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Age-related maculopathy and diabetes

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PURPOSE. *To compare the prevalence of age-related maculopathy (ARM) in a sample of diabetic patients with the general population.*

METHODS. *Binocular indirect ophthalmoscopy, biomicroscopy, and fluorescein angiography. Retrospective prevalence study; descriptive-observational case-control type. Two different groups were analyzed from a sample of 1000 consecutive files of diabetic patients: 1) 65 to 74 years old (n = 263) and 2) 75 years and older (n = 199). Prevalence was compared to that of the general population in a control group and the following epidemiologic studies: Beaver Dam Eye Study, Framingham Eye Study, Blue Mountains Study, and Rotterdam Eye Study.*

RESULTS. *In diabetic patients aged 75 or older, prevalence of ARM was as follows: early lesions 2.51% (5/199), late lesions (ARMD) 2.51% (5/199). In comparison, the risk in patients 75 or older is as follows: control group (ARMD): OR 4.79, 95% CI 1.778–12.033, p (Fisher) 0.0005; Beaver Dam Eye Study (ARMD): OR 2.93, 95% CI 1.152–7.450, p (Fisher): 0; Blue Mountains Eye Study (ARMD): OR 3.06, 95% CI 1.208–7.754, p (Fisher): 0; Framingham Eye Study (ARM): OR 6.73, 95% CI 3.041–14.880, p (Fisher): 0; Rotterdam Eye Study: p (Fisher) 0.133.*

CONCLUSIONS. *1) A lower prevalence of ARM was found in the sample of diabetic patients aged 75 or older than in the general population (with the exception of the Rotterdam study). 2) Prevalence of ARM was even lower in diabetic patients presenting diabetic retinopathy, whether or not they had been treated with photocoagulation. 3) In diabetic patients, the exudative form was more frequent than the atrophic form, in an inverse ratio to that of the general population. (Eur J Ophthalmol 2008; 18: 949-54)*

KEY WORDS. *Age-related maculopathy, Age-related macular degeneration, Diabetes, Diabetic retinopathy*

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INTRODUCTION

Age-related macular degeneration (ARMD)—the late stage of age-related maculopathy (ARM)—and diabetic retinopathy (DR) are the two pathologies that produce most cases of legal blindness in adults in industrialized societies in the Western world (1). As well as genetic, inflammatory, and metabolic factors and various risk factors proper to each, in the physiopathology of both disorders there is a point in common: the central role of angiogenesis factors (2-5). Studies evaluating the possibility of an association between the two pathologies have reached contradictory conclusions (6-14) (Available at: http://www.ncbi.nlm.nih.gov/pubmed/3877089?ordinalpos=82&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.)

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Our clinical experience has been that the prevalence of ARM is lower in diabetic patients than in the general population. With this hypothesis, we made an observational retrospective study comparing the prevalence of early and late ARM lesions in a series of diabetic patients with the prevalence found in the general population in a control group and in four important epidemiologic studies: the Beaver Dam Eye Study, Framingham Eye Study, Rotterdam Eye Study, and Blue Mountains Eye Study.

METHODS

A retrospective study was made of 1000 consecutive files of diabetic patients examined between April 2003 and October 2005 in the Diabetes Section of the Retina Center of the Ophthalmology Service of the Hospital de Clínicas "José de San Martín" of the National University of Buenos Aires.

Institutional Review Board (IRB)/Ethics Committee approval was not required for this study.

In order to study the prevalence of ARM in diabetic patients within the at-risk age group, and to make a comparison with the prevalence of ARM found in the general population in the large epidemiologic studies, patients were considered who were 65 years of age or over, subdivided into the two age groups analyzed in those studies: sample A (patients from 65 to 74 years of age) and sample B (patients 75 or more years of age).

In the sample, 263 patients were between 65 and 74 years (sample A: n = 263) and 199 were 75 or more years of age (sample B: n = 199). Previously, 47 records were discarded because they did not contain all the necessary data.

As well as the detailed description of the retina examination made by experts (indirect binocular ophthalmoscopy, biomicroscopy, color retinography, and/or fluorescein angiography, according to the findings), the following data were considered: age, sex, type of diabetes, duration of diabetes, frequency of monitoring glycemia, monitoring of glycosylated hemoglobin, arterial hypertension, smoking, and sedentary lifestyle (Tab. I).

Control group

In order to compare the prevalence of ARMD in the highest risk group, a retrospective study was made of 200 consecutive files of 75-year-old or older nondiabetic patients (Tab. II).

Terminology

To precisely define the diagnostic criteria and terms to be used for describing and classifying the findings of the retina examination, the following norms were followed: 1) for diabetic retinopathy, the International Classification proposed by the Global Diabetic Retinopathy Project Group was used (15); 2) for ARM, early and late lesions were considered separately, reserving the term ARMD exclusively for the latter (late lesions) in accordance with the International Age-Related Maculopathy Epidemiologic Study Group (16, 17).

Early ARM lesions included drusen—hard/soft (isolated and/or confluent), pigmentary macular alterations, and hyper- or hypopigmentation. Late ARM lesions (ARMD) included atrophic or dry form or neovascular or exudative form.

RESULTS

The sample of diabetic patients from 65 to 74 years of age included 263 individuals. Among them, 40.35% showed some degree of retinopathy (106/263). Forty-five

TABLE I - DIABETIC PATIENTS WITH AGE-RELATED MACULOPATHY (65 years old or older) (N = 15)

	Early lesions	**Late lesions (ARMD)**
Total	6	9
Type of lesions	Hard drusen 2 Soft drusen 3 Focal hyperpigm 1	Exudative form 7 Dry form 2
Mean age, y	75	76
Sex, F/M	4/2	Exudative: 5/2 Dry: 1/1
Type of diabetes	Type I 0% Type II 100%	Type I 11.11% Type II 88.99%
Duration of the diabetes, yr	5	13
Control for HbA1c	66%	100%
Arterial hypertension	60%	75%
Smoking	25%	25%
Sedentary lifestyle	25%	60%
Diabetic retinopathy	0%	11% (1/9)
Type of retinopathy		1 case of mild nonproliferating diabetic retinopathy

had received panretinal photocoagulation and 12 had received focal or grid macular laser; none of them presented AMD lesions.
This subsample presented the following prevalence of ARM: early ARM lesions: 1 patient (1/263 = 0.38%); late ARM lesions (ARMD): 4 patients (4/263 = 1.52%).
The sample of diabetic patients 75 years of age or older included 199 individuals. Among them, 30.15% showed some degree of retinopathy (60/199). Twenty had received panretinal photocoagulation, and 19 had received focal or grid macular laser; none of them presented AMD lesions.
The prevalence of ARM found was as follows: early ARM lesions: 5 patients (5/199 = 2.51%); late ARM lesions (ARMD): 5 patients (5/199 = 2.51%) (Tab. I).

Prevalence of ARM in the general population

Table III presents the prevalence of ARM in the general population (control group and epidemiologic studies: Beaver Dam Eye Study, Framingham Eye Study, Blue Mountains Eye Study, and Rotterdam Eye Study) and the prevalence found in the sample of diabetic patients (18).
The difference was statistically significant and the risk was simultaneously greater of having ARM in the general population group vs the sample of diabetic patients in the following cases.

TABLE II - CONTROL GROUP (Nondiabetic patients 75 years old or older*) (N = 200)

Sex	Female 71.5% (143/200)/Male 28.5% (57/200)
No ARMD	89% (176/200)
ARMD	11% (22/200); Dry form: 50% (11/22), Exudative form: 40.90% (9/22), Mixed: 9.09% (2/22)

*Mean age = 81 years (range 75-99)

Control group (75 years or older)

The prevalence of early ARM lesions in this group was 12% (24/200). Among them, 50% (12/24) presented macular pigment epithelial abnormalities, and 50% (12/24) presented macular drusen. p (Fisher) = 0.000179; OR 5.29, 95% CI 1.98–14.17. The prevalence of late AMR lesions (ARMD) in control group was 11% (22/200). Among them, 50% (11/22) presented the dry form, 40.9% (9/22) presented the exudative form, and 9.09% (2/22) were mixed. p (Fisher) = 0.0005; OR 4.7955, 95% CI 1.7781–12.0334.

Beaver Dam Eye Study

Early ARM lesions in the 65 to 74 age group were p (Fisher) = 0, OR 58.54, 95% CI 8.171/419.33; early ARM lesions in age group 75 years or older were p (Fisher) = 0, OR 16.23, 95% CI 6.584/40.012; late ARM lesions (ARMD) in age group 75 years of age or older were p (Fisher) = 0.009, OR 2.930, 95% CI 1.152/7.450.

Framingham Eye Study

Early and late ARM lesions and visual acuity equal to or less than 20/30 in general population age group 65 to 74 years of age were p (Fisher) = 0.0005, OR 4.462, 95% CI 1.601/12.433. Early and late ARM lesions (AMD) and visu-

TABLE III - PREVALENCE OF AGE-RELATED MACULOPATHY: DIABETIC PATIENTS VS GENERAL POPULATION

	Early lesions (64–75 yr)	**Late lesions (64–75 yr)**	**Early lesions (≥75 yr)**	**Late lesions (≥75 yr)**
Diabetic sample	0.38% (1/263)	1.52% (4/263)	2.51% (5/199)	2.51% (5/199)
Control group				11 % (22/200)
Beaver Dam	18.3% (227/1243)	1.4% (17/1243)	29.50% (210/712)	7.02% (50/712)
Framingham Eye Study	Early + late 6.4% (55/853)		Early + late 19.7% (78/396)	
Blue Mountains	8.5% (102/1198)	0.70% (8/1198)	17% (128/752)	7.31% (55/752)
Rotterdam Eye Study		0.68% (16/2358)		4.96% (85/1713)

al acuity equal to or less than 20/30 in general population, age group 75 or more years old, were p (Fisher) = 0, OR 6.727, 95% CI 3.041/14.880.

Blue Mountains Eye Study

Early ARM lesions in general population, age group 65 to 74 years of age, were p (Fisher) = 0, OR 24.383, 95% CI 3.386/175.578. Early ARM lesions in general population, age group 75 or more years old, were p (Fisher) = 0. OR 7.959, 95% CI 3.210/19.731. Late ARM lesions (ARMD) in general population, age group 75 or more years old, were p (Fisher) = 0.006, OR 3.061, 95% CI 1.208/7.754.

Rotterdam Eye Study

The prevalence of ARM showed no statistically significant differences with respect to that found in our sample of diabetic patients (Tab. IV).

Statistical analyses

Based on the prevalence in exposed and nonexposed subjects, the attributable risk, relative risk, and estimated relative risk (OR) were determined with a confidence interval of 95%. The alpha significance level was 0.05% (Fisher). The program EPIINFO 6.04 was used.

DISCUSSION

ARMD and DR are the two pathologies that produce most cases of legal blindness in adults in industrialized societies in the Western world.

It is remarkable that, given the overwhelming epidemiologic importance of this fact and with a shared physiopathologic aspect (angiogenesis), the published works analyzing whether there is an association between these are scarce and, even more so, that their results are contradictory. There are publications that conclude stating the existence of such an association (6, (Available at: http://www.ncbi.nlm.nih.gov/pubmed/3877089?ordinalpos=82&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum) 8), while others reject this (1, 7, 9-14).

Our clinical experience leads us to believe that the prevalence of ARM is lower in diabetic patients than in the general nondiabetic population. This is the hypothesis underlying the present comparative (descriptive, observational, and retrospective) prevalence study.

The term ARM was used to cover both early lesions (drusen

TABLE IV - AGE-RELATED MACULOPATHY: RISK ANALYSIS GENERAL POPULATION VS DIABETIC PATIENTS

		Relative risk	95% CI	OR	95% CI	p (Fisher)
Control group	LL ≥75			4.79	1.7781–12.9334	0.0005
Beaver Dam						
Eye Study	EL 65–74	48,030	6,767–340.911	58.53	8.1716–419.334	0
	LL 65–74					0.513
	EL ≥75	11.739	4.904–28.100	16.231	6.584–40.012	0
	LL ≥75	2.795	1.130–6.914	2.930	1.152–7.450	0.009
Framingham	EL + LL 64–75	4.239	1.551–11.588	4.463	1.602–12.433	0.0005
Eye Study	EL + LL ≥75	5.600	2.634–11.906	6.728	3.042–14.881	0
Blue Mountain	EL 65–74	22.392	3.138–159.776	24.383	3.386–175.578	0
Eye Study	LL 65–74					0.154
	EL ≥75	6.774	2.811–16.328	7.959	3.210–19.731	0
	LL ≥75	2.911	1.181–7.175	3.062	1.209–7.754	0.006
Rotterdam						
Eye Study	LL 65–74					0.133
	LL ≥75				0.078	

EL = Early age-related maculopathy lesions; LL = Advanced or late age-related maculopathy lesions

and/or pigmentary macular alterations) and late lesions (atrophic or dry as well as exudative or neovascular). The expression "age-related macular degeneration" was reserved exclusively for the late or advanced forms.

In terms of the type of late ARM lesions, it is interesting to note the higher prevalence in our diabetic patients sample of the exudative or neovascular form over the atrophic or dry form in an inverse proportion to its prevalence in the general population.

Even though the internal analysis of our sample comparing diabetic patients with ARM vs diabetic patients without ARM is outside the scope of the present work and will be the basis of another presentation, it obliges us to make a brief comment: diabetic patients with ARM have been described as neither more hyperglycemic, nor more obese, nor more hypertensive than diabetics without ARM. But, at the same time, the relative risk of mortality for cardiovascular reasons in diabetic patients with ARM is 4.7 times higher than in diabetic patients without ARM (8).

In our series, diabetic patients with ARM show no significant differences in relation to the total sample of diabetics, either in two recognized ARM risk factors (age and smoking) or in other parameters such as arterial pressure, type of diabetes, or glycemia monitoring. The most significant difference between the two groups was the prevalence of diabetic retinopathy: 35.25% in the total sample vs 6.66% among diabetics with ARM (Tab. I).

This coincides with the conclusions of Zylbermann et al, who detected a low prevalence of the exudative form of ARMD in diabetic patients with retinopathy vs diabetics who did not present retinopathy (1). This finding coincides with the communications of Benson et al and Klein et al (7, 13). The second finding in Zylbermann et al's study was that the prevalence of the exudative form was lower in photocoagulated diabetic patients vs diabetic patients whose retinopathy required no photocoagulation—0% vs 3.3%.

In our sample, of the seven diabetic patients presenting the exudative form of ARMD, only one presented DR (mild nonproliferative DR). In our series, no diabetic patient with photocoagulated retinopathy presented ARM in any of its stages.

To make the comparative study between the prevalence of ARM in our sample of diabetic patients and the prevalence of ARM in the general population, the data were matched with a control group and the following epidemiologic studies: Beaver Dam Eye Study, Framingham Eye Study, Blue Mountains Eye Study, and Rotterdam Eye Study (6, 7, 12, 18-21) (Tab. III).

For this analysis, the same age groups were considered in our study as in the epidemiologic studies cited: 65 to 74 years (n = 263) and patients over 75 years of age (n = 199).

The results show, except for the Rotterdam Eye Study, that in the high ARM risk age group (75 or more years of age), all the differences were statistically significant in the sense of a lower prevalence of ARM in the diabetic patients. (The OR for the general population was between 2.9 and 4.7 for late lesions in that age group) (Tab. IV).

It is important to stress two aspects of the Rotterdam Eye Study: 1) it shows a lower prevalence of ARM in this European population than similar populations in the United States, and 2) its diagnostic method based on 35º nonstereoscopic color photographs may give an underestimate.

Early ARM lesions in the 65-74 years old age group were statistically significant lower in our sample of diabetic patients than general population in all epidemiologic studies. The differences of prevalence of late lesions in this age group were statistically significant in the same sense with the results of the Framingham Eye Study.

The authors whose studies show the nonexistence of an association between diabetes and ARM have put forward various theories: 1) one possible explanation is that the alteration of the metabolic activity of the neurosensory retina and the pigmentary epithelium, plus the vascular effect on the choroids generated by the diabetes, could reduce the production of detritus that accumulates in Bruch membrane and form the drusen; 2) an alternative hypothesis is that the modification of the structure of Bruch membrane in diabetes may interfere with the deposit of the material that forms the drusen (1).

Nevertheless, the physiopathologic link of angiogenesis factors such as VEGF, angiopoietin, and insulin-like growth factor-1, added to inflammatory, hemorheologic, and endothelial dysfunction factors present in the diabetic patients, have been clearly associated with ARMD (2, 22).

The contradictory aspects of the relation between diabetes and ARM may be connected with genetic and physiopathologic differences between the retinal angiogenesis (diabetes) and the choroidal-subretinal angiogenesis (ARMD), as well as the metabolic and histologic factors already mentioned.

In conclusion, according to the data from our sample:

1) The prevalence of ARM (both early as well as late lesions) in diabetic patients is significantly lower than in the general population in the high-risk age group of 75 years and over.

2) The prevalence of ARM is even lower among diabetic patients with retinopathy, whether or not they have been treated with photocoagulation, suggesting the hypothesis that

the retinopathy may act as an additional "protection factor." 3) In diabetic patients, the exudative form was more frequent than the atrophic form, in an inverse ratio to that of the general population.

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