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Changing trends in the prevalence of diabetic retinopathy in type 1 diabetes mellitus from 1990 to 2018: A retrospective study in a Portuguese population

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ABSTRACT

Purpose: To estimate the prevalence of diabetic retinopathy /(DR) in a Portuguese population with type 1 diabetes (T1DM).
Methods: Retrospective review of all patients with T1DM, whose reference center was Centro Hospitalar de São João, a tertiary center in Portugal, who were diagnosed between 1990 and 2018. DR was classified based on fundus examination in medical records as (0) no evidence of retinopathy, (1) mild non-proliferative retinopathy (NPDR); (2) moderate to severe non-proliferative retinopathy (NPDR) and (3) proliferative retinopathy (PDR). Patients were classified according to the eye with a worse retinopathy stage. Follow-up was considered as time between the diagnosis of diabetes and the last funduscopic evaluation.
Results: 233 patients met the inclusion and exclusion criteria. The prevalence of any DR at less than 5, 10, 15, 20 and more than 20-years of DM was 1.8%, 10.4%, 34.8%, 54.1% and 71.2% respectively. The overall prevalence of DR was 43.3% (n = 101). At the last observation, 43 patients (18.5%) had mild NPDR, 34 patients (14.6%) had moderate to severe NPDR and 24 patients (10.3%) had PDR. The longer the disease duration, the higher the number of patients with DR.
Conclusion: The prevalence of DR in our cohort was 34.8% after 15 years of systemic disease and

Abbreviations: **DR**, diabetic retinopathy; **T1DM**, type 1 diabetes mellitus; **DM**, diabetes mellitus; **WESDR**, Wisconsin Epidemiologic Study of Diabetic Retinopathy; **EURODIAB**, European Diabetes Centers Study of Complications in Patients with Insulin- dependent Diabetes Mellitus; **DCCT**, Diabetes Control and Complications Trial; **PDR**, proliferative diabetic retinopathy; **NPDR**, non-proliferative diabetic retinopathy; **HbA1c**, hemoglobin A1c; **WDRS**, Wisconsin Diabetes Registry Study; **EDIC**, Epidemiology of Diabetes Interventions and Complications

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54.1% after 20 years, which is lower than what has been reported in the literature. Further multicentric prospective studies, are needed to clarify changes in the epidemiology of DR in type 1 diabetics.

1. Introduction

Diabetic retinopathy (DR) remains one of the leading causes of visual impairment in industrialized countries [1–3]. Data from large worldwide epidemiologic studies indicate that the incidence of type 1 diabetes mellitus (T1DM) has been increasing by 2% to 5% worldwide [4]. Despite the marked advances in diabetes mellitus (DM) care in the last years, DR remains a major microvascular complication [5].

Traditionally, estimates from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) from the 1980s and the European Diabetes Centers Study of Complications in Patients with Insulin-dependent Diabetes Mellitus (EURODIAB) from the 1990s have been used for estimating incidence and progression of DR. The WESDR reported retinopathy to be present in nearly all patients with T1DM after 14 years of systemic disease and in all patients with T1DM after 25 years of diagnosis [6–7]. In the EURODIAB study the prevalence of retinopathy in type 1 diabetics was 82% after 20 years or more of diabetes [8].

The Diabetes Control and Complications Trial (DCCT) was published in 1993 and it documented that intensive diabetes management can prevent or delay end organ complications. As a result the management of DM has changed as most physicians target near physiological glycemic levels [9]. Moreover, treatment innovations including multiple daily injection regimens, continuous subcutaneous insulin infusion with external pumps, new insulin analogues with more physiologic pharmacokinetic characteristics, wide- spread self-monitoring, and improved treatment of comorbidities, have all allowed a better control of DM [5,10]. These extraordinary changes in DM management in the past decades, may have changed the epidemiological patterns of DR.

There is evidence that the prevalence and incidence of DR, including proliferative diabetic retinopathy (PDR), may be decreasing in patients more recently diagnosed with type 1 diabetes [5,10–13]. These lower rates of DR may reflect a better control of blood glucose levels and known risk factors associated with the development of DR (e.g. hypertension, dyslipidemia and smoking). The history of DR in T1DM may be changing.

Contemporary data on DR prevalence in type 1 DM remains scarce. Given the progressive changes in the standard of care of diabetic patients, reanalysis of DR epidemiology using large studies are necessary.

The aim of this study is to evaluate prevalence of DR in a Portuguese population with type 1 diabetes.

2. Methods

A retrospective analysis of all patients with type 1 DM attending the Endocrinology Department of Centro Hospitalar de São João (CHSJ) and referred to either the Ophthalmology Department of CHSJ or the national diabetic retinopathy screening program for routine eye examination. Data collection was performed through the clinical files of each patient.

This study was conducted in accordance with the Helsinki Declaration and was approved by the Ethics Committee of Centro Hospitalar de São João.

2.1. *Sample*

Our target population included all DM1 patients from the referral regions of CHSJ, aged >18 years and alive at the time of the study (2018).

Using the last available census and epidemiological records, from 2011 the hospital referral region of this tertiary center has a population of around 340.000, with about 200.000 aged above 18 [INE, Censos] [14]. A Portuguese study has estimated, the prevalence of T1DM in the North of Portugal to be 1.66 cases per 1000 [15]. Assuming these estimations, a population of about 330 T1DM patients is expected in our referral region.

The initial sample was composed by 469 patients diagnosed with DM1 between 1950 and 2010. Patients diagnosed before the DCCT era (before 1990) were excluded. Patients with unknown date of DM1 onset, uncertain diagnosis, incomplete medical records and without ophthalmologic observation were also excluded. After applying the exclusion criteria, 233 patients diagnosed between 1990 and 2018 were included. The sample size met our initial estimates, and we were able to consider the sample as an adequate representation of our target population.

2.2. *Ophthalmologic evaluation*

Screening and grading of DR was performed in routine ophthalmological visits of the tertiary center using indirect funduscopy under pharmacological mydriasis. The results were obtained from medical charts. In some patients, in which this information was not available in medical charts, the investigators searched for fundus photography available in the national diabetic retinopathy screening program. Briefly, in this screening program two 45° retinal fields are photographed (one centered on the macula and the other on the optic disc). Diabetic retinopathy was classified as (0) no evidence of retinopathy, (1) mild non-proliferative diabetic retinopathy (NPDR); (2) moderate to severe NPDR and (3) proliferative retinopathy (PDR). Patients with panretinal photocoagulation were included in the latter group. Patients were classified according to the eye with the worse retinopathy stage.

The overall prevalence of any DR at 5, 10, 15, 20 and more than 20-years of type 1 DM was calculated.

Follow-up time was considered as time between the diagnosis of DM and the last fundus evaluation.

2.3. Endocrinological evaluation

Data on the date of DM1 onset and years of DM1 until the last follow-up were collected from medical charts.

For metabolic control assessment, all hemoglobin A1c (HbA1c) measurements available for each patient on medical records were collected and the mean HbA1c for each patient was calculated. Only patients with at least two measurements were included.

HbA1c levels were determinated by methods certified by the National Glycohemoglobin Standardization Program (NGSP), traceable to the reference of the Diabetes Control and Complications Trial (DCCT) and calibrated according to the standardization of the International Federation of Clinical Chemistry and Laboratory Medicine [16].

2.4. Treatment

Individual information regarding insulin therapy were collected. For further statistical analysis patients were classified based on the presence/absence of an insulin pump. Patients without insulin pumps were classified as using "functional insulin therapy" (carbohydrate counting for insulin dosing) or "fixed-dose insulin therapy".

2.5. Co-morbilities and late complications of DM1

The existance of co-morbilities and late complications were evaluated from clinical charts and defined according to the following criteria.

Hypertension was defined in subjects with a blood pressure 140/90 mmHg or who reported being on treatment for hypertension [17]. Dyslipidaemia was diagnosed if: one lipid variable was permanently increased or if patients reported treatment for dyslipidemia. The cut-offs used were: LDL cholesterol (low-density lipoprotein) >149 mg/dl; HDL cholesterol (high-density lipoprotein) <40 mg/dl for males and <50 mg/dl for females; TG cholesterol (triglyceride) >150 mg/dl; and, total cholesterol >200 mg/dl [18].

The patients' data on height, weight, body mass index (BMI), systolic and diastolic blood pressure at final follow-up were collected.

Data on social demography data (self-reported tobacco consumption and physical activity) were collected from the clinical files. If at least one cigarette per day was reported, patients were classified as smokers. Physical activity was considered if the patient reported weekly physical activity (either gym, walking, or group activities).

The presence and absence diabetic neuropathy and nephropathy was also collected.

2.6. Laboratorial data

Data collection also included the following variables: total cholesterol, LDL and HDL lipoprotein, TG, serum creatinine and 24-hour microalbuminuria. Glomerular filtration rate was calculated using the Cockcroft-Gault formula.

2.7. Statistical analysis

Categorical variables are presented as frequencies and percentages and were compared using Chi-square or Fisher tests when appropriate. Continuous variables are presented as mean ± standard deviation or as median (interquartile range) depending on the type of distribution and were compared using Mann-Whitney or independent t-tests. A p value of $p < 0.05$ was considered statistically significant. All data was analysed using statistical software SPSS Version 23 for Windows.

3. Results

A total of 233 type 1 diabetic patients were included in this study. Of these, 126 (54.1%) were males. The median age at DM onset was 21 (range, 1–63) and 37 (range, 17–95) at the last

Table 1 – Baseline demographic and clinical characteristics of type 1 *diabetic mellitus* patients included in the study.

Baseline demographic and clinical characteristics of the study group	
Sociodemographic Factors	
Age at follow up, *years*	37 [17–95]
Sex	
Men	126 (54.1)
Current or former Smoker	68 (29.2)
Self-reported physical activity	52 (22.3)
DM related Factors	
Age at DM diagnosis	21 [1–63]
Duration of DM, *years*	14 [0–57]
Mean HbA1c, %	8.2 [5.3–12.7]
DM treatment regimen	
Insulin pump	25 (11.2)
Insulin regimen	
– Functional insulin therapy	63 (21.7)
– Fixed insulin therapy	136 (68.3)
Risk factors and co-morbidities	
BMI, kg/m^2	25.07 ± 4.01
SBP, *mmHg*	126 ± 4
DBP, *mmHg*	75 ± 14
Treated hypertension	67 (29.1)
Treated dyslipidemia	89 (39.2)
Nephropathy	46 (21.8)
Neuropathy	30 (16)
Laboratory parameters	
Total cholesterol, *mg/dL*	177.3 ± 63.2
HDL cholesterol, *mg/dL*	55.3 ± 13.1
LDL cholesterol, *mg/dL*	99.7 ± 26.3
TG, *mg/dL*	108.1 ± 71.4
Urine microalbuminuria/24 h > 30 mg/dl	37 (19.7)
GFR, *ml/min/1.73* m^2	80.7 ± 39.1

Values are presented as n(%) or as mean ± standard deviation. DM = diabetes mellitus. HbA1c = glycated hemoglobin. BMI = body mass index. SBP = systolic blood pressure. DBP = diastolic blood pressure. HDL = high density lipoprotein. LDL = low density lipoprotein. TG = triglycerides. GFR: glomerular filtration rate.

follow-up. Table 1 documents the baseline demographic and clinical characteristics of the study group.

The overall prevalence of DR was 43.3% (n = 101/233). At the last visit 43 patients (18.5%) had mild NPDR, 34 patients (14.6%) moderate to severe NPDR and 24 patients (10.3%) had PDR. Fig. 1 shows the prevalence of diabetic retinopathy according to DR severity.

DR was more frequent among patients with a longer duration of DM (median 19 years [range 2–57] vs 10 years [range 0–28] years, $p < 0.001$). The longer the systemic disease lasted, the higher the number of patients with DR. The prevalence of DR at 5, 10, 15, 20 and more than 20 years of DM was 1.8%, 10.4%, 34.8%, 54.1% and 71.2% respectively. Fig. 2 shows the prevalence of diabetic retinopathy by years of systemic disease.

The three patients (1.8%) that had DR with 5 years of DM had mild NPDR. The prevalence of all stages of DR increased consistently overtime, except for mild NPDR, which was similar at 15 and 20 years of follow up (23.7% and 22.7% respectively). Table 2 documents the prevalence of DR by severity within subgroups of DM duration.

The frequency of PDR increased with the number of years of systemic disease. There were no cases in patients with 5 years of diagnosis, but the prevalence was 3.8%, 15.5% and 24.2% in patients with 10, 15 and 20 years of DM respectively. The overall prevalence of PDR was 10.3% (24 cases). Four patients included in the PDR group were reported as very severe NPDR treated with laser panphotocoagulation. Patients with PDR had a longer disease duration than those without PDR (median 19 years [range 9–57] vs 13 years [range 0–42], $p = 0.005$).

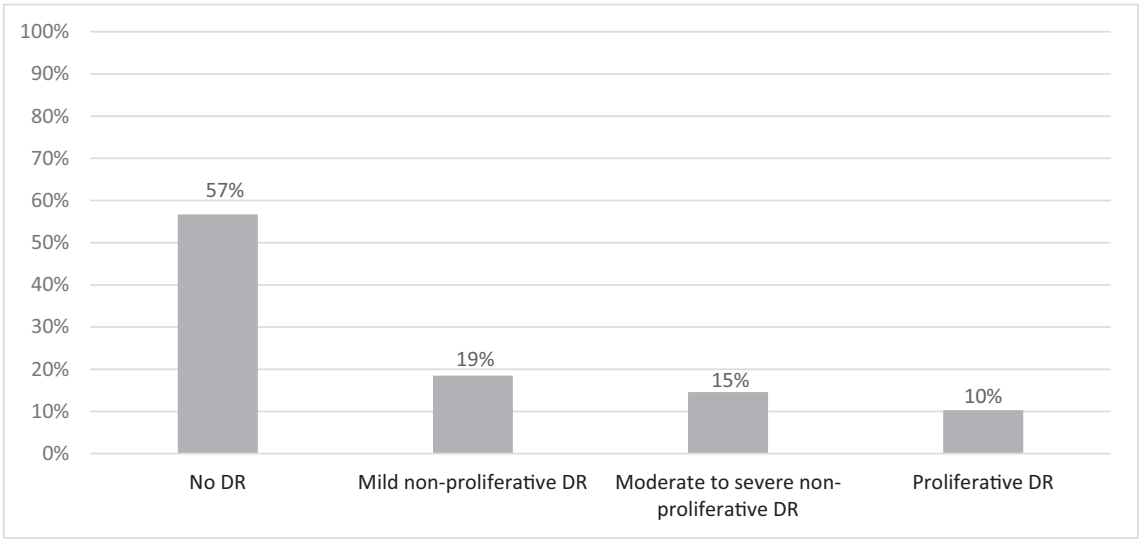

Fig. 1 – Overall prevalence of diabetic retinopathy according to DR severity. *DR = diabetic retinopathy.*

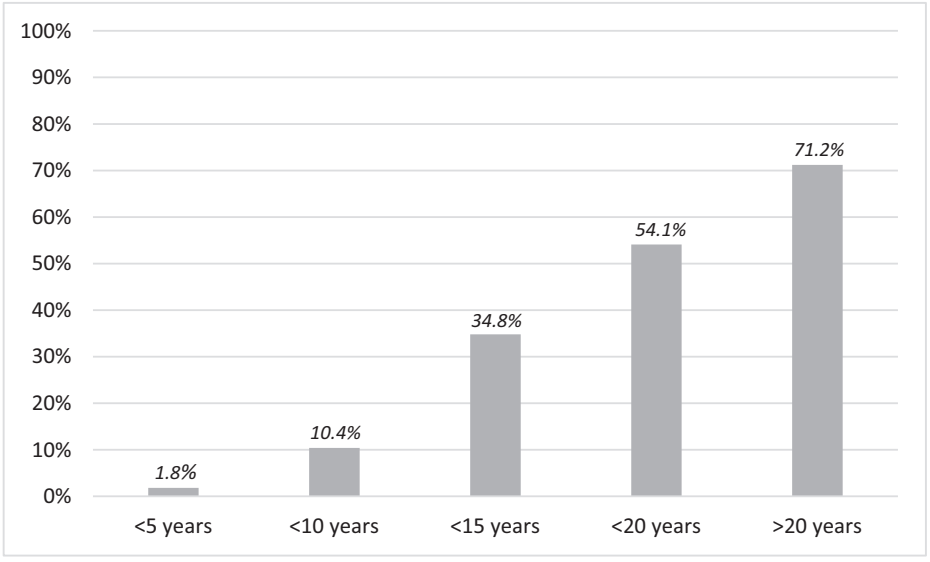

Fig. 2 – Diabetic retinopathy prevalence by years of systemic disease.

Table 2 – Prevalence of DR by severity within subgroups of DM duration.

DM duration	n	DR total *n* (%)	Type of DR		
			Mild non-proliferative retinopathy *n* (%)	Moderate to severe non-proliferative retinopathy *n* (%)	Proliferative retinopathy *n* (%)
0–4 years	170	3 (1.8%)	3 (1.8%)	0 (0%)	0 (0%)
5–9 years	154	16 (10.4%)	12 (7.8%)	1 (0.6%)	3 (1.9%)
10–14 years	132	46 (34.8%)	29 (22%)	12 (9.1%)	5 (3.8%)
15–19 years	98	53 (54.1%)	23 (23.7%)	14 (14.4%)	15 (15.5%)
>20 years	66	47 (71.2%)	15 (22.7%)	16 (24.2%)	16 (24.2%)

DR = diabetic retinopathy; DM = diabetes mellitus.

DR was equally frequent amongst males and females (p = 0.15). No associations were found between the prevalence of DR and the age at DM1 diagnosis (p = 0.76).

During a mean period of 13.5 ± 11 years since the initial diagnosis of T1DM, 10 ± 5 HbA1c values were collected per patient. Concerning the long-term metabolic control, significant differences were found. A positive association was found between the prevalence of DR and mean HbA1c. Patients with DR at follow-up presented a higher mean HbA1c than patients without DR (mean HbA1c in patients with DR = 8.9 ± 1.5% , mean HbA1c in patients without DR = 8.0 ± 1.5%, p < 0.001). Fig. 3 shows the mean HbA1c levels of patients with and without DR at follow-up. Mean HbA1c levels were higher in patients with PDR than with NPDR (mean 9.6 ± 1.7% vs 8.7 ± 1.4%, p = 0.01).

According to the American Diabetes Association, a reasonable HbA_1c goal for many nonpregnant adults is 7% (53 mmol/mol) [19]; we grouped our cohort into two groups: mean HbA1c bellow or at 7% and higher than 7%. The first group included 45 patient and the second 188. The prevalence of DR in these two groups were significantly different; those with a better metabolic control presented a much lower prevalence of DR (8.9%) vs (91.1%), (p < 0.001).

4. Discussion

The data reported provides a population-based information on current epidemiology of DR prevalence in T1DM patients. We analyzed, in a long-term follow-up, a cohort composed of a population of all known T1DM diagnosed after 1990 in the hospital's referral region. Remarkably, we reported a lower rate of DR and PDR than previous studies. The overall prevalence of DR was 43.3% and the overall prevalence of PDR was 10.3%.

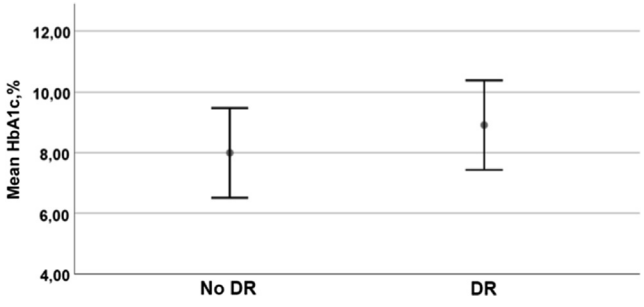

Fig. 3 – The figure represents the mean glycated hemoglobin (HbA1c) and the respective standard deviation in patients with and without diabetic retinopathy (DR) at final evaluation. *DR = Diabetic Retinopathy; Error bars represent the standard deviation.*

Only 34.8% of the patients with T1DM had any form of DR after fifteen years of systemic disease.

Other studies, including the WESDR and the Danish Cohort of Paediatric Diabetes 1987, reported retinopathy to be present in nearly all patients with T1DM after 15 years of disease and in all patients with 20 years of disease [6,8,20]. In our cohort we observed a lower prevalence of DR; 34.8% and 54.1% after the first fifteen and twenty years of disease respectively. Other studies and meta-analyses have also suggested an overall decline in retinopathy incidence and progression rates [5,10–12]. The Wisconsin Diabetes Registry Study (WDRS) was conducted in a cohort of patients diagnosed with T1DM in the same geographic region as the WESDR cohort, but 8–34 years later. They found that retinopathy was less frequent and less severe than in the WESDR cohort. About 73% of patients presented DR after 14 years of systemic disease [21]. Moreover, a Norwegian prospective study from 2018 reported a lower rate of any DR of 68% after 20 years DM [22]. Yau et al, conducted a meta-analysis from population-based studies in 2012 and estimated that the prevalence of DR after 20 years or more of DM was 76.37% [23]. In Portugal, a study conducted in 1992, analysed a cohort of 1302 type 1 diabetics and reported a prevalence of DR of 89.8% after at least 15 years of diagnosis. This prevalence was much higher than the one we report [24]. In contrast, only two studies have reported an increase in DR prevalence [25–26].

This variability of results across multiple studies might be explained by the different study methodologies, by the fact that DR rates fluctuate from different geographic regions, and by the fact that there are different treatment options available in different regions of the world. Furthermore, these different studies cannot be compared amongst themselves due to all the differences in data acquisition.

In our study, we observed that the longer the systemic disease lasted, the higher the number of patients with DR. The duration of T1DM is still the main predictor for the development of DR and the risk of developing retinal disease is cumulative as time of disease progresses. Even though it seems that patients are developing DR later in time after the diagnosis, one must not forget that as each year progresses there is a higher likelihood that a patient will have the first manifestations so screening programs must be thoroughly employed.

Regarding the prevalence of PDR, the majority of the studies are reporting a decrease in PDR prevalence within the

T1DM population [7,10,27–28]. We reported an overall prevalence of PDR of 10.3%, that is consistent with recent published studies [22,28]. In our study, patients with severe NPDR treated with laser panphotocoagulation were included in the PDR group, wich is an overestimation of the prevalence of PDR. We included these patients in the PDR group because it would not be possible to evaluate the history of this condition and some of these patients would eventually develop proliferative disease. Due to the seriousness of this late stage of the retinal disease we preferred to overestimate its prevalence; nonetheless, the prevalence is still inferior to what has been reported. The most recently publication from the WESDR group (2008), found that rates of PDR have declined in patients diagnosed with T1DM. This data suggests that the number of persons with or that will develop PDR over the next 25 years has been overestimated [7]. Kyoto et al reported that the 20-year rate of progression to laser-requiring retinopathy (predominantly PDR), was 23–33% in patients recruited prior to 1979; this figure dropped markedly to 18% in those recruited from 1980 to 84, and further to 6.4% in those recruited after 1985 [28]. Again, these results might be explained by the more aggressive therapeutic regimens and improvements in glycaemic control.

In our study, we included patient with only 5 years of disease and we found that 1.8% had mild non-proliferative DR. Although the American Diabetes Association consensus recommends screening for DR patients with more than 5 years of T1D [19], some studies, revealed that patients with T1D and less than 5 years of disease could present DR [20,29]. The WESDR study reported 49% positive findings for retinopathy when diabetes duration is less than 4 years [7]. Similar results were found by Malone et al, in which 44% individuals with less than 5 years of DM had DR, from which 6 cases had preproliferative DR [29]. This data suggests that in patients with very poor metabolic control, screening for DR should be performed during the first years after diagnosis of type 1 diabetes.

Concerning the evaluation of determinant factors for the development of DR, our results confirmed that the mean value of HbA1c was highly predictive of DR. In our sample, patients with DR presented higher mean HbA1c than patients without DR and that the mean HbA1c was higher in patients with PDR. These findings are in accordance to previous studies [5,7,10]. Interestingly, in our study, having a mean HbA1C lower than 7% meant a substantial reduction in the prevalence of DR (8.9% vs 91.1%, $p < 0.001$) showing that this cut-off may be important for the prevention of the disease.

Overall, our outcomes suggest the positive impact of improved diabetes management during the past decades [5,9,10]. Hyperglycemia is a firmly established risk factor for development of any retinopathy. The DCCT conclusively demonstrated that intensive control of blood glucose levels significantly reduced the risk of microvascular complication for persons with T1DM [9]. Its application in clinical practice may have reduced the prevalence of DR in T1DM patients in the last two decades.

The strengths of our study are as follows: (i) given the lack of data on DR prevalence in Portugal in the most recent years we provide contemporary data on this topic; (ii) a large population size was analysed; (iii) our study was conducted with a long-term follow-up; (iiii) and in contrary with most studies that excludes individuals with older-onset diabetes, our cohort included patient with T1DM diagnosed in all age groups.

Our study has several important limitations. Firstly, this is a retrospective study in which many variables were collected from data available in medical charts. This data was originally collected for clinical purposes and not for this analysis which may have diminished the quality of the data. There were cases of missing data regarding the baseline retinopathy level of participants and it is possible that very early cases of DR might not have been reported or could have been under-reported. These cases were excluded. In addition, for some variables there was a substantial amount of missing data, especially for insulin regimen (type of insulin) and metabolic control of T1DM (the number of HbA1c per time interval were variable from patient to patient), co-morbidities and other late complications of T1DM (for example macrovascular complications). Finally, we only analysed patients referred to our hospital, constricting the geographic region studied; consequently, it is not possible to generalize the results to the general population.

Nonetheless, previous studies reported that DR is almost universal (>95%) between patients with more than 15 years of T1DM. We reported that prevalence of DR has declined, and in our cohort the prevalence of DR after 15 years of systemic disease was 34.8% and 54.1% after 20 years, which is a significant difference from the studies of the 1990s.

Further prospective studies with a systematically collected data on metabolic control and using standardized screening methods for DR for the study population are needed to clarify this possible change in the epidemiology of DR in type 1 diabetics. Studying larger cohorts would also improve the accuracy its prevalence. Careful usage of National Databases used in DR screening programmes are a possible way to overcome the limitations of our study and clarify possible factors involved in these changing trends. However, it seems that improved medical care has led to a great reduction in this blinding complication of T1DM.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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