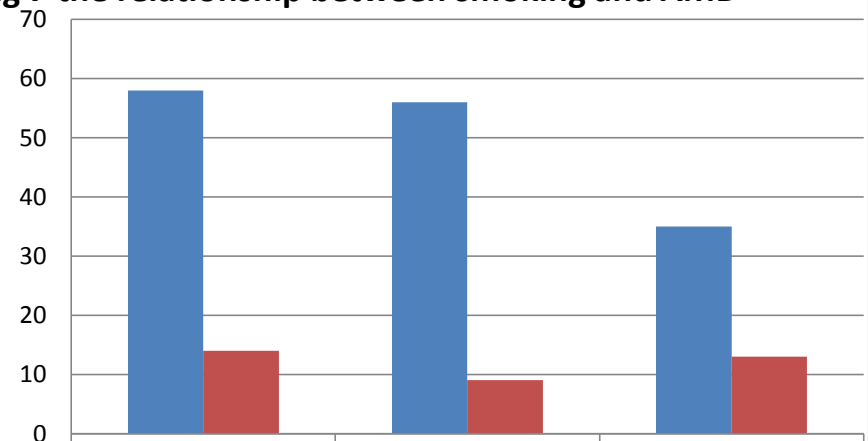
	Early AMD	Dry AMD	Wet AMD
Female	40	34	38
Male	32	31	10

Fig 6 the relationship between race and AMD severity



	Caucasian	Black	Others	
Early AMD	45	24	3	
Dry AMD	49	7	9	
Wet AMD	39	7	2	

Fig 7 the relationship between smoking and AMD



	Early AMD	dry AMD	wet AMD
Smoking	58	56	35
No smoking	14	9	13