

Impact of age-related macular degeneration on diabetic retinopathy: An electronic health record based big data analysis from a tertiary eye centre in South India

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Purpose: To determine whether the presence of age-related macular degeneration (AMD) decreases the risk of diabetic retinopathy. **Methods:** This was a retrospective, case-cohort study performed in patients with a systemic diagnosis of diabetes at a tertiary health care center from May 2011 to April 2020. A total of 43,153 patients (1,024 AMD patients and 42,129 non-AMD patients) were included in the analysis. A total of 1,024 age and diabetes mellitus (DM) duration-matched controls were chosen from the non-AMD group for risk factor analysis. The severity of diabetic retinopathy was compared between the patients with AMD and the patients without AMD. **Results:** Out of the enrolled 43,153 diabetic patients, 26,906 were males and 16,247 were females. A total of 1,024 patients had AMD and 42,129 had no AMD. The mean age of the cohort was 58.60 ± 0.09 years. The overall prevalence of DR was noted to be 22.8% (9,825 out of 43,153 eyes). A significantly lower prevalence of diabetic retinopathy (DR) (23% in non-AMD, 11.4% in AMD, OR = -0.43, $P < 0.001$), non-proliferative diabetic retinopathy (NPDR) (12% in non-AMD, 8.2% in AMD, OR = -0.66, $P < 0.001$), and proliferative diabetic retinopathy (PDR) (11% in non-AMD, 3.2% in AMD, OR = -0.27, $P < 0.001$) was seen in the AMD patients. No significant difference was seen between the dry and wet AMD. On multivariate logistic regression analysis, the lower age, absence of AMD, and male gender were associated with a higher risk of PDR. **Conclusion:** The presence of AMD was noted to statistically reduce the risk of DR. Our results may be useful in the field of resource allocation and awareness of DR.

Key words: Age-related macular degeneration, AMD, diabetic retinopathy, DR

Age-related macular degeneration (AMD) is the leading cause of blindness among the elderly.^[1] Diabetic retinopathy (DR) is the fifth leading cause of preventable blindness and the most common cause of blindness among people with diabetes.^[2] Considering the fact that a majority of individuals affected with diabetes and AMD are elderly,^[3] blindness can result in a significant social and economic burden in this population.

There are conflicting reports regarding the relationship between AMD and DR in the literature. Srinivasan *et al.*^[4]

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and Borrone *et al.*^[5] reported a lower prevalence of AMD in people with diabetes. The analysis of the Medicare databases found a higher incidence of AMD in patients with severe DR.^[6] However, the Beaver Dam study did not find any significant association between diabetes and the incidence of AMD.^[7]

India is reported to have the second highest number of people with diabetes in the world following China.^[8] In 2019, 77,005,600 people were estimated to have diabetes in India.^[8] According to the national sample survey data in India between 2004 and 2014, the prevalence of self-reported diabetes showed the highest increase among the young-old (aged 60–64).^[9] This is also a vulnerable age for vision loss due to AMD. It is crucial to understand the AMD-DR relationship in this vulnerable group in the Indian population.

This study was thus designed to estimate the relationship between AMD and DR using a large electronic medical record (EMR) database of a tertiary eye care institute in South India.

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Methods

This was a retrospective study done at a tertiary eye care center in South India. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board.

Study design

Data of all the patients with a systemic diagnosis of “diabetes mellitus” were retrieved from the electronic medical records (EMR) from May 1, 2011 to April 30, 2020. The parents/guardians filled a standard consent form for electronic data privacy at the time of registration. Each patient’s data which were entered into a browser-based eyeSmart electronic medical records system (EMR) were reviewed.

The eyeSmart EMR system had a pre-formatted template, which was completed by trained ophthalmic personnel and ophthalmologist. Apart from querying the International Classification of Diseases (ICD) 9th revision coding of AMD, DM, and DR, all patient records underwent keyword search of “Diabetes,” “Diabetic,” and “Diabetes Mellitus,” “Age-related macular degeneration,” “ARMD,” “AMD,” “Drusen,” “Geographic Atrophy,” “GA,” “choroidal neovascularization,” “CNV,” “neovascular membrane,” and “CNVM” in systemic history, retina evaluation and plan of management notes. The patients with a diagnosis of diabetes mellitus aged ≥ 40 years were included for further analysis. The patients having any pre-existing ocular conditions (high myopia, diffuse chorioretinal atrophy secondary to uveitis, and retinal dystrophies) or treatment history (anti-vascular endothelial growth factor and pan-retinal photocoagulation) that could have altered the natural history of DR were excluded.

After all the inclusion and exclusion criteria, the included patients with diabetes were classified as “AMD—Early or Late” (AMD group), and patients without AMD (non-AMD group). The early AMD was defined as the presence of drusen (discrete whitish-yellow spots located external to the neuroretina or retinal pigment epithelium) or the presence of drusen with retinal pigment epithelium (RPE) pigmentary abnormalities (areas of hyperpigmentation or hypopigmentation). Late AMD was defined as the presence of dry AMD (geographic atrophy of the RPE in the absence of neovascular AMD) or neovascular AMD (RPE detachments, which may be associated with neurosensory retinal detachment, subretinal or sub-RPE neovascular membranes, epiretinal, intraretinal, subretinal, or sub-pigment epithelial scar/glial tissue or fibrin-like, deposits, and subretinal hemorrhages not related to other retinal vascular diseases). Each of the two groups was then sub-classified based on the status of diabetic retinopathy into “any Diabetic Retinopathy (DR)” or “no DR”; The DR group was further classified into non-proliferative DR (NPDR) and proliferative DR (PDR) based on the international classification of diabetic retinopathy severity scales. [Fig. 1]. We further sub-classified the late AMD into active CNVM and atrophic stage of ARMD (scarred CNVM or GA) and analyzed the prevalence of PDR.

In order to assess the possibility of any graded influence of AMD on DR, no DR, the prevalence of all the three levels, i.e., no DR, NPDR, and PDR, were calculated in the AMD and the non-AMD groups separately, followed by the determination

of the odds ratio. Age, gender, duration of diabetes, history of hypertension, duration of hypertension, history of dialysis/nephropathy, and glycosylated hemoglobin (HbA1c) values, recorded from the patient’s first visit to the clinic, were established as the baseline variables (BVS) as these variables have been demonstrated to correlate with the severity of DR.^[10-12] Due to a significant difference in the values of the average age and duration of diabetes in the AMD and non-AMD groups, an age and DM duration-matched non-AMD control group was created. The combined cohort of the AMD patients and non-AMD-matched controls were put into a regression model. In order to assess the protective role of AMD on the severe forms of DR (i.e., PDR), the BVS and “AMD” (presence or absence of AMD), were taken as the independent variables and tested against any possible effect on “PDR” as the dependent variable, using the binary logistic regression analysis.

Matching

Based on the characteristics of the AMD group, age and DM duration-matched controls were selected from the non-AMD group, before performing the regression analysis. Due to the presence of an unequal distribution of age and DM duration between the AMD and non-AMD groups, the “nearest-neighbor matching” method was used, which selects the nearest possible match for every value in case a one-to-one match is not available (249 patients did not have an exact match), with the help of the R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

Statistical analysis

The age, DM duration, duration of hypertension, and HbA1c values were expressed as mean \pm 95% confidence interval. The missing data in HbA1c (1,705 missing values) and duration of

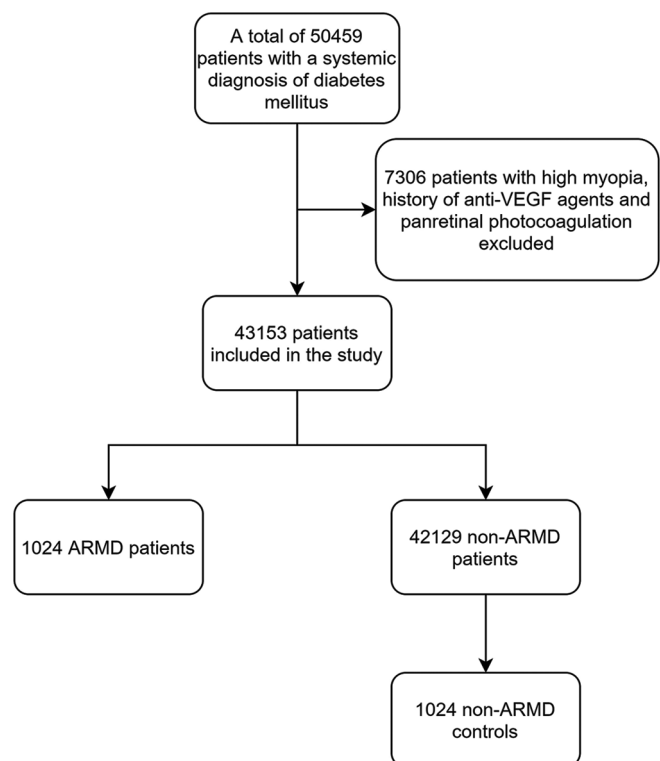


Figure 1: Chart showing the selection of cases in AMD and non-AMD groups

DM (402 missing values) were adjusted using the imputation analysis. The odds ratio (OR) calculation, logistic regression, and imputation analysis were done using SPSS v. 20.0 (IBM Corp., Armonk, NY, USA). A *P* value of 0.05 was considered significant.

Results

Of the 50,459 records, the records of 43,153 (26,906 males and 16,247 females) people with diabetes who fulfilled the inclusion and exclusion criteria were included in the analysis. These included 1,024 AMD and 42,129 non-AMD patients.

The mean age of the patients was 58.6±0.1 years (64.9±0.6 years in the AMD group and 58.5±0.1 years in the non-AMD group). The mean duration of diabetes was 9.1±0.1 years (9.8±0.5 years in the AMD group and 9.1±0.1 years in the non-AMD group).

Table 1 shows the prevalence of DR in the AMD versus the non-AMD groups. The overall prevalence of DR was noted to be 22.8% (9,825 out of 43,153 eyes). The patients without AMD had a statistically higher prevalence of all types of DR (*P* < 0.001) compared to the AMD group. The patients with AMD had lesser odds of having DR (OR = 0.43, *P* < 0.01).

Table 1: Prevalence of diabetic retinopathy in AMD and no AMD

	No AMD (n=42,129) n (%)	AMD (n=1,024) n (%)	Odds ratio, OR, <i>P</i>
No DR	32421 (76.9%)	907 (88.6%)	2.32, <i>P</i> <0.001
DR	9708 (23.0%)	117 (11.4%)	0.43, <i>P</i> <0.001
NPDR	5054 (12.0%)	84 (8.2%)	0.66, <i>P</i> <0.001
PDR	4655 (11.0%)	33 (3.2%)	0.27, <i>P</i> <0.001

AMD: Age-related macular degeneration, OR: Odds ratio, DR: Diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy

Table 2: Prevalence of diabetic retinopathy in early and late AMD

	Early AMD (n=166) n (%)	Late AMD (n=858) n (%)	Odds ratio, OR, <i>P</i>
No DR	142 (85.5%)	765 (89.2%)	1.39, <i>P</i> =0.18
DR	24 (14.5%)	93 (10.8%)	0.72, <i>P</i> =0.18
NPDR	18 (10.8%)	66 (7.7%)	0.69, <i>P</i> =0.17
PDR	6 (3.6%)	27 (3.1%)	0.87, <i>P</i> =0.75

Early and late AMD: Early and late age-related macular degeneration, OR: Odds ratio, DR: Diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy

Table 3: Comparison of baseline variables in the ARMD and no-ARMD control groups

	AMD (n=1,024)	Non-AMD (n=1,024)	<i>P</i>
Mean age (years) ± 95% CI	64.9±0.6	64.8±0.6	0.63
M:F	631/393	646/378	0.49
Duration of diabetes (years)*	9.8	9.7	0.86
Hypertension (yes/no)	590 (57.6%)	578 (56.4%)	0.59
Mean duration of HT (years)±95% CI	9.8±0.5	9.9±0.5	0.71
Mean HbA1c (%)*	7.8	7.9	0.47

*Standard deviation is missing due to pooled data after imputation, AMD: Age-related macular degeneration, M:F: Male:Female, HT: Hypertension, HbA1c: Glycosylated hemoglobin

Table 2 shows the prevalence of DR in the early and late AMD. There were no statistically significant differences in the prevalence of DR in the early and late AMD.

Surprisingly, on sub-dividing the late AMD into active and atrophic AMD, we found a statistically significant higher prevalence of PDR in the active CNVM group compared to the atrophic stage (OR = 2.7, *P* value = 0.01) [Fig. 2]. The prevalence of PDR was 3.75, 5.9, and 2.2% in early ARMD, active CNVM, and the late atrophic stage, respectively.

Table 3 shows the comparison of the baseline characteristics of AMD and non-AMD (age and duration of diabetes matched). Both groups had no statistical difference in their BVS.

Table 4 shows the results of the binary logistic regression for possible factors which could affect the occurrence of PDR. On binary logistic regression analysis, older age, presence of AMD, and shorter duration of diabetes were associated with a lower risk of PDR in the univariate analysis. In the multivariate analysis, older age (OR: 0.96, 95% CI: 0.93–0.98), *P*: 0.003, women (OR: 0.49, 95% CI: 0.28–0.86), *P*: 0.01, and presence of AMD (OR: 0.19, 95% CI: 0.10–0.35), *P*: <0.001 were the protective independent factors associated with PDR after adjusting for the duration of diabetes and hypertension, and HbA1c.

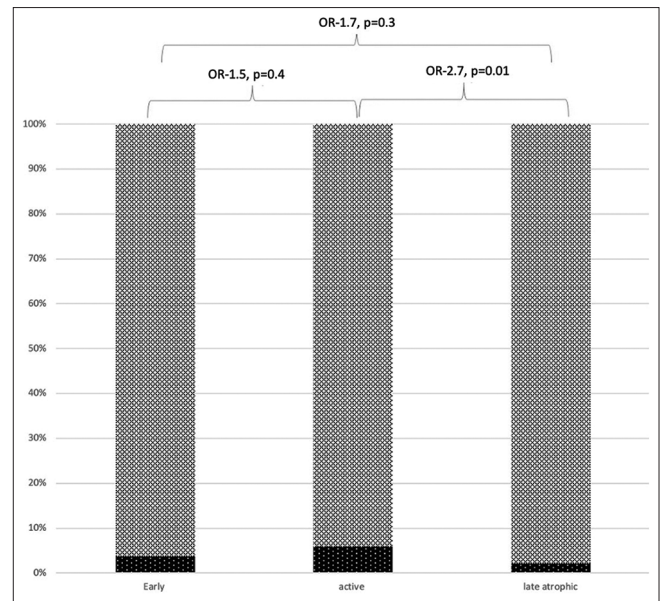


Figure 2: Figure showing the comparison of the risk of proliferative diabetic retinopathy in various stages of AMD

Table 4: Regression analysis for risk factors for proliferative diabetic retinopathy

Variables	Univariate analysis				Multivariate analysis			
	P	OR	95% CI		P	OR	95% CI	
			Lower	Upper			Lower	Upper
Age (years)	0.001	0.97	0.96	0.99	0.003	0.96	0.93	0.98
Gender (women)	0.10	0.75	0.54	1.06	0.01	0.49	0.28	0.86
AMD	<0.001	0.23	0.15	0.34	<0.001	0.19	0.10	0.35
HbA1c*	0.56	1.04	0.91	1.19	0.34	1.08	0.92	1.26
Duration of DM (years)	0.03	1.02	1.00	1.04	0.12	1.03	0.99	1.07
Hypertension	0.06	0.74	0.53	1.01	0.26	0.28	0.03	2.65
Duration of HT (years)	0.86	0.99	0.96	1.03	0.89	0.99	0.96	1.04

*Imputed values, AMD: Age-related macular degeneration, DM: Diabetes mellitus, HbA1c: Glycosylated hemoglobin, HT: Hypertension, OR: Odds ratio

Discussion

Our study is based on the large dataset ($n = 50,459$ records) extracted from the institute's EMRs database. Our EMR design conforms to the institutionally agreed-upon standards, ensures the mandatory entry of certain important fields, and restricts the data loss, thus, providing high-quality reproducible data for audit, research, and designing evidence-based treatment protocols. To our knowledge, this is the first major study using robust data collected from EMR to study the effect of AMD on DR in populations with diabetes.

In the current study, the prevalence of DR in the "no-AMD" group was found to be 23% which was similar to the global estimate of 27% whereas the prevalence of DR in the AMD group was 11.4% for any DR which was significantly lower than the global estimates [Table 1].^[13] This reduction in the prevalence was observed across all grades of DR. However, there was no significant difference in the DR presence between the early and late groups of AMD. We have also noted that the presence of AMD decreased the risk of developing PDR. This might be due to the fact that the pathophysiological process of DR is directly or indirectly related to the ischemic status of the viable retina and the presence of AMD reduces the oxygen demand of the retina by affecting the outer retina metabolism. Even though the manifestations of AMD are localized to the macula, it is primarily a disease of the choroid. The outer retina is dependent on the choroidal circulation for its metabolism and any atrophy of the outer retina secondary to reduced choroidal circulation in AMD might alter the response of the retinal tissue to ischemic stimuli. This was further supported by the fact that on sub-group analysis, the atrophic stages of AMD had a lower prevalence of PDR than the active CNVM stage. We hypothesize that the altered outer retina status in AMD may directly affect the severity of diabetic retinopathy and plays a role in reducing the chances of development or progression of DR.

The previous studies have reported DM as a risk factor for AMD. Chen X, *et al.*^[14] in a systemic review and meta-analysis on DM and the risk of AMD concluded that DM is a risk factor for AMD. Whereas studies by Raman *et al.*^[15] and Borrone *et al.*^[5] reported that a lower prevalence rate of AMD in the population with diabetes and DM acts as a protective factor against AMD, which is a similarity observed in our study. But the above studies did not mention the relationship between AMD and

DR. In 2017, Srinivasan *et al.*^[4] reported that the presence of DR acts as a protective factor for AMD but did not specify whether vice-versa can be said. There are no new studies to report on this influence AMD and DR which have been observed in the current study.

Apart from AMD, older age was also found to be significantly associated with a lesser severity of DR in our study, although the strength of this association was weak. One possible explanation may be an increased fundus tessellation or a thinner choroid, common to both AMD and increasing age. A literature review has shown that an increased fundus tessellation is associated with reduced severity of DR and a thinner choroid has been found in less severe forms of DR (although conflicting results have been published).^[16-19] In our study, both the groups (AMD and non-AMD) were matched to age and duration of DM. Thus, any choroidal changes secondary to age and systemic diabetes would have been equally distributed between the AMD and non-AMD groups. The AMD remained to be statistically significantly associated with a reduced risk of DR, even in multivariate analysis. Interestingly, we did not find any significant difference in the prevalence of DR between the dry and wet AMD group wherein choroidal atrophy is seen in both the sub-types. The protective effect of the resultant drop in oxygen demand appears to be similar in both groups.

The strength of the study is the large reliable dataset obtained from EMR, which helps in understanding the large-scale picture of the disease burden at the baseline and its rate of progression over time. This estimation may help in designing the budget, allocating the health resources, and might help as a strategic groundwork for the government to design any program. The limitations are that we cannot extrapolate the study data to the general population as the study was conducted at a tertiary health care center and there was no relevant national or state data on AMD for comparison. Second, we encountered a lot of missing HbA1c values. This could have resulted in an inaccurate estimate of the association with PDR in the regression analysis. The differences in the duration of DM and systemic control might have influenced the results as some values were extrapolated. Being a retrospective study, it has its limitations, but those might be limited due to the large sample size obtained from the well-documented database.

Conclusion

In conclusion, AMD (dry and wet) appears to statistically decrease the risk of the development of DR. The results of our study would be useful for physicians and policymakers for future studies on resource allocation and awareness of DR in India.

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Conflicts of interest

There are no conflicts of interest.

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