

## DIABETES AND OTHER RISK FACTORS IN PATIENTS WITH AGE-RELATED MACULAR DEGENERATION

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### Abstract

**Background and aims:** Our aim was to evaluate the association between the potential risk factors and the different stages of age-related macular degeneration (AMD) in a population aged 52-85 years. **Material and methods:** One hundred and ten patients with different stages of AMD were evaluated by direct interview for identifying possible present factors risk and were subjected to a detailed ophthalmological examination, including measurement of the macular area by the Spectral Domain-Optical Coherence Tomograph Heidelberg Engineering (SD-OCT). For the grading of AMD we used the International Classification and Grading System for Age-Related Maculopathy. **Results:** In our study, diabetes, arterial hypertension, dyslipidemia and smoking were risk factors for AMD. A longer history of diabetes or smoking status was associated with stage 3 or 4 of AMD. We found no statistical significant association between pseudophakia and AMD. **Conclusions:** Further investigation is needed to identify and to clarify the association between these possible risk factors and AMD.

**key words:** age-related macular degeneration, type 2 diabetes mellitus, arterial hypertension, dyslipidemia, smoking, pseudophakia

### Background and aims

Age-related macular degeneration (AMD) is a leading cause of severe and irreversible visual loss, affecting the population aged 40 years and older [1]. According to the World Health Organization, AMD is more frequent in developed countries [2]. It is estimated that

nearly 8 million people will be affected with AMD by the year 2020 [3].

There are 2 types of AMD: the wet (exudative, neovascular) form that is responsible for 10-20% of the cases, with a fast and severe visual loss and the dry (non-exudative, non-neovascular) form with a slower and progressive evolution.

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In the pathogenesis of AMD, there were cited non modifiable risk factors such as advanced age, sex and genes. Different studies associated AMD with modifiable risk factors such as cigarette smoking, hypertension, elevated values of cholesterol, diabetes and cataract surgery [4-9].

The investigation of risk factors for AMD is essential in understanding the pathogenesis and progression of the disease, but the most important is to identify preventive measures and better treatments.

The aim of our study was to evaluate the association between the potential risk factors and the different stages of AMD in a population aged 52-85 years.

### Material and method

We evaluated one hundred and ten patients with diagnosed AMD who required medical services in the period April-July 2013 within the Ophthalmology Department of the University of Szeged. After obtaining informed consent, the patients underwent a medical interview and a complete ophthalmological examination. The study respected the Helsinki Declaration and was approved by the Ethical Board of the University of Szeged.

Clinical data were collected from all patients using direct and detailed patient interview focusing on sex, age, general and ocular diseases history, history of ocular surgery and personal habits such as cigarette smoking. Arterial hypertension, diabetes and dyslipidemia were considered present if the patient was previously diagnosed by an internal medicine specialist with or without current usage of medications. History of duration of these diseases was also documented. For the smoking habit, the first question was if the patient ever smoked. If the answer was positive, the patient was asked for how long he or she had been smoking (years), the number of cigarettes (per day) and the actual

status (still smoking/stopped smoking and for how long).

The ophthalmological examination was performed after pupil dilatation with Neo-Synephrine and included identification and measurement of the macular lesions using the Spectral Domain Optical Coherence Tomograph (SD-OCT), Heidelberg Engineering, from the Ophthalmology Department of the University of Szeged.

The AMD was graded according to the International Classification and Grading System for Age-Related Maculopathy in 5 stages: no signs of AMD or the presence of one small drusen  $<63\mu\text{m}$  as stage 0; soft distinct drusen ( $\geq 63\mu\text{m}$  and  $< 125 \mu\text{m}$ ) or only pigmentary abnormalities as stage 1. Early AMD includes stage 2 with soft distinct drusen ( $\geq 125 \mu\text{m}$ ), reticular drusen only, or soft distinct drusen ( $\geq 63 \mu\text{m}$  and  $< 125 \mu\text{m}$ ) with pigmentary abnormalities and stage 3 where the pigmentary abnormalities are associated with bigger dimensions of the reticular drusen or soft distinct drusen ( $\geq 125 \mu\text{m}$ ) as shown in [Figure 1](#).

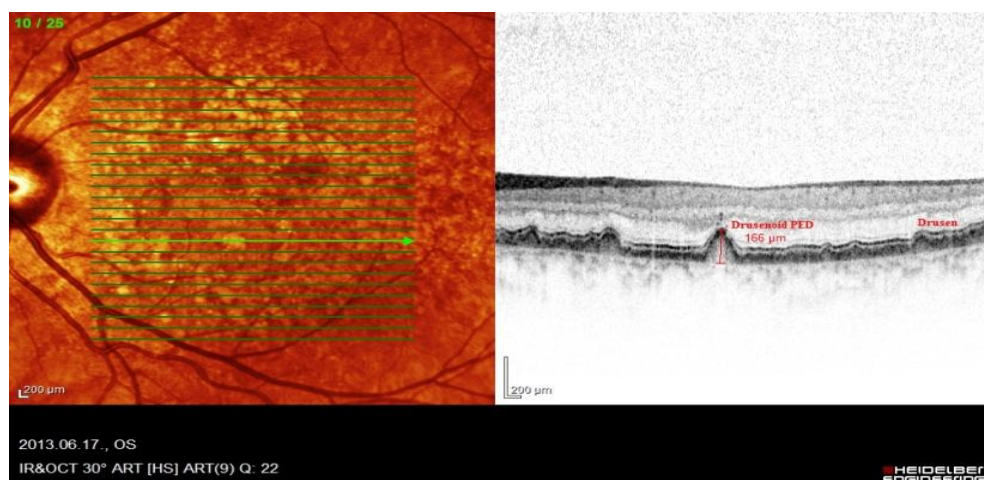
Stage 4 (also known as late AMD) is divided in 2 types: the dry form (geographic atrophy)-demarcated area, larger than  $175 \mu\text{m}$  with the apparent absence of the retinal pigment epithelium (RPE) and visible choroidal vessels ([Figure 2](#)) and the wet-AMD ([Figure 3](#)) defined by the presence of a RPE detachment (serous or hemorrhagic) and/or subretinal hemorrhage, and/or subretinal neovascular membrane, and/or periretinal fibrous scar [10,11].

Lesions that could be considered to be the results of other diseases such as: chorioretinitis, ocular trauma, high myopia or congenital diseases defined the exclusion criteria. We also excluded the patients with evolved cataract opacities that could interfere with the fundus examination and staging of the AMD.

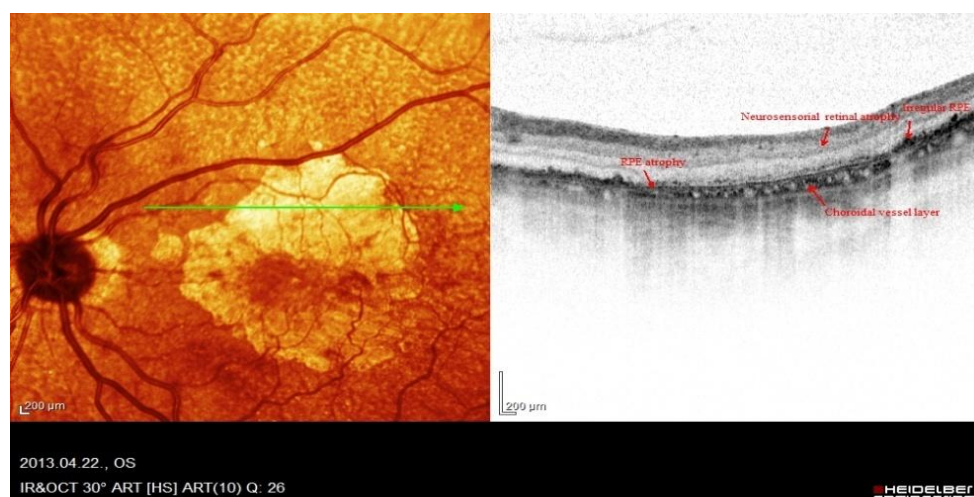
The statistical analysis was performed using EpiInfo 7.1.2 coupled with data management

performed in Microsoft Excel. Besides the standard descriptive statistics, the statistical method included risk analysis using group-wise

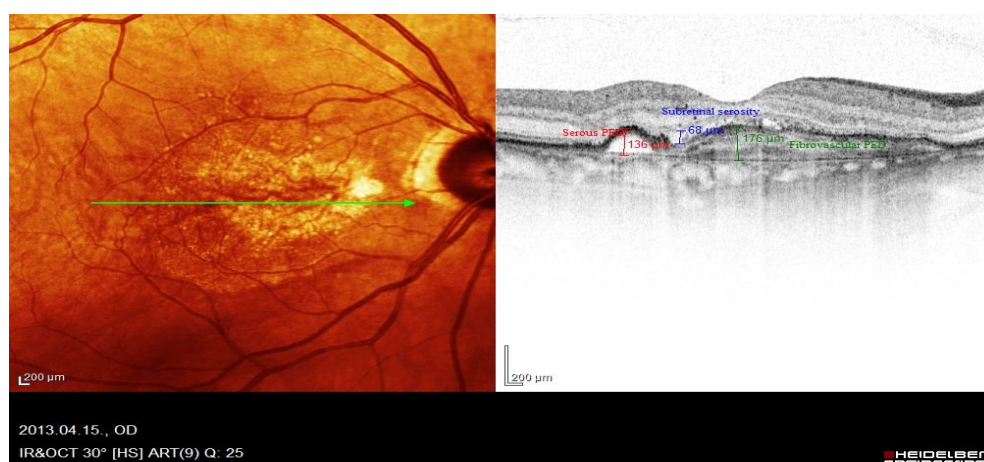
odds calculation of Odds Ratio (OR) as the measure of risk. The statistical significance was considered for the threshold  $p=0.05$ .



**Figure 1.** Stage 3 of AMD: drusenoid PED (drusenoid pigment epithelial detachment), drusen.



**Figure 2.** Stage 4 of nonexudative AMD.



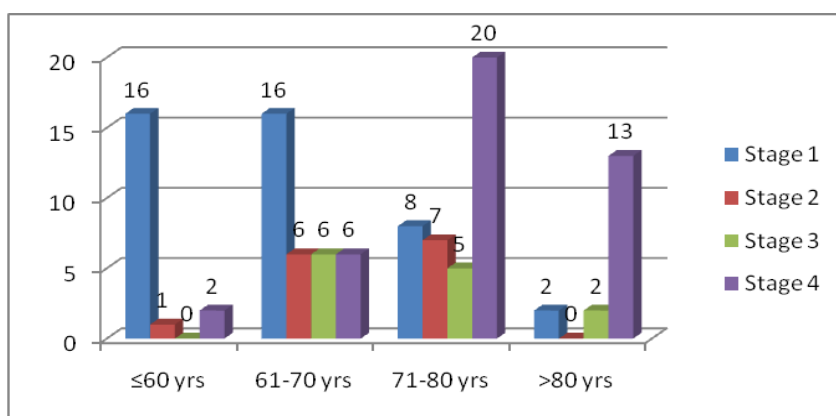
**Figure 3.** Stage 4 of exudative AMD: serous PED, subretinal fluid, fibrovascular PED.

## Results

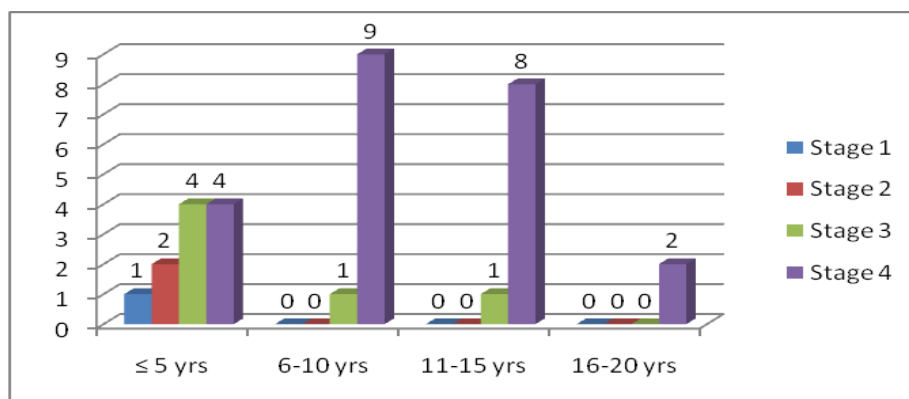
In our study from 110 patients, 76 were females (69.1%) and 34 males (30.9%). Patients were aged between 52 and 85 years, with a medium age of 71 years. 42 of the patients in the study group (38.18%) were diagnosed with stage 1 of AMD, 14 (12.72%) with stage 2, 13

(11.18%) with stage 3 and 41 (37.27%) with stage 4.

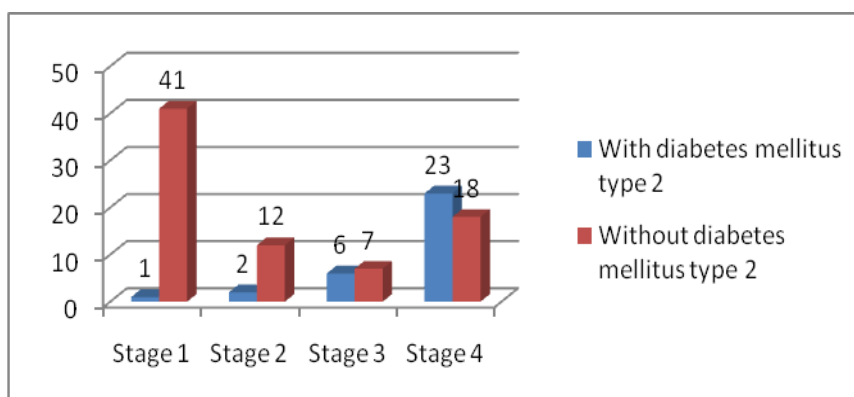
When analyzing the association between age and the stage of the ocular disease, we found that age above 70 years is statistically significantly associated with stages 3 and 4 of the disease: OR=6.55 (2.84 – 15.08),  $p < 0.001$  (Figure 4).



**Figure 4.** Distribution of patients according to the AMD stage and age group.



**Figure 5.** Distribution of T2DM patients according to the AMD stage and diabetes duration.



**Figure 6.** Distribution of patients according to the stage of AMD and the presence of T2DM.

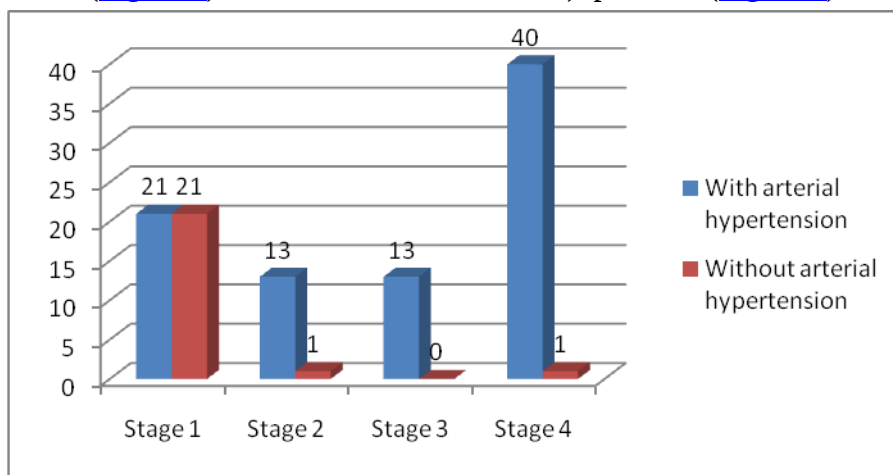
We analyzed the obtained data, taking into account the presence of the risk factors and also the duration (in years) of the associated diseases.

Type 2 diabetes mellitus (T2DM) was present in 32 patients (29.1%): 22 females (68.75%) and 10 males (31.25%) and was associated with late-AMD if the history of the diabetes was more than 6-10 years (Figure 5).

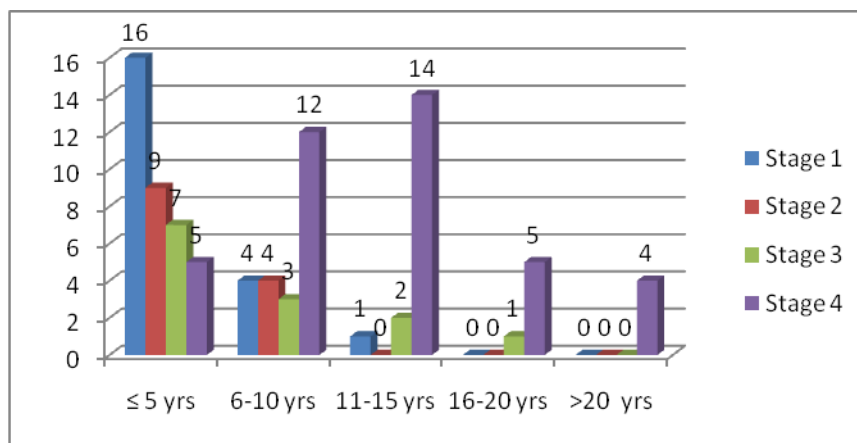
In patients with no history of T2DM, we identified more frequently drusens and pigmentary abnormalities characteristic for the stages 1 or 2 of AMD (Figure 6).

The relationship between T2DM and the presence of stages 3 and 4 of AMD has proven to be statistically significant: OR= 20.49 (5.69 – 73.72),  $p < 0.001$ .

Hypertension was present in 87 patients (79.1%): 54 females (62.1%) and 33 males (37.9%). We have investigated the possible association between arterial hypertension and the presence of advanced stages of the disease (3 and 4) and we have found a statistical significant relationship between them: OR= 34.29 (4.41 – 266.34),  $p < 0.001$  (Figure 7).



**Figure 7.** Distribution of the patients according to the stage of AMD and the presence of arterial hypertension.

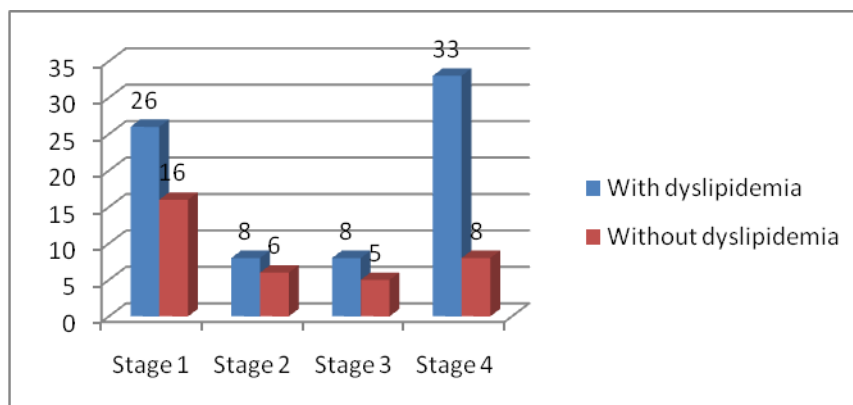


**Figure 8.** Distribution according to the stage of AMD and the duration of hypertension.

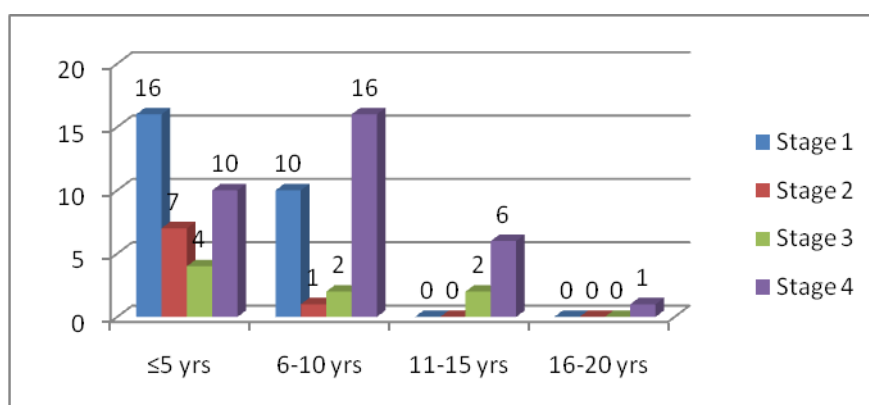
Furthermore, a history of hypertension for longer than 5 years seems to be associated with advanced stages of AMD (Figure 8).

Dyslipidemia was present in 75 patients (68.2%): 52 females (69.3%) and 23 males (30.7%). Patients with dyslipidemia had all 4

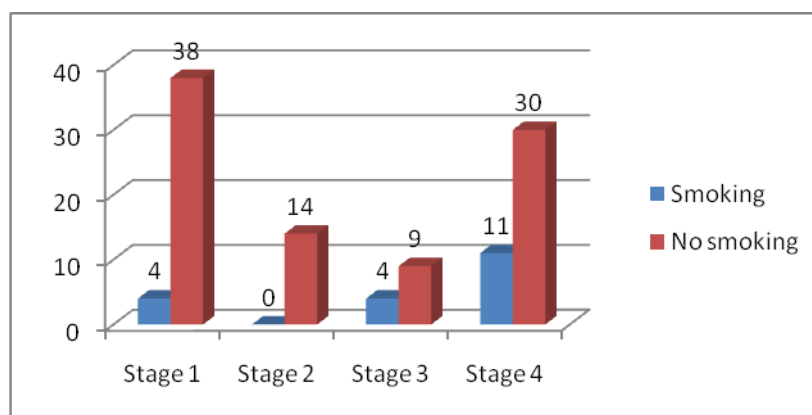
stages of AMD (Figure 9). We have investigated the possible association between dyslipidemia and presence of advanced stages of AMD and found a statistical significant relationship between dyslipidemia and stage 4 of AMD: OR=2.65 (1.06 – 6.59),  $p = 0.01$ .



**Figure 9.** Distribution of patients according to the stage of AMD and the presence of dyslipidemia.



**Figure 10.** Distribution of patients according to the stage of AMD and dyslipidemia duration.



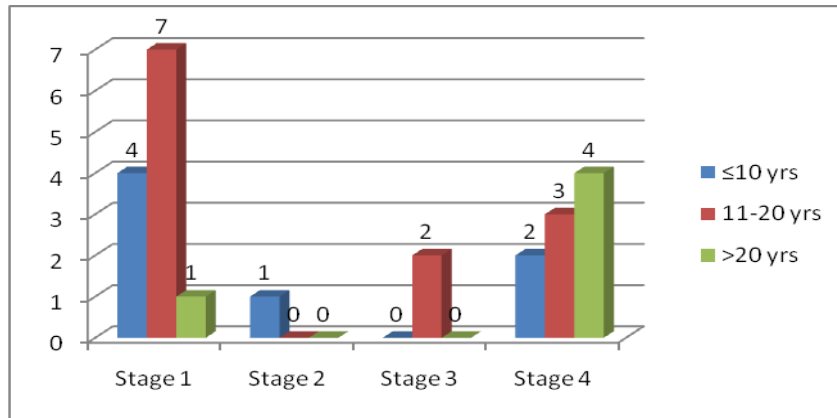
**Figure 11.** Distribution of patients according to the stage of AMD and smoking status (history of smoking or current smoking).

As shown in [Figure 10](#), patients with a more recent onset of dyslipidemia had more frequently stage 1 AMD.

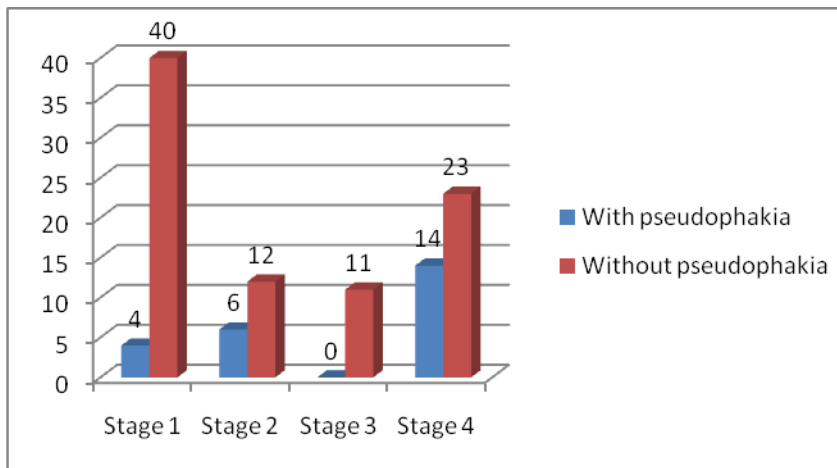
In our study group we identified 43 patients (39.1%) with a history of smoking or still active smokers: 32 females (74.4%) and 11 males (25.6%). When analyzing the association between smoking and the stage of AMD, we found that smoking (present or past) is

significantly associated with stages 3 and 4 of the disease: OR= 5 (1.53 – 16.24),  $p= 0.002$  ([Figure 11](#)).

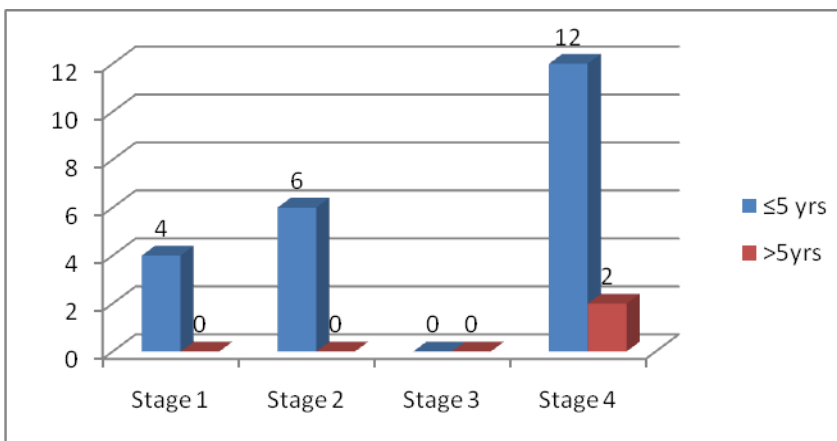
Of the 43 patients with a history of smoking, 24 were active smokers (55.8%): 20 females (83.3%) and 4 males (16.7%). A smoking history longer than 20 years was present especially in patients with late AMD ([Figure 12](#)).



**Figure 12.** Distribution of active smokers according to the stage of AMD and smoking duration.



**Figure 13.** Distribution of patients according to the stage of AMD and the presence of pseudophakia.



**Figure 14.** Distribution of patients according to the stage of AMD and pseudophakia duration.

Pseudophakia was present in 24 patients (21.8%): 18 females (75%) and 6 males (25%). When analyzing the association between the presence of pseudophakia and the stage of AMD, we found no statistical significant association between them:  $p=0.06$  (Figure 13).

The distribution of the patients according to the stage of the AMD and the duration of pseudophakia showed us that patients with cataract surgery performed more than 5 years ago had only stage 4 of the macular disease (Figure 14).

## Discussions

As it is reported in different studies worldwide, age is the most important non modifiable risk factor associated with AMD [12-15]. In our study, we identified that the prevalence of the late stages of AMD is higher in patients older than 70. The Hisayama Study from Japan, performed in a population aged 50 years and older, identified a prevalence of early AMD of 12.7% and of late AMD of 0.87% [16]. The Shihpai Eye Study from Taiwan confirmed the importance of age in the pathology of early and late AMD, but after comparing subject groups with different ages, the authors conclude that early AMD is more frequent after the age of 69 and late AMD after 85 years old [17]. Their results in the age group 65-74 years are similar with those reported in other studies such as the Multiethnic Study of Atherosclerosis (MESA) [18]. In this study, the prevalence of AMD was higher in White (5.5%), Hispanics (4.5%) and Chinese (5.0%) people, but lower in Blacks (2.1%). In the Beijing Eye Study the prevalence of AMD was 2.5% [8]. The Andhra Pradesh Eye Disease Study showed that the adjusted prevalence of AMD was significantly higher in subjects aged 60 years or older: OR= 3.55 (1.61-7.82) [19].

Smoking is the most consistent modifiable risk factor associated with AMD [20,21]. Thus, the review of 13 studies found a statistically significant association between smoking and AMD, with increased risks for active-smokers or subjects with a history of smoking compared with never-smokers [22]. The South Indian Andhra Pradesh Study (2005) identified a higher prevalence of AMD in the smokers group compared with never smokers. This study also reported a non-statistically significant association with the different types and quantities of nicotine by comparing the home made traditional cigars with the classical filtered cigarettes [19]. The Shihpai Eye Study identified

smoking as a non significant risk factor for AMD [17].

Dyslipidemia was associated with early AMD in a Korean Study [23]. High serum levels of HDL cholesterol were associated with an increased risk of early AMD in The Rotterdam Eye Study, with neovascular AMD in the Eye Disease Case-Control Study and with soft drusen in the cross-sectional POLA Study [24-26]. In our study we have found a statistical significant relationship between dyslipidemia and stage 4 of AMD. However, many epidemiologic studies didn't detect an association between dyslipidemia and late AMD. Thus, the Beaver Dam Eye Study and the Blue Mountains Eye Study have reported that high serum levels of HDL cholesterol may have a small effect in reducing the risk for late AMD [27,28].

The association between arterial hypertension and AMD is questionable. Our study showed that hypertension is a risk factor for the late-AMD. The AREDS (Age Related Eye Disease Study) study identified a statistically significant association between systemic hypertension, smoking and large drusen or neovascular AMD [6]. The Rotterdam Study identified an association with hypertension for all subtypes of AMD [29]. The Beaver Dam Eye Study showed an association only for the neovascular AMD [30]. However, a number of studies have failed in identifying a significant association between any stage of AMD and systemic hypertension [26]. The Andhra Pradesh Eye Disease Study in South India found no association with arterial hypertension, but identified higher odds of AMD in the hypertensive patients group [19].

A publication from 2007, within the AREDS study, concluded that a protective factor for AMD may be a reduced glycaemic index in nondiabetic subjects [31,32]. In our study we identified that late-AMD is associated with a history of diabetes of more than 6-10 years.

AMD after cataract surgery has been identified in different studies. The Andhra Pradesh Eye Disease Study, the Beaver Dam Eye Study and the Blue Mountains Eye Study demonstrated an association between cataract surgery and AMD [19,33,34]. In our study we haven't found a statistical significant association between pseudophakia and AMD.

Our study has several limitations. First, due to the small size of our study group, the statistical conclusions cannot be extended to the general population aged over 50 years. According to literature the female sex is more affected by the AMD disease, but taking into account the number of our patients we cannot conclude. Another limitation of the study is that we could not identify from the history of previous ophthalmological examination if the patients that underwent cataract surgery had

before or after the medical procedure the characteristic AMD modifications.

## Conclusions

In summary, we have observed different associations between AMD and modifiable risk factors. Avoiding smoking and control of diabetes, hypertension and dyslipidemia have the potential to reduce the risk of developing AMD. However, further investigation is needed to identify and to clarify the association between these possible risk factors and AMD.

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