

## Three Years Follow-Up Incidence of Retinopathy, In Type 1 Diabetic Patients, In a Population-Based Screening Program with Digital Retinal Photographs

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### Abstract

**Purpose:** To determine the incidence of diabetic retinopathy (DR) and risk factors associated with its development in a cohort of patients with type 1 diabetes mellitus (DM 1), after three years of follow up, with annual retinal photograph by teleophthalmological means.

**Methods:** Prospective cohort study of DM 1 patients, medically assisted in the Puerta del Mar Hospital Endocrinology Unit between 2009 and 2010, without DR, or with any degree of retinopathy that requires no treatment. Patients undergo endocrinological study. Control of blood glucose, glycosylated hemoglobin (HbA1c), blood pressure, dyslipidemia, renal dysfunction and smoking were recorded. Annually, three pictures are taken in each eye with a non-mydratic digital retinal camera and are included in the intranet tool of the Andalusian Integral Diabetes Plan for remote analysis and grading. The cumulative incidence of DR after three years of follow up and the relationship between the recorded risk factors and the onset of DR is analyzed

**Results:** One hundred and forty-three patients were included in the study. The incidence of RD at 3 years follow-up was 23.1%. Baseline HbA1c showed a clear trend towards significance to the development of the RD ( $p=0.06$ ). The duration of diabetes and other considered risk factors showed no significant values in the statistical analysis.

**Conclusions:** This study provides the first results of cumulative incidence of DR in a cohort of DM 1 patients, followed-up through the Tele-ophthalmology tool of the Integral Diabetes Plan of Andalucía, which was 23.1%. Only baseline HbA1c showed a trend toward significant association in the development of RD.

**Keywords:** Retinopathy; Diabetic patients; Digital Retinal Photographs

### Introduction

Diabetic retinopathy is the leading cause of legal blindness in working age, in the developed world [1], being the most important early onset ocular complication of diabetes mellitus (DM). Different studies claim that most DM1 patients have retinopathy after 15 years of disease. The Diabetes Control and Complications Trial (DCCT) have greatly strengthened the evidence that a good glycemic control prevents or slows the microvascular complications of diabetes, including retinopathy [2].

At this time, the Andalusian Health System has a network of over 140 retinographs connected by intranet for remote assessment of diabetic patients.

In 2004 started the IT application for the Diabetic Retinopathy Early Detection Program (DREDP) included in the Comprehensive Plan for Diabetes in Andalucía [3]. Diabetic retinopathy detection in DM type 2 patients is performed by retinal photographs which are inserted into the intranet and are remotely evaluated by general practitioners. Pathological, doubtful or non-valuable images are

referred to the ophthalmologist through the intranet. Pictures of diabetic patients who have no prior eye examination or who have not been diagnosed as diabetic retinopathy are taken. In 2009, images of type 1 diabetic patients reviewed in several hospital endocrinology units were added.

Different ophthalmological societies and study groups have established deadlines for the review of the fundus in diabetic patients. Maguire y cols suggest that adolescents (in reasonable metabolic control) could safely be screened every 2 years rather than the currently recommended 1-year interval [4,5]. The final goal of the research group is to determine the frequency of screening for diabetic retinopathy in DM1 patients older than 14 years.

Our first efforts focused on DM1 patients followed-up annually at the University Hospital Puerta del Mar of Cadiz to analyze the cumulative incidence after three years for diabetic retinopathy and the relationship with systemic risk factors (HbA1c, HTA, DLP, albuminuria, smoking) that can precipitate its development.

## Methods

### Study Population

This project consists of a prospective cohort study nested, within a population screening program for the early detection of diabetic retinopathy (DREDP) of Andalusia, with a follow-up of three years.

One hundred eighty-nine patients with DM1, aged over 14 years, completed the study protocol at the Puerta del Mar University Hospital.

Under the terms approved by the ethics committee of the Hospital, absence of retinopathy and mild to moderate retinopathy not susceptible to treatment were inclusion criteria. No valuable images and other retinal pathologies were exclusion criteria. Patients with retinopathy were included in a sub-group to analyze the factors for diabetic retinopathy worsening. (and are not analyzed in this paper.) We consider "worsening" when retinopathy needs treatment. Qualitative and quantitative differences in the criteria of "onset of retinopathy" and "worsening" lead us to analyze separately the results for each sample group and presented in different reports.

### Procedure

Annually and for 3 consecutive years, three photographs were taken in each eye with a retina digital non-mydratic camera and the influence of independent variables (years of evolution of DM, glycemic control, hypertension, nephropathy, dyslipidemia, and smoking) were analyzed at the onset and progression of DR. The degree of DR was classified according to the international scale of gravity agreed in 2002 on a proposal from the American Academy of Ophthalmology.

### Retinography management

The non-mydratic retinal camera Topcon NW-100 was used for diabetic retinopathy screening. In absence of DR, three photographs in each eye, focusing on the central, nasal and temporal fundus fields were obtained every year. Images were made by a trained nurse experienced in handling retinal fundus camera. All the images were uploaded to a central server. General practitioners and endocrinologists give the first results, and they send the pathological images, through the IT application, to specialized ophthalmologists to evaluate and classify the degree of DR.

### Statistical analysis

Statistical calculations were performed using IBM SPSS Statistics 22. The procedures were approved by institutional review board at Puerta del Mar University Hospital and adhered to the principles of the Declaration of Helsinki.

## Results

A total of 189 patients were studied. At baseline, 143 patients (75.6%) did not show DR while 46 (24.3%) did. These 46 patients were not included in the calculation of incidence. After 3 years of follow up, 33 patients developed DR, finding an incidence of 23.1%. Of all patients who develop DR, 24 (16.8%) developed mild DR and 9 (6.3%) moderate DR. We have not found any cases with severe or proliferative diabetic retinopathy.

Table 1 shows the patient characteristics and their relationship to the development of DR. Duration of diabetes or the presence of other risk factors such as hypertension, dyslipidemia, and microalbuminuria showed no statistically significant values. However, we found clear trend to statistical significance ( $p=0.06$ ) at baseline HbA1c for the development of DR. Table 2 shows the cumulative incidence recorded annually in each of the 4 retinal photographs that have been made to patients.

	(n=143)	Valor P
Age (years)	33.83 ± 12.2	0.934
Gender % (male/female)	46.2 / 53.8	
Diabetes duration (years)	15.7 ± 11.8	0.523
HbA1c baseline	7.6 ± 1.1	0.06
Hypertensión (>140/90 mmHg)	13.3%	0.54
Smoking	21.7%	0.684
Dyslipidemia	14.7%	0.563
Diabetic Nephropaty	5.6%	0.198

**Table 1:** Characteristics of the study population and regarding the development of DR.

Percentile	HbA1c	DR/N	Incidence DR (%)
0-25	4.9-6.8	3/33	9.1
25-50	6.9-7.5	10/35	28.6
50-75	7.6-8.3	9/35	29.7
75-100	8.4-11.4	9/30	30

**Table 2:** Incidence of DR, shows quartile glycosylated hemoglobin.

## Discussion

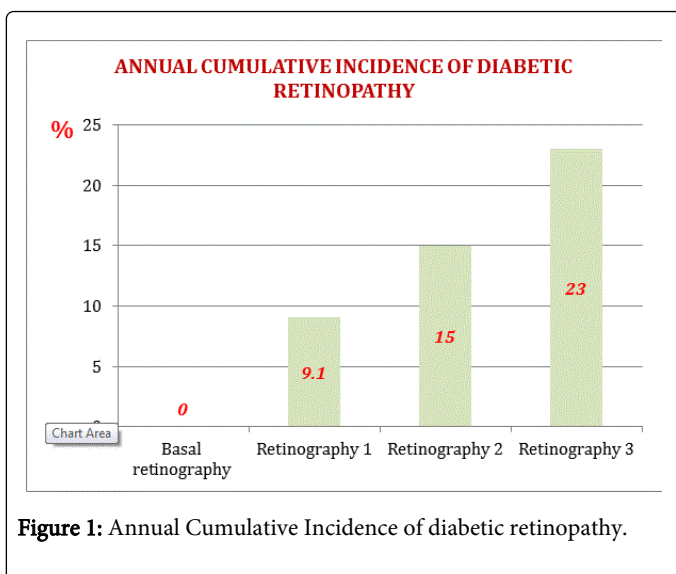
Our 3-year study was consistent with similar studies published to date. The Blue Mountains Eye Study (BMES) (5) obtained an incidence of 22.2% similar to our result of 23%. However, studies such as the Liverpool Diabetic Eye Study [6,7] and DIRECT Prevent 1 [8] exceeded 30% in five years; possibly our shorter follow-up is associated with a lower incidence. The study conducted at the Hospital of Lariboisiere in Paris [9] shows similar results to ours, but with a significantly lower incidence of 14%, possibly because it includes DM type 1 and 2, which makes the results not be comparable in all respects.

In our study, the mean years of diabetes duration was  $15.7 \pm 11.8$  years, the same as the Liverpool Diabetic Eye Study [6,7] and significantly higher than other studies as the AusDiab study [10] of Australia that was 5 years and at BMES (5) was 7.4 years.

The duration of diabetes and HbA1c levels are the most important risk factors to date for the incidence of RD. We found no statistically significant for any relationship, however HbA1c values show a clear trend toward significance ( $p=0.06$ ). These results are consistent with those obtained by Broe et al. [11] in a study of a Danish cohort and

Verdaguer et al. [12] conducted in the Ophthalmological Foundation of the Andes.

Despite being a prospective cohort our results have the inconvenients of an insufficient sample and a short follow-up. Furthermore patients are closely monitored in hospital consultations of Endocrinology. May be we need a higher volume of patients and/or a longer follow-up for extrapolating our results to the general population. It would be very important in the near future, to incorporate into this cohort to all people with type 1 diabetes to assess the actual cumulative incidence of diabetic retinopathy in our setting Figure 1.



**Figure 1:** Annual Cumulative Incidence of diabetic retinopathy.

In summary, our study provides the first results of a cohort of DM 1 patients in Cadiz (Andalusia, Spain) at 3 years follow up. The only value found with clear trend towards statistical significance was baseline HbA1c. Other factors such as years of evolution, hypertension, dyslipidemia, smoking and nephropathy showed no significance, meanwhile other studies showed significance with years of evolution [13] and renal involvement [14]. The more prolonged follow-up of this cohort will establish with more precision the risk of progression of retinopathy and severe vision loss and permit us to know risk factors that should be considered with priority.

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