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ORIGINAL ARTICLE

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Risk factors for prevalent diabetic retinopathy and proliferative diabetic retinopathy in type 1 diabetes

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Abstract

Purpose Age at diagnosis of type 1 diabetes (DM1) has been implied as an important factor associated with the development of the microvascular complications. Our aim was to identify factors associated with prevalent diabetic retinopathy (DR) and proliferative diabetic retinopathy (PDR) in DM1 people with early and late-onset.

Methods We reviewed medical records from all DM1 people from the reference area of a tertiary center (about 340,000 persons). Univariate and multivariate logistic regression were used to assess the relationship between potential risk factors (sociodemographic, diabetes-related, co-morbidities, and laboratory parameters) and prevalent DR/PDR. We performed an analysis comparing patients diagnosed before (early-onset) and after (late-onset) 18 years of age.

Results We included 140 patients in early-onset DM1 group and 169 in late-onset DM1 group. Longer duration of diabetes and HbA1c remained associated with prevalent DR in both groups after adjusting for potential risk factors. Nephropathy was associated with prevalent DR in the late-onset group but not in the early-onset group. Peripheral neuropathy remained associated with prevalent PDR when modeled together in the multivariate model. High BMI demonstrated a significative association with PDR in early but not in the late-onset DM1 group.

Conclusions Although previous reports suggest that age at DM1 diagnosis may have a role in DR prevalence, the risk factors for DR in early and late-onset DM1 were similar for both groups. Duration of disease and lifelong metabolic control were the major predictors for DR in both groups. Nephropathy was associated with DR in patients with late-onset disease. Neuropathy was associated with PDR occurrence in both groups. BMI was associated with PDR early-onset DM1 group.

Keywords diabetic retinopathy · type 1 diabetes · late-onset · risk factors · microvascular disease

Introduction

Type 1 diabetes (DM1) is one of the most common childhood chronic diseases, and its prevalence is increasing [1]. There are 1.1 million children and adolescents with DM1 worldwide and 132,600 new cases occur each year in people aged 0–19 years [2]. While correct diagnosis of DM1 in young people is usually straightforward, because it accounts for most cases of diabetes in that population [3], the identification of DM1 in adults can be challenging. These patients may be erroneously classified with certain forms of type 2 diabetes because of its much higher

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prevalence in adults [4]. Consequently, few studies on epidemiology, natural history and characteristics of DM1 diagnosed in adults are available, as compared to those reporting on early-onset DM1. It is important to include this population in current DM1 studies because of its high prevalence: recent research using genomic methods has suggested that over 42% of DM1 occurs after age 30 [5].

Diabetic retinopathy (DR) is the leading cause of visual impairment and blindness among DM1 people [6] and represents significant social and financial burden for the healthcare systems [7]. The complex pathogenesis of diabetic complications, namely DR, is not fully understood, and the identification of the determinants for its development is essential to reduce the morbidity associated with the disease. Several studies have been conducted [8–13] and well-known risk factors for development and progression of DR include duration of diabetes and metabolic control. However, the relationship between DR and other predictors is not so consistent. In addition, in people with DR, it is also essential to analyze risk factors for progression to the proliferative form of the disease—proliferative diabetic retinopathy (PDR)—because of its higher potential for severe visual impairment [14].

As DR is a marker for generalized microvascular damage, by predicting risk factors for DR we are also indirectly increasing the power for detecting other microvascular complications that cannot be as easily and non-invasively diagnosed [7]. To know the different risk factors for DR it is essential that we can implement solid strategies capable of delaying visual impairment and other microvascular complications in this chronic disease [15].

It is known that DR is rare in patients before puberty [16] and this seems to be independent of the years of diagnosis before puberty [17]. Therefore, age at diagnosis is an important risk factor for the development of DR [16, 18]. Because many DM1 with late-onset disease are underdiagnosed, it is still not clear if an older age of diagnosis has implications in the development of retinal disease. With this study we aimed to investigate factors associated with the prevalence of DR and PDR among DM1 people, and to determine if these factors are different in people that are diagnosed with the system disease after 18 years of age.

Methods

This was an observational retrospective study performed by two departments (Ophthalmology and Endocrinology) from a Tertiary Portuguese Care Center (Centro Hospitalar de São João (CHSJ), Porto, Portugal). All procedures were performed in accordance with the ethical standards of the Ethics Committee of Centro Hospitalar de São João/Faculty of Medicine of Porto University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Sampling

Our target population consisted of all diagnosed DM1 subjects from the reference area of CHSJ, aged > 18 years and alive at the time of the study (2018).

According to the last available local census and epidemiological records, this Center serves a population of about 340,000 persons, of which 200,000 are aged above 18 [19]. According to a previous study performed in Portuguese young adults, the prevalence of DM1 in the mentioned geographical region was estimated at 1.66 cases per 1000 [20]. Assuming these estimations, in the reference area of CHSJ, 330 cases of DM1 are expected to exist.

By merging medical registries, we found 469 subjects diagnosed with DM1 between 1950 and 2017 and we reviewed their medical records. From those, we excluded cases where the diagnosis of DM1 was doubtful by analyzing medical records (uncertain type 1 or type 2 diabetes). We also excluded those with incomplete medical records including absent date of DM1 diagnosis; absent ophthalmologic evaluation after DM1 with adequate DR grading; and, without an endocrinological evaluation. Subjects that did not have at least one fundus ophthalmologic and endocrinological evaluations in the 5 years that preceded the study were also excluded.

After applying the exclusion criteria, 309 subjects were included. The sample size met our initial estimates, and we were able to consider the sample as to adequately represent our target population. From these subjects, 169 (55%) were diagnosed after 18-year-old. In this study we defined early-onset DM1 as DM1 detected before 18 years of age and late-onset DM1 as DM1 detected after 18 years of age.

Ophthalmologic evaluation

DR status was classified as present/absent based on fundoscopy findings in medical records from the last ophthalmological evaluation. We considered absent DR if there was no evidence in medical records of any DR manifestation (microaneurysms, cotton wool spots, intraretinal hemorrhages or macular edema). We also analyzed subjects based on the presence of PDR and compared them with those with non-proliferative DR. Classification was based on fundus descriptions in medical records. People with panretinal photocoagulation were also included in the PDR group. If there was asymmetric retinopathy, the eye with the worst condition was used for classification.

Endocrinological and other evaluations

Data on the date of birth, decade of DM1 diagnosis, and years of DM1 until the last follow-up were extracted. Date of birth was dichotomized in order to adjust the results to eventual changes in the management of DM1. We used the 1970s cutoff as in this date, the National Diabetes Data Group and the World Health Organization developed improved diagnostic criteria [21] for the diagnosis of diabetes that involved measuring glucose tolerance using an oral glucose tolerance test (OGTT). Data regarding the date of DM1 diagnosis were also dichotomized for adjustments purpose. However, in this case, we adopted the 2000's cutoff because people diagnosed after this date were probably treated taken into account the conclusions from the Diabetes Control and Complications Trial (1983–1993) [22] and from the United Kingdom Prospective Diabetes Study (1977–1997) [23] regarding the importance of metabolic control.

The lifelong metabolic control was estimated by extracting all available glycosylated hemoglobin (HbA1c) in the medical records for each patient. We used the final averaged value as an estimate of the patient's metabolic control. At least two values separated by one year were required to include the patient in this analysis. No time frame was considered as exclusion criteria.

Other data extracted for analysis included history of hypertension, dyslipidemia, peripheral neuropathy and nephropathy. The diagnosis of hypertension was considered based on medical records if any the following criteria were met: (1) the patient was taking anti-hypertensive medications; (2) the patient had been diagnosed with hypertension regardless of treatment status. The diagnosis of dyslipidemia was considered the diagnosis was considered based on medical records if any of the following criteria were met: (1) the patient was taking lipid-lowering medications; (2) the patient had been diagnosed with dyslipidemia regardless of treatment status. Peripheral neuropathy or nephropathy (classified as present/absent) were diagnosed based on medical records. We also extracted information regarding the last two available body mass index estimates (kg/m^2), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) evaluations for each individual and averaged.

Data regarding laboratory parameters were also collected. For the following variables, the last two available measurements at the follow-up for each patient were averaged and inputted for analysis: total cholesterol, high and low-density lipoprotein, alanine transaminase, aspartate aminotransferase, gamma-glutamyltransferase, triglycerides, serum creatinine, uric acid and 24-h microalbuminuria. Glomerular filtration rate was calculated using the Cockcroft-Gault formula $\frac{(140-\text{age})\times\text{body mass}}{\text{serum creatinine}\times 72}$ (× 0.85 if woman).

Sociodemographic data

Data on self-reported regular alcohol, tobacco consumption and physical at the last endocrinology evaluation. Because information on these variables is only frequently registered in medical records if present, we had to consider the codification in these variables as yes or no/unknown. Tobacco consumption was considered if the subjects reported to be current or former smokers. Regular alcohol consumption was considered if the patient reported daily consumption of any alcoholic drink. This outcome was considered if the patient reported daily alcohol consumption (regardless of the type of drink). We did not consider the number of drinks per week because of incomplete medical records. Physical activity was considered if the patient reported weekly physical activity (either gym, walking, or group activities).

Statistical analysis

Each potential predictor for DR prevalence was evaluated for its univariate association with DR using exact logistic regression (people without retinopathy were used as the reference group). From these analyses, exact p values were generated thus indicating the significance of the association between each predictor and any DR. For continuous predictor variables, we assessed the assumption of a linear association with DR through visual inspection, and those deemed to have a nonlinear association were modeled as categorical variables, with cut points chosen based on the shape of their association with diabetic retinopathy as well as clinical significance. Predictors were kept in the final model if they were significant at a p value of 0.10 or smaller. All the significant predictors at this point were modeled together in a final logistic regression model. Interaction models were used to evaluate possible co-related variables. Predictors with a p value of 0.10 or greater were removed from the model through forward selection. Odds ratios (ORs) and 95% confidence intervals (CIs) were generated for the predictors that remained in the model. The complete analysis was performed for both groups (early and late-onset DM1).

Results

We included 309 DM1 subjects (51% men, $n = 158$) diagnosed between 1950 and 2017. Mean duration of DM was 19.8 ± 12.3 years and 169 (54.7%) had DR (17.5% PDR). In all, 169 patients were diagnosed with DM1 after the age of 18 (late-onset DM1) and 140 patients were diagnosed with DM1 before the age of 18 (early-onset DM1). Age at diagnosis in the sample is detailed in Fig. 1.

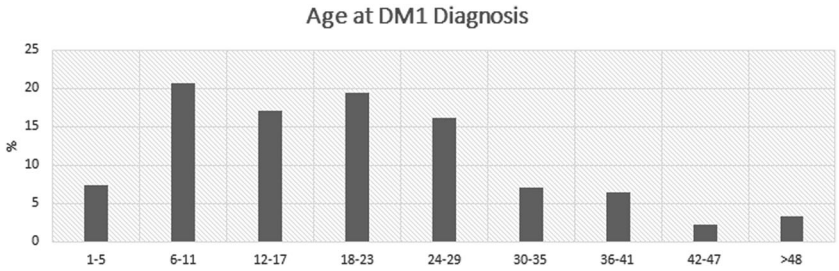

Fig. 1 Percentage of patients in the sample ($n = 309$) by age at type 1 diabetes (DM1) diagnosis

Factors associated with DR and PDR in early-onset DM1

Table 1 shows the overall frequencies and descriptive statistics for the potential predictors reported for prevalent DR and prevalent PDR in patients with early-onset DM1 ($n = 140$), along with the p values summarizing the univariate association of each predictor with either DR or PDR. Median number of HbA1c values per patient was 10 (interquartile range 9, $n = 135$ patients included in this analysis).

Briefly, patients with prevalent DR had longer duration of DM1 and superior mean HbA1c. They were more prone to have systemic hypertension, dyslipidemia, nephropathy, and peripheral neuropathy. Patients with prevalent DR also had superior serum levels of gamma-glutamyltransferase and urine microalbuminuria, as well as inferior glomerular filtration rate. This group also reported less frequent physical activity when compared to the group of patients without DR.

Patients with PDR had longer duration of DM1 and superior mean HbA1c. This group of patients also had a superior BMI and systolic blood pressure. They were more prone to have dyslipidemia, nephropathy and peripheral neuropathy. Patients with prevalent DR also had superior serum levels triglycerides and urine microalbuminuria.

Duration of diabetes and mean HbA1c maintained significative associations with prevalent DR when modeled together in the multivariate model (Table 2). Peripheral neuropathy and BMI demonstrated a significative association with PDR in the final model after adjusting for covariates (Table 3).

Factors associated with DR and PDR in late-onset DM1

Table 4 demonstrates the frequencies and descriptive statistics for the potential predictors reported for prevalent DR and prevalent PDR in patients with late-onset DM1 ($n = 169$). Median number of HbA1c values per patient was 9 (interquartile range 7, $n = 159$ patients included in this analysis).

Briefly, patients with prevalent DR had longer duration of DM1, superior mean HbA1c and superior systolic blood pressure. They were more prone to have systemic hypertension, dyslipidemia, nephropathy and peripheral neuropathy. This group also had inferior glomerular filtration rate and reported less frequent physical activity when compared to the group of patients without DR.

Patients with PDR more prone to have systemic hypertension and peripheral neuropathy than those with DR but without PDR.

Tables 5 and 6 show the associations for the predictors in the final multivariate models for any DR and for PDR, respectively, in this subgroup. In the final models, decade of birth, duration of diabetes, presence of nephropathy and mean HbA1c maintained significative associations with prevalent DR when modeled together in the multivariate model. However, there was a significant interaction between decade of birth and duration of disease (those born before had superior duration of disease, $p = 0.019$). Peripheral neuropathy demonstrated a significative association with PDR in the final model after adjusting for covariates.

In summary, duration of disease and lifelong metabolic control were the major predictors for DR. Besides these factors, we found that nephropathy was associated with prevalent DR in patients with late-onset disease. Peripheral neuropathy was associated with PDR occurrence in both early and late diagnosed DM1. BMI was also associated with PDR in patients with early-onset DM1.

Discussion

In this study, we investigated several potential risk factors for prevalent DR and PDR in DM1 people with early and late-onset. After adjusting for all covariates, duration of diabetes and mean HbA1c maintained significative associations with prevalent DR in both analyzed groups. Nephropathy was also associated with prevalent DR but only on patients diagnosed after the age of 18. Diabetic peripheral neuropathy demonstrated a significative association with PDR when modeled together with all the other risk factors in both groups evaluated in this study. For

Table 1 Univariate associations with prevalent diabetic retinopathy (DR) and proliferative DR (PDR) for the included predictors, in patients with early-onset (before 18 years of age) type 1 diabetes (DM1)

Potential associated factors	Any DR vs No DR			PDR vs No PDR		
	No DR ($n = 55$)	Any DR ($n = 85$)	p value	DR (non-PDR) ($n = 53$)	PDR ($n = 32$)	p value
Sociodemographic factors						
Sex			0.422			0.328
Men	24 (43.6)	31 (50.6)		29 (54.7)	14 (43.8)	
Women	43 (56.4)	42 (49.4)		24 (45.3)	18 (56.3)	
Decade of Birth ≤ 1970	9 (16.4)	41 (48.2)	<0.001[a]	23 (43.4)	18 (56.3)	0.252
Regular Alcohol intake	4 (7.3)	7 (8.2)	0.836	6 (11.3)	1 (3.1)	0.213
Current or former Smoker	9 (16.4)	20 (23.5)	0.309	14 (26.4)	6 (18.8)	0.422
Self-reported physical activity	15 (27.3)	9 (10.6)	0.013[a]	9 (17.0)	0 (0.0)	0.999
DM related factors						
Decade of diagnosis ≥ 2000	33 (60.0)	16 (19.3)	<0.001[a]	13 (25.5)	3 (9.4)	0.081[a]
Age at DM diagnosis	11.4 ± 3.78	9.63 ± 4.34	0.015[a]	9.9 ± 4.5	9.17 ± 4.0	0.452
Duration of DM, years	15.2 ± 8.34	29.2 ± 11.5	<0.001[a]	27.4 ± 11.3	30.5 ± 11.4	0.067[a]
Mean follow-up HbA1c, %	8.10 ± 1.53	8.70 ± 1.47	<0.023[a]	8.47 ± 1.33	9.11 ± 1.63	0.056[a]
Risk factors and co-morbidities						
BMI, kg/m^2	24.5 ± 3.2	24.2 ± 4.0	0.675	23.3 ± 3.3	25.6 ± 4.8	0.019[a]
SBP, mmHg	124 ± 11	127 ± 14	0.282	125 ± 12	130 ± 17	0.095[a]
DBP, mmHg	73 ± 10	72 ± 12	0.586	71 ± 10	73 ± 11	0.555
Treated hypertension	12 (22.2)	38 (45.2)	<0.007[a]	21 (39.6)	17 (54.8)	0.178
Treated dyslipidemia	10 (19.2)	44 (53.7)	<0.001[a]	22 (43.1)	22 (71.0)	0.016[a]
Nephropathy	3 (6.3)	28 (37.8)	0.001[a]	11 (23.9)	17 (60.7)	0.002[a]
Neuropathy	4 (9.3)	26 (24.6)	<0.053[a]	7 (16.7)	9 (39.1)	0.050[a]
Laboratory parameters						
AST, U/L	24.1 ± 11.2	22.2 ± 8.2	0.281	21.6 ± 7.5	23.1 ± 9.3	0.474
ALT, U/L	20.8 ± 12.8	21.5 ± 16.2	0.816	19.0 ± 6.7	25.5 ± 24.3	0.118
GGT, U/L	20.1 ± 16.4	33.1 ± 46.6	0.061[a]	27.0 ± 21.7	44.5 ± 72.8	0.224
Total cholesterol, mg/dL	175 ± 33.3	177 ± 35.0	0.781	177 ± 33.4	176 ± 38.5	0.916
HDL cholesterol, mg/dL	57.2 ± 14.4	55.3 ± 13.1	0.437	55.2 ± 12.5	55.6 ± 14.4	0.914
LDL cholesterol, mg/dL	101.5 ± 24.0	104.0 ± 46.0	0.723	109.0 ± 52.9	94.6 ± 27.8	0.187
TG, mg/dL	95.2 ± 61.0	105.1 ± 63.4	0.378	95.8 ± 63.9	122.5 ± 59.6	0.093[a]
Urine microalbuminuria > 30 mg/24 h	3 (6.1)	20 (29.0)	0.005[a]	8 (18.2)	12 (48.0)	0.011[a]
TSH, ng/dL	1.76 ± 1.6	1.74 ± 1.1	0.948	1.63 ± 0.99	1.92 ± 1.16	0.261
Uric acid, mg/dL	7.88 ± 8.9	6.11 ± 6.7	0.277	6.95 ± 8.48	4.81 ± 1.69	0.286
GFR, ml/min/1.73 m^2	98.5 ± 17.8	85.5 ± 23.8	<0.003[a]	85.2 ± 26.2	86.1 ± 19.8	0.881

Values are presented as n (%) or as mean ± standard deviation

DR diabetic retinopathy, *PDR* proliferative diabetic retinopathy, *DM* diabetes mellitus, *HbA1c* glycated hemoglobin, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyltransferase, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *TG* triglycerides, *TSH* thyroid-stimulating hormone, *GFR* glomerular filtration rate

[a]Included in the final models

patients diagnosed before the age of 18, BMI also demonstrated an association with PDR when modeled together with all the other risk factors.

Previous studies have investigated possible predictors for DR in people with diabetes. However, as verified by a recent metanalysis [4], few studies include adult-onset diabetes and even fewer include subjects who have been diagnosed with DM1 over the age of 40. A recent research using genomic methods has suggested that over 42% of DM1 occurs after age 30 [5]. Therefore, there is an unmet need to evaluate risk factors for microvascular complications in patents with adult-onset DM1.

Table 2 Multivariate risk factor model for prevalent diabetic retinopathy (DR) in patients with early-onset (before 18 years of age) type 1 diabetes (DM1)

	Any DR[a]		
Variable	OR	95%CI	*p* value
Duration of DM	1.23	1.12–1.35	<0.001
Mean HbA1c	2.35	1.47–3.76	<0.001

Hosmer and Lemeshow test: $p = 0.462$. Omibus test: $p < 0.0001$

DR diabetic retinopathy, *HbA1c* glycosylated hemoglobin, *DM* diabetes mellitus, *CI* confidence interval, *OR* odds ratio

[a]The model predicts 55.5% of the outcome (Nagelkerk R^2)

Table 3 Multivariate risk factor model for prevalent proliferative diabetic retinopathy (PDR) in patients with early-onset (before 18 years of age) type 1 diabetes (DM1)

	PDR[a]		
Variable	OR	95%CI	*p* value
Neuropathy	6.76	1.25–36.6	0.027
BMI	1.34	1.08–1.67	0.009

Hosmer and Lemeshow test: $p = 0.210$. Omibus test: $p = 0.001$

PDR proliferative diabetic retinopathy, *BMI* body mass index, *CI* confidence interval, *OR* odds ratio

[a]The model predicts 34.6% of the outcome (Nagelkerk R^2)

The influence of age at DM1 onset on the occurrence of microvascular complications as DR has been demonstrated in literature. Hammes et al. [24] reviewed a large cohort of people ($n = 18{,}891$) with childhood, adolescent or adult-onset of type 1 diabetes from the prospective German Diabetes Documentation System survey concluding that subjects aged over 15 at onset have the lowest protection against advanced DR. In contrast, Hietala et al. [25] found that the highest risk for DR was in the age-at-onset group 5–14 years, whereas the lowest risk was in the age-at-onset group 15–40 years. In agreement with these last authors, Kullberg et al. [18] reported that the prevalence of DR increases in subjects aged 15–19 at onset but decreases at onset ages between 30 and 35. However, this study analyzed a population of "440 patients with type 1 diabetes onset before the age of 36 years". Recently, Forga et al. [26] studied a broad range of ages of DM1 diagnosis and also concluded that the rate of DR is higher in subjects who were older at DM1 diagnosis. This could be because of the "protective factor" that occurs before the onset of puberty that has been described [17]. Age at diagnosis has been thus been referred an important risk factor for the development of DR [16, 18]. Because many DM1 patients with late-onset disease are underdiagnosed, we evaluated if older age of diagnosis has implications in the development of retinal disease, and if risk factors for DR were similar between young and adult-onset DM1.

In this study, duration of the disease and metabolic control were found to be predictors of DR, which is consistent with existing literature [6, 8, 10, 27–29]. DM duration was a strong risk factor for any DR, even after controlling for all other significant predictive variables in the model, including HbA1c.

After adjustments, only peripheral neuropathy (in both groups) and BMI (in early-onset group) remained associated with PDR. Curiously, DM-related factors (duration of disease and metabolic control) lost their impact after controlling for the other variables; this means that, in our sample, the determinants for having PDR when comparing to non-proliferative disease may be more related to the concomitant co-morbidities. The association between peripheral neuropathy and PDR was explored in two previous studies performed by Klein et al. [30] and Pemp et al. [31]. It is well known that diabetes induces peripheral nerve fiber loss which results in different forms of peripheral diabetic peripheral neuropathy including dysfunction of motor, sensory and autonomic fibers [30].

This study has as major strengths its representative character of the target population and the embracement of a long period of DM1 duration and a wide range of ages at DM1 diagnosis, thus allowing a broad characterization of the different stages of the disease. Furthermore, we thoroughly evaluated several potential predictors of DR including sociodemographic characteristics, DM-related parameters, clinicals risk factors, comorbidities, and laboratory parameters. We are aware that it is important to understand if patients with a late diagnosis of DM1 have different risk factors for the development of DR. We have analyzed the data in two different groups, based on the age of diagnosis (before and after 18 years of age) and report these novel findings.

Our study has limitations. First, its retrospective nature impairs direct and solid causal associations. Secondly, we only evaluated patients from a reference area in the North of Portugal. The study included a homogeneous population at a single center thus not allowing for generalization of the results to other populations. In addition, we were dependent on medical records with all its inherent biases. We included data from patients diagnosed and managed with between 1950 and 2017. Although we included a stratification, the change in diagnosis, management and treatment of diabetes in that time frame could not be completely controlled. The method we used for the diagnoses of hypertension and dyslipidemia may have misclassified some patients as patients may be treated with angiotensin-converting-enzyme inhibitors and statins for renal and cardio-protection. Alcohol and tobacco consumption as well as physical activity practice had to be codified as yes or no/unknown, so possible additional effects may have been masked by this codification. In addition, it would have been

Table 4 Univariate associations with prevalent diabetic retinopathy (DR) and proliferative DR (PDR) for the included predictors, in patients with late-onset (after 18 years of age) type 1 diabetes (DM)

Potential associated factors	Any DR vs No DR			PDR vs No PDR		
	No DR ($n = 85$)	Any DR ($n = 84$)	p value	DR (non-PDR) ($n = 62$)	PDR ($n = 22$)	p value
Sociodemographic factors						
Sex			0.812			0.047[a]
Men	45 (52.9)	46 (54.8)		38 (61.3)	8 (36.4)	
Women	40 (47.1)	38 (45.2)		24 (38.7)	14 (63.6)	
Decade of Birth ≤ 1970	47 (55.3)	78 (92.9)	<0.001[a]	57 (91.9)	21 (95.5)	0.587
Regular Alcohol intake	10 (11.9)	15 (17.9)	0.281	11 (17.7)	4 (18.2)	0.963
Current or former Smoker	31 (36.5)	24 (28.6)	0.274	21 (33.9)	3 (13.6)	0.082[a]
Self-reported physical activity	24 (28.2)	13 (15.5)	0.048[a]	9 (14.5)	4 (18.2)	0.684
DM related factors						
Decade of diagnosis ≥ 2000	71 (83.5)	26 (31.3)	<0.001[a]	19 (31.1)	7 (31.3)	0.954
Age at DM diagnosis	29.9 ± 10.9	28.7 ± 8.52	0.444	29.1 ± 8.2	30.6 ± 8.3	0.215
Duration of DM, years	9.8 ± 7.8	23.3 ± 10.3	<0.001[a]	22.4 ± 10.3	26.0 ± 10.5	0.176
Mean follow-up HbA1c, %	7.90 ± 1.46	8.49 ± 1.34	<0.010[a]	8.35 ± 1.25	8.87 ± 1.51	0.120
Risk factors and co-morbidities						
BMI, kg/m^2	25.5 ± 3.6	25.9 ± 5.6	0.556	26.4 ± 4.7	26.7 ± 4.9	0.660
SBP, mmHg	126 ± 16	133 ± 16	0.028[a]	130 ± 16	138 ± 17	0.105
DBP, mmHg	75 ± 10	74 ± 10	0.452	74 ± 10	75 ± 11	0.508
Treated hypertension	20 (23.5)	48 (57.8)	<0.001[a]	31 (50.8)	17 (77.3)	0.037[a]
Treated dyslipidemia	34 (40.5)	56 (67.5)	<0.001[a]	40 (65.6)	16 (72.7)	0.540
Nephropathy	10 (12.7)	30 (39.0)	<0.001[a]	22 (37.3)	8 (44.4)	0.586
Neuropathy	7 (9.5)	32 (47.8)	<0.001[a]	20 (23.5)	12 (70.6)	0.034[a]
Laboratory parameters						
AST, U/L	23.4 ± 9.6	24.9 ± 9.4	0.729	22.6 ± 7.6	22.7 ± 5.7	0.923
ALT, U/L	25.2 ± 15.5	24.4 ± 11.8	0.712	23.7 ± 11.3	21.2 ± 3.5	0.223
GGT, U/L	25.5 ± 17.0	32.1 ± 29.5	0.059[a]	31.5 ± 33.7	25.7 ± 18.1	0.994
Total cholesterol, mg/dL	181 ± 96.6	173 ± 33.6	0.549	169 ± 26.5	172 ± 40.0	0.863
HDL cholesterol, mg/dL	53.8 ± 12.5	56.4 ± 10.1	0.289	57.7 ± 11.1	54.4 ± 7.5	0.537
LDL cholesterol, mg/dL	96.7 ± 26.6	95.7 ± 24.6	0.942	93.2 ± 19.8	98.8 ± 34.1	0.756
TG, mg/dL	110.3 ± 86.4	104.4 ± 52.3	0.910	94.4 ± 34.7	93.4 ± 49.0	0.377
Urine microalbuminuria//24 h	9.7 (9.0)	140 (414)	0.107	69.4 (143)	379 (822)	0.173
TSH, ng/dL	1.67 ± 0.85	1.75 ± 1.12	0.903	1.65 ± 1.04	1.84 ± 1.44	0.919
Uric acid, mg/dL	7.40 ± 12.5	5.63 ± 8.1	0.656	5.69 ± 9.22	5.57 ± 1.88	0.719
GFR, ml/min/1.73 m^2	92.5 ± 21.9	76.5 ± 25.5	<0.002[a]	83.6 ± 26.8	72.0 ± 23.8	0.101

Values are presented as n (%) or as mean ± standard deviation

DR diabetic retinopathy, *PDR* proliferative diabetic retinopathy, *DM* diabetes mellitus, *HbA1c* glycated hemoglobin, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyltransferase, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *TG* triglycerides, *TSH* thyroid-stimulating hormone, *GFR* glomerular filtration rate

[a]Included in the final models

important to correlate our findings with macrovascular disease, but this data was not collectible from our medical records.

In conclusion, this research suggests that although previous studies have demonstrated that age at DM1 diagnosis may have a role in DR prevalence, the risk factors for DR in early and late-onset DM1 patients are similar. Duration of disease and lifelong metabolic control remain the major predictors for DR. Besides these factors, we found nephropathy to be associated with prevalent DR in patients with late-onset DM1 but not in patients with early-onset. Peripheral neuropathy was associated with PDR occurrence

Table 5 Multivariate risk factor model for prevalent diabetic retinopathy (DR) in patients with late (after the age of 18) onset type 1 diabetes (DM1)

	Any DR[a]		
Variable	OR	95%CI	*p* value
Decade of Birth ≤ 1970	0.28	0.08–1.02	0.053
Duration of DM	1.15	1.08–1.22	<0.001
Mean HbA1c	1.54	1.06–2.23	0.023
Nephropathy	3.31	1.06–10.3	0.039

Hosmer and Lemeshow test: $p = 0.406$. Omibus test: $p < 0.0001$

DR diabetic retinopathy, *HbA1c* glycosylated hemoglobin, *DM* diabetes mellitus, *CI* confidence interval, *OR* odds ratio

[a]The model predicts 58.8% of the outcome (Nagelkerk R^2)

Table 6 Multivariate risk factor model for prevalent proliferative diabetic retinopathy (PDR) in patients with late (after the age of 18) onset type 1 diabetes (DM1)

	PDR[a]		
Variable	OR	95%CI	*p* value
Peripheral Neuropathy	3.60	1.10–11.8	0.03

PDR proliferative diabetic retinopathy, *CI* confidence interval, *OR* odds ratio

[a]The model predicts 10.3% of the outcome (Nagelkerk R^2)

in both groups whilst an increased BMI was also associated with PDR in patients with early-onset disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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