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PERFIL CARDIOVASCULAR E RETINOPATIA EM DOENTES COM DIABETES: ESTUDO RETROSPETIVO EM PRÁTICA CLÍNICA REAL

CARDIOVASCULAR PROFILE AND RETINOPATHY IN A COHORT OF DIABETIC PATIENTS: A REAL-WORLD RETROSPECTIVE STUDY

PERFIL CARDIOVASCULAR Y RETINOPATÍA EN UNA COHORTE DE PACIENTES DIABÉTICOS: ESTUDIO RETROSPECTIVO CON DATOS DE VIDA REAL

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RESUMO

Introdução: A retinopatia diabética (RD) é uma das principais complicações microvasculares da diabetes mellitus (DM) e uma importante causa de deficiência visual. Para além da hiperglicemia crónica, fatores de risco cardiovascular como a hipertensão arterial (HTA) e a dislipidemia podem influenciar o seu desenvolvimento e progressão. A avaliação do perfil cardiovascular nas pessoas com diabetes pode melhorar a compreensão dos fatores associados a RD e contribuir para estratégias preventivas mais eficazes.

Objetivo: Analisar o perfil cardiovascular e a sua associação com a RD numa coorte de doentes com DM.

Métodos: Estudo observacional retrospectivo transversal realizado em 6.674 doentes com DM acompanhados nos Cuidados de Saúde Primários em Ávila entre 2010 e 2024. Foi efetuada uma análise bivariada para avaliar a associação entre HTA, dislipidemia e RD.

Resultados: A prevalência de HTA foi de 70,24% e a de dislipidemia de 70,77%. A RD foi detetada em 28,05% dos doentes. A HTA foi mais frequente nos doentes com RD em comparação com aqueles sem RD, enquanto a dislipidemia apresentou uma distribuição homogénea entre os grupos.

Conclusão: A RD apresentou uma elevada prevalência na coorte estudada. A HTA associou-se à presença de RD, enquanto a dislipidemia não mostrou diferenças entre os grupos.

Palavras-chave: retinopatia diabética; hipertensão arterial; dislipidemia; risco cardiovascular

ABSTRACT

Introduction: Diabetic retinopathy (DR) is one of the main microvascular complications of diabetes mellitus (DM) and a significant cause of visual impairment. In addition to chronic hyperglycemia, cardiovascular risk factors such as arterial hypertension (HTN) and dyslipidemia may influence its development and progression. Assessing the cardiovascular profile in people with diabetes can improve our understanding of the factors associated with DR and contribute to more effective preventive strategies.

Objective: To analyze the cardiovascular profile and its association with DR in a cohort of patients with DM.

Methods: A retrospective cross-sectional observational study was conducted in 6,674 patients with DM managed in Primary Care in Ávila between 2010 and 2024. A bivariate analysis was performed to evaluate the association between HTN, dyslipidemia, and DR.

Results: The prevalence of HTN was 70.24%, while dyslipidemia was present in 70.77% of patients. DR was detected in 28.05% of the cohort. HTN was more frequent in patients with DR compared to those without DR, whereas dyslipidemia showed a homogeneous distribution between groups.

Conclusion: DR showed a high prevalence in the studied cohort. HTN was associated with the presence of DR, whereas dyslipidemia showed no differences between groups.

Keywords: diabetic retinopathy; hypertension; dyslipidemia; cardiovascular risk

RESUMEN

Introducción: La retinopatía diabética (RD) es una de las principales complicaciones microvasculares de la diabetes mellitus (DM) y una causa relevante de discapacidad visual. Además de la hiperglucemia crónica, factores de riesgo cardiovascular como la hipertensión arterial (HTA) y la dislipemia pueden influir en su desarrollo y progresión. La evaluación del perfil cardiovascular en las personas con diabetes puede mejorar la comprensión de los factores asociados a la RD y contribuir a la elaboración de estrategias preventivas más eficaces.

Objetivo: Analizar el perfil cardiovascular y su asociación con la RD en una cohorte de pacientes con DM.

Métodos: Estudio observacional retrospectivo transversal realizado en 6.674 pacientes con DM atendidos en Atención Primaria en Ávila entre 2010 y 2024. Se efectuó un análisis bivalente para evaluar la asociación entre HTA, dislipemia y RD.

Resultados: La prevalencia de HTA fue del 70,24% y la de dislipemia del 70,77%. La RD se detectó en el 28,05% de los pacientes. La HTA fue más frecuente en los pacientes con RD respecto a aquellos sin RD, mientras que la dislipemia presentó una distribución homogénea entre ambos grupos.

Conclusión: La RD mostró una elevada prevalencia en la cohorte estudiada. La HTA se asoció con la presencia de RD, mientras que la dislipemia no mostró diferencias entre grupos.

Palabras clave: retinopatía diabética; hipertensión arterial; dislipemia; riesgo cardiovascular

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INTRODUCTION

Diabetes mellitus (DM) represents one of the most critical public health challenges globally, with a rising prevalence driven by population aging and lifestyle shifts. Chronic hyperglycemia induces progressive vascular damage, leading to both macrovascular and microvascular complications. Among the latter, diabetic retinopathy (DR) is one of the most specific microvascular sequelae and stands as a leading cause of preventable vision loss in developed countries; in Spain, it constitutes the primary cause of preventable visual acuity loss (Sun et al., 2022; Suárez Pita et al., 2016).

Nationally, the prevalence of DR in Spain is estimated to be approximately 15,28% , although recent studies suggest significant variations depending on geographic region and the burden of associated risk factors (Teo et al., 2021; Castell et al., 2022; Soriguer et al., 2012; Romero-Aroca et al., 2022). The pathogenesis of DR is multifactorial. Although diabetes duration and metabolic control—measured via glycated hemoglobin (HbA1c)—are critical determinants, the progression of retinal damage is tightly linked to the presence of other cardiovascular risk factors (Solomon et al., 2017; Stratton et al., 2001). Among these, dyslipidemia and systemic hypertension (HTN) play pivotal roles. Impaired lipid metabolism not only accelerates macrovascular atherosclerosis but also exacerbates biochemical cascades such as oxidative stress and endothelial dysfunction, pathways shared by retinal microangiopathy and diabetic nephropathy (ElSayed et al., 2023; Simó and Hernández, 2019). Similarly, HTN is not only a risk factor for the development of DR, but its tight control is imperative to prevent microvascular progression (Stratton et al., 2001). In recent years, evidence has suggested a potential synergistic interaction among these cardiovascular risk factors, implying that their accumulation may compound microvascular damage and accelerate DR progression (Solomon et al., 2017; Stratton et al., 2001; ElSayed et al., 2023; Bosch et al., 2002; Yau et al., 2012). However, evidence from real-world populations, particularly within systematic population-based DR screening programs, remains limited.

The objective of this study is to analyze the cardiovascular profile (dyslipidemia, hypertension, and HbA1c), age, sex, and type of diabetes, and their association with DR within a cohort of 6,674 diabetic patients enrolled in a population-based screening program. These findings aim to contribute to optimizing the multifactorial management of cardiovascular risk in patients with diabetes.

THEORETICAL FRAMEWORK

Diabetic retinopathy: concept and pathophysiology

DR is defined as a highly specific microvascular complication of both type 1 and type 2 diabetes mellitus (Suárez Pita et al., 2016). Its pathogenesis is complex and multifactorial, stemming from chronic hyperglycemia, which triggers at least five deleterious biochemical pathways: the polyol pathway, the hexosamine pathway, the protein kinase C (DAG-PKC) activation pathway, the accumulation of advanced glycation end-products (AGEs), and oxidative stress (Simó and Hernández, 2019). Histologically, early retinal microvascular changes include basement membrane thickening and pericyte loss, leading to the disruption of tight junctions between endothelial cells (Simó and Hernández, 2019). This disruption of the blood-retinal barrier increases vascular permeability, promoting the development of microaneurysms, hemorrhages, and exudates (Simó and Hernández, 2019; Suárez Pita et al., 2016). In advanced stages, tissue ischemia and neuronal hypoxia stimulate the release of proangiogenic factors, primarily vascular endothelial growth factor (VEGF), resulting in the fragile neovascularization characteristic of the proliferative phase (Simó and Hernández, 2019; Suárez Pita et al., 2016).

Classification of diabetic retinopathy

To clinically define the severity of DR, this study adopts the International Clinical Disease Severity Scale developed by the Global Diabetic Retinopathy Project Group (GDRPG) (Yau et al., 2012). Five levels of severity are established based on ophthalmoscopic findings:

- **No apparent retinopathy:** No visible microaneurysms or diabetic retinal lesions.
- **Mild non-proliferative DR (NPDR):** Presence of microaneurysms only.
- **Moderate NPDR:** Microaneurysms associated with intraretinal hemorrhages (<20 in each quadrant), hard exudates, or venous beading in only one quadrant.
- **Severe NPDR (4-2-1 Rule):** Presence of at least one of the following: severe hemorrhages in all 4 quadrants, prominent venous beading in ≥ 2 quadrants, or prominent intraretinal microvascular abnormalities (IRMA) in ≥ 1 quadrant.
- **Proliferative DR (PDR):** Definite neovascularization, preretinal hemorrhage, or vitreous hemorrhage.

Diabetic retinopathy screening

Because diabetic retinopathy is frequently asymptomatic in its early stages, systematic screening is the only effective tool to prevent avoidable blindness (Yau et al., 2012; Suárez Pita et al., 2016; Cebrián-Cuenca et al., 2021). Follow-up clinical screening timelines are established according to the type of diabetes, in line with international clinical guidelines:

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- Type 2 Diabetes: retinography is performed at the time of diagnosis due to the possibility of prior undiagnosed, silent disease progression.
- Type 1 Diabetes: screening is initiated 5 years after the initial diagnosis.

Cardiovascular profile: hypertension, dyslipidemia, and glycated hemoglobin in diabetic patients

The cardiovascular profile of diabetic patients is characterized by a clustering of risk factors that compound systemic damage; specifically, the coexistence of metabolic and hemodynamic disturbances exacerbates capillary vulnerability (Yau et al., 2012; ElSayed et al., 2023). In this study, the cardiovascular profile is operationally defined through three critical determinants:

- Glycated hemoglobin (HbA1c): Understood conceptually as the gold-standard biomarker of sustained glucotoxicity, reflecting average plasma glucose over the preceding three months. It is considered the core modifiable risk factor in diabetic ocular pathology, as chronic hyperglycemia directly drives microvascular injury (Solomon et al., 2017; Suárez Pita et al., 2016).
- Hypertension (HTN): Serves as a hemodynamic stress factor that exacerbates endothelial dysfunction (Stratton et al., 2001). Operationally, in this study, HTN is defined by the presence of a previously coded diagnosis in the electronic health records of the public health system.
- Dyslipidemia: An alteration in lipid metabolism that, beyond its established role in macrovascular atherosclerosis, exacerbates oxidative stress and endothelial inflammation (Simó and Hernández, 2019).

Analyzing these variables in combination is justified because they configure a profile of high microvascular vulnerability through synergistic action. While HbA1c represents the primary pathophysiological trigger of capillary damage, HTN and dyslipidemia act as biochemical and mechanical exacerbators that accelerate the transition from non-proliferative phases to vision-threatening stages (Yau et al., 2012; Sociedad Española de Cardiología, 2023).

2. METHODS

2.1 Ethical considerations

The study protocol was approved by the Drug Research Ethics Committee (CEIm) of the Ávila Health Area in February 2024. Authorization was obtained from the Nuestra Señora de Sonsoles Hospital to access clinical data and fundus photographs from the provincial screening program. All patient data were completely anonymized in compliance with Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR) and the Spanish Organic Law 3/2018 on Personal Data Protection and Guarantee of Digital Rights, in accordance with the tenets of the Declaration of Helsinki.

A waiver of informed consent was requested and granted due to the retrospective nature of the study. This request was justified by the logistical impossibility of contacting patients whose interactions with the healthcare system occurred in the past, and because no data within the dataset allowed for patient re-identification. This study does not involve a prospective clinical trial, but rather a retrospective review of historical clinical records.

2.2 Study design and population

A retrospective observational study was conducted on a cohort of DM patients undergoing primary care-based population screening for DR in the province of Ávila, Spain. Clinical records were consecutively collected between 2010 and 2024. Inclusion criteria comprised patients with diabetes who participated in the population screening program and had at least 75% of the clinical variables documented, with particular focus on cardiovascular risk factors (HTN, dyslipidemia, HbA1c), age, sex, and type of diabetes. No limits were placed on age, minimum time since diabetes diagnosis, or the presence of concurrent non-diabetic retinal diseases. Duplicated screening entries were excluded. The final analysis cohort consisted of 6,674 patients.

Analytical denominators vary across specific parameters due to the progressive exclusion of missing data resulting from the 75% completeness threshold. Complete-case analysis was prioritized where appropriate to preserve statistical power.

2.3 Definitions

Hypertension (HTN): a validated diagnosis recorded by the patient's primary care physician.

Dyslipidemia: A validated diagnosis recorded by the patient's primary care physician based on total cholesterol levels.

HbA1c: identified through laboratory records, adopting an HbA1c threshold of $\geq 6.5\%$ as the diagnostic criterion for DM, and 5.7% - 6.4% for prediabetes (Suárez Pita et al., 2016).

Diabetic Retinopathy: the presence or absence of DR and its severity stages were defined according to the GDRPG International Scale (Yau et al., 2012).

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2.4 Statistical analysis

Qualitative variables (sex, type of diabetes, presence of HTN, and presence of dyslipidemia) are expressed as absolute frequencies (n) and percentages (%). Quantitative variables are presented as mean ± standard deviation ($X \pm DE$) for normally distributed data, or as median and interquartile range (IQR) for non-normally distributed data (determined via the Kolmogorov-Smirnov test).

For bivariate inferential analysis, the significance of differences in qualitative variables across DR severity stages was assessed using Pearson's Chi-squared test. For quantitative variables (age and HbA1c), the Kruskal-Wallis test was used due to non-normal distributions.

The distributions of age and HbA1c were evaluated using a combination of analytical and graphical methods. Given our large sample size, formal normality tests (e.g., Kolmogorov-Smirnov or Shapiro-Wilk) are practically invalidated due to mathematical hypersensitivity, which rejects the null hypothesis even under clinically negligible deviations from normality. Thus, assessment of normality was strictly grounded on skewness coefficients and visual inspection of density plots.

To identify independent demographic, metabolic, and cardiovascular predictors of DR while controlling for confounding, a multivariable binary logistic regression model was constructed. The dependent variable was defined as the presence or absence of DR (binary). Adjusted odds ratios (aOR) and their corresponding 95% confidence intervals (95% CI) were calculated.

For all analyses, statistical significance was set at $p < 0,05$. Statistical processing and data analyses were performed using IBM SPSS software (version 27.0; IBM Corp., Armonk, NY, USA).

3. RESULTS

The study population had an advanced mean age ($68.39\% \pm 12.32$ years) and a predominantly male distribution (56.83%). Reflecting global epidemiological patterns, the vast majority of patients had type 2 diabetes (95.88%), compared to 4.12% with type 1. Baseline glycemic control showed a mean HbA1c of $7.09\% \pm 1.61\%$.

Regarding the concurrent cardiovascular profile, a high burden of metabolic and hemodynamic risk factors was observed: 70.24% of patients had a diagnosis of HTN, and 70.77% had dyslipidemia.

The overall prevalence of screen-detected DR was 28.05% ($n = 1,778$). When broken down by severity, the most common clinical form was mild NPDR (14.31% of the total sample), followed by moderate NPDR (10.40%). Advanced stages (severe NPDR and PDR) were identified in 3.35% of the screened population (2.26% for severe NPDR and 1.09% for PDR).

When stratified by DR severity, mean age remained stable across stages. In contrast, HbA1c levels steadily increased with increasing DR severity. The sex distribution remained predominantly male across all categories, HTN and dyslipidemia maintained high levels across all grades, and type 2 diabetes remained the dominant form of the disease.

Table 1 - General characteristics of the cohort

Study variables	Valid cases (N)	n / mean	% / SD (SE)
Quantitative variables			
Age (years)	6.653	68,39	12,32 (0,15)
Glycated hemoglobin (HbA1c, %)	6.267	7,09	1,61 (0,02)
Qualitative variables			
Sex	6.671		
• Men		3.791	56,83%
• Women		2.880	43,17%
Type of diabetes	6.464		
• Type 1		266	4,12%
• Type 2		6.198	95,88%
HTN	6.503		
• No		1.935	29,76%
• Yes		4.568	70,24%
Dyslipidemia	6.453		
• No		1.886	29,23%
• Yes		4.567	70,77%
Diabetic retinopathy	6.338		
• Absence of RD		4.560	71,95%
• Presence of RD		1.778	28,05%
Diabetic retinopathy severity	6.338		
• No apparent DR (Grade 1)		4.560	71,95%
• Mild NPDR (Grade 2)		907	14,31%
• Moderate NPDR (Grade 3)		659	10,40%
• Severe NPDR (Grade 4)		143	2,26%
• Proliferative DR (Grade 5)		69	1,09%

Note: for quantitative variables, the Mean and Standard Deviation (SD) are presented, with the Standard Error (SE) in parentheses. For qualitative variables, absolute frequencies (n) and relative percentages (%) are shown. Variations in the total number of valid cases (N) reflect missing data.

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Table 2 - Clinical and demographic variables stratified by DR severity stage

Variables and statistics	No apparent DR (Grade 1)	Mild NPDR (Grade 2)	Moderate NPDR (Grade 3)	Severe NPDR (Grade 4)	Proliferative DR (Grade 5)
Quantitative variables					
Age (years)	(N = 4550)	(N = 905)	(N = 655)	(N = 143)	(N = 68)
* Mean +/- SD	67,98 +/- 11,88	68,73 +/- 12,82	69,42 +/- 12,74	67,36 +/- 13,68	65,72 +/- 14,73
* Range [Min - Max]	[17,00 - 102,00]	[22,00 - 93,00]	[21,00 - 95,00]	[23,00 - 90,00]	[20,00 - 88,00]
HbA1c (%)	(N = 4299)	(N = 854)	(N = 630)	(N = 136)	(N = 65)
* Mean +/- SD	6,89 +/- 1,61	7,23 +/- 1,30	7,88 +/- 1,58	8,46 +/- 1,99	8,19 +/- 1,91
Qualitative variables					
	n (%)	n (%)	n (%)	n (%)	n (%)
Sex	(N = 4558)	(N = 907)	(N = 659)	(N = 143)	(N = 69)
* Men	2566 (56,30%)	543 (59,87%)	391 (59,33%)	76 (53,15%)	44 (63,77%)
* Women	1992 (43,70%)	364 (40,13%)	268 (40,67%)	67 (46,85%)	25 (36,23%)
HTN	(N = 4464)	(N = 889)	(N = 643)	(N = 142)	(N = 67)
* No	1389 (31,12%)	246 (27,67%)	163 (25,35%)	37 (26,06%)	18 (26,87%)
* Yes	3075 (68,88%)	643 (72,33%)	480 (74,65%)	105 (73,94%)	49 (73,13%)
Type of diabetes	(N = 4453)	(N = 885)	(N = 639)	(N = 142)	(N = 67)
* Type 1	106 (2,38%)	55 (6,21%)	56 (8,76%)	13 (9,15%)	16 (23,88%)
* Type 2	4347 (97,62%)	830 (93,79%)	583 (91,24%)	129 (90,85%)	51 (76,12%)
Dyslipidemia	(N = 4458)	(N = 877)	(N = 642)	(N = 142)	(N = 67)
* No	1293 (29,00%)	259 (29,53%)	180 (28,04%)	47 (33,10%)	18 (26,87%)
* Yes	3165 (71,00%)	618 (70,47%)	462 (71,96%)	95 (66,90%)	49 (73,13%)

Bivariate inferential analysis of risk factors

Quantitative variables evaluated using the Kruskal-Wallis test showed statistically significant differences across groups for both HbA1c and age. The upward trend of mean glycated hemoglobin levels in direct relation to increasing DR severity is illustrated in Figure 1. Among the qualitative variables analyzed using Pearson's Chi-squared test, a statistically significant association was observed with the type of diabetes and the presence of HTN. In contrast, no statistically significant association was found with sex or dyslipidemia.

Table 3 - Bivariate inferential analysis of risk factors according to DR severity

Study variable	Statistical test	Test statistic	Degrees of freedom	Actual p value	Clinical interpretation
HbA1c	Kruskal-Wallis	Chi-cuadrado = 491.6	4	< .001	Critical and strong association
Type of diabetes	Chi-cuadrado de Pearson	Chi-cuadrado = 155.0	4	< .001	Very strong association
Age	Kruskal-Wallis	Chi-cuadrado = 17.8	4	.001	Significant association
HNT	Chi-cuadrado de Pearson	Chi-cuadrado = 12.1	4	.016	Statistically significant
Sex	Chi-cuadrado de Pearson	Chi-cuadrado = 7.41	4	.116	No association (p > 0.05)
Dyslipidemia	Chi-cuadrado de Pearson	Chi-cuadrado = 1.76	4	.780	No association (p > 0.05)

Based on these findings, variables demonstrating statistical significance in the bivariate analysis (p < 0.05) were selected to construct the final multivariate logistic regression model.

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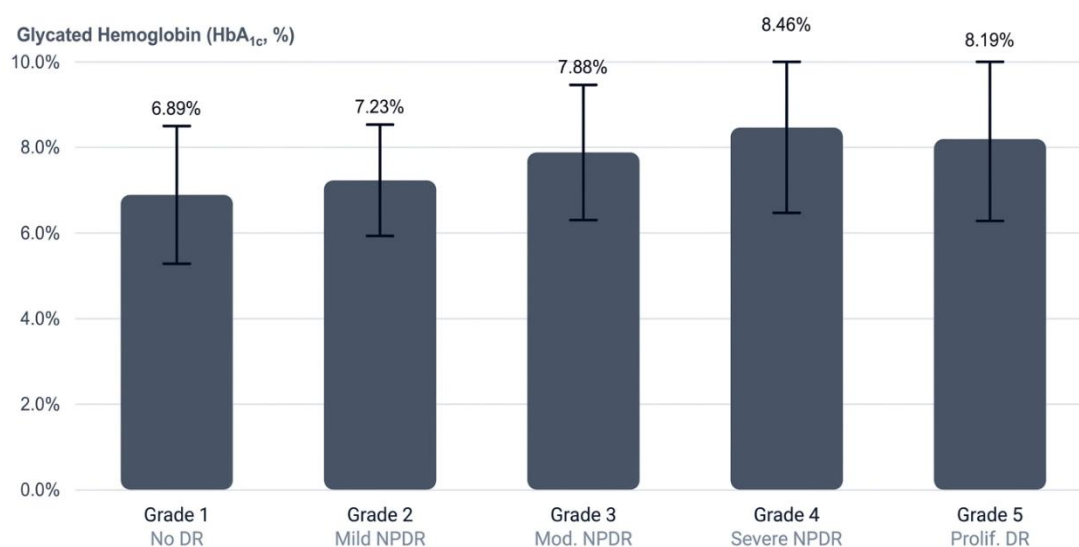


Figure 1 - Mean glycated hemoglobin (HbA1c) levels by diabetic retinopathy severity grade. Error bars represent standard deviations.

Multivariate binary logistic regression analysis

To assess the independent and isolated effect of variables significantly associated in the bivariate phase, a multivariate binary logistic regression model was constructed (N = 5815), with the presence of diabetic retinopathy (DR = 1) defined as the dependent outcome of interest against its absence (RD = 0).

Table 4 - Multivariate binary logistic regression model for predicting DR

Predictor variable	Estimate (Log Odds)	Standard Error (SE)	Z statistic	P value	Odds Ratio (OR)	95% confidence Interval (lower - upper)
Age (years)	0.0187	0.00287	6.51	< .001	1.019	1.013 - 1.025
HbA1c (%)	0.3781	0.02284	16.55	< .001	1.460	1.396 - 1.526
Type of diabetes (Type 2 vs Type)	-1.4974	0.15631	-9.58	< .001	0.224	0.165 - 0.304
HNT (yes vs no)	0.2664	0.07379	3.61	< .001	1.305	1.129 - 1.508

Note: 5,815 patients included in the final adjusted model. Overall model performance measures: Deviance = 6,455; AIC = 6,465; McFadden's = 0.0616.

All clinical predictors entered into the final mathematical model retained a highly significant independent association ($p < 0.001$). HbA1c levels consolidated as the continuous factor with the greatest impact on the risk of developing the pathology ($Z = 16.55$; $p < .001$), with each percentage point increase in HbA1c associated with a 46% increase in the odds of having retinopathy (aOR = 1.460; 95% CI: 1.396 - 1.526).

Furthermore, the presence of HTN significantly increased the risk of retinal damage by 30.5% ($Z = 3.61$; $p < .001$; OR = 1.305; IC 95%: 1.129 - 1.508), whereas each additional year of age represented a linear increase of 1.9% in the odds of having the disease ($Z = 6.51$; $p < .001$; OR = 1.019; IC 95%: 1.013 - 1.025). Finally, diabetes type exhibited a significant inverse coefficient when contrasting type 2 against type 1 diabetes as the reference ($Z = -9.58$; $p < .001$; OR = 0.224; IC 95%: 0.165 - 0.304).

4. DISCUSSION

Main findings and glyceic control

The fundamental finding of this study is the confirmation of the critical and dominant role of glyceic control, measured via HbA1c, in the development and progression of diabetic retinopathy. In our bivariate analysis, HbA1c demonstrated the strongest association among all variables (Chi-squared = 491.6, $p < .001$), a dominance that was consolidated in the adjusted multivariate model, where each percentage point increase in HbA1c raised the risk of retinopathy by 46% (aOR = 1.460; 95% CI: 1.396 - 1.526). The magnitude of this odds ratio is particularly notable when compared to the international literature. While landmark, highly controlled clinical trials such as the UKPDS (United Kingdom Prospective Diabetes Study) and the DCCT (Diabetes Control and Complications Trial) estimated microvascular risk reductions of between 25% and 37% per percentage point reduction in HbA1c

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(Stratton et al., 2001), our cohort in Ávila shows an estimated impact of up to 46% in a real-world clinical practice setting. This upward discrepancy suggests that in the general patient population, where treatment adherence, comorbidities, and follow-up are more heterogeneous than in structured clinical trials, the impact of poor glycemic control is amplified. The robustness of this association confirms that optimizing HbA1c remains the modifiable strategy with the greatest potential impact on preventing this complication.

The impact of diabetes type and cardiovascular factors

Beyond glycemic control alone, our study confirms the multifactorial nature of DR. HTN was identified as a highly significant independent predictor in the multivariate model, increasing the risk of retinal damage by 30.5% (aOR = 1.305; 95% CI: 1.129 - 1.508; $p < 0.001$).

The clinical relevance of this 30.5% excess risk lies in its demonstration that blood pressure does not act as a mere bystander, but rather as an accelerator of damage on an already compromised metabolic foundation. Our findings closely align with the blood pressure control arm of the historic UKPDS, which demonstrated that tight blood pressure control achieved a microvascular risk reduction nearly comparable to that of tight glycemic control (UK Prospective Diabetes Study Group, 1998). Translating this debate to a real-world setting, the fact that HTN maintains such a distinct statistical significance ($p < 0.01$) in a multivariate model requires us to re-evaluate clinical strategies in primary care. Obsessively pursuing glycemic targets is insufficient; if clinicians overlook blood pressure optimization, they leave a critical pathway for microvascular disease progression unaddressed.

Additionally, patient age exhibited an independent linear relationship with retinopathy risk (aOR = 1.019 per year; $p < 0.01$). Although a 1.9% annual increase may seem modest in isolation, its cumulative effect over decades is substantial in real-world databases. This pattern largely reflects survival bias and the cumulative duration of disease exposure inherent to older patients in cross-sectional and retrospective designs, reminding us that time is a persistent adversary to microcirculation.

An aspect of particular interest in the logistic regression model was the behavior of diabetes type. Using type 1 diabetes as the reference, patients with type 2 diabetes exhibited a significantly lower risk of DR (aOR = 0.224; $p < 0.01$). Epidemiologically, this coefficient should not be misinterpreted as an intrinsic "protective" factor of type 2 diabetes, but rather as a direct reflection of the clinical aggressiveness and chronology of metabolic exposure that characterizes each condition.

Patients with type 1 diabetes typically experience onset at an early age, implying they accumulate decades of exposure to a chronic hyperglycemic environment during their years of longest life expectancy. Furthermore, they completely lack endogenous insulin secretion, leading to greater glycemic lability with sharp fluctuations and acute hyperglycemic spikes that damage the vascular endothelium more rapidly. In contrast, type 2 diabetes is usually diagnosed later in life and is accompanied by a period of residual pancreatic beta-cell function, despite concurrent insulin resistance. Our bivariate data clearly reflect this asymmetry: in advanced stages of the disease (such as proliferative DR), the proportion of patients with type 1 diabetes is proportionally much higher relative to the total size of their group in the sample (Chi-squared = 155.0, $p < 0.01$). This marked difference is consistent with epidemiological records from the WESDR (Wisconsin Epidemiologic Study of Diabetic Retinopathy) (Klein et al., 1984) and highlights that the type 1 diabetes population in our community presents a significantly higher microvascular vulnerability profile that must be prioritized in clinical screening and follow-up strategies.

These findings reinforce the importance of an integrated approach to the diabetic patient, in which DR must be understood within the context of global cardiovascular risk. In population-based screening programs, identifying patients with multiple risk factors can optimize clinical stratification. This need for large-scale optimization and stratification in real-world practice aligns with recent international guidelines, which advocate for the integration of automated algorithms and large-scale data analysis to predict individual risks of microvascular progression (Cheloni et al., 2025; Ting et al., 2024).

Variables with no statistical association: sex and dyslipidemia

Patient sex showed no association with the severity of the pathology ($p = 0.116$), consistent with the international consensus that retinal microvascular vulnerability affects men and women equally, depending on clinical management rather than biological sex (Yau et al., 2012).

Notably, dyslipidemia did not reach statistical significance in our bivariate analysis ($p = 0.780$). We suggest this phenomenon may be due to treatment bias in our cohort, where a high rate of statin prescription for systemic cardiovascular prevention in primary care could be masking the theoretical deleterious effect of lipids. Because this dataset consists of patients with established diabetes, the vast majority are on active, protocol-driven statin therapy due to strict cardiovascular prevention guidelines. Statin therapy not only normalizes plasma lipid profiles but also exerts pleiotropic vasculoprotective, anti-inflammatory, and endothelial-stabilizing effects that may neutralize and mask the theoretical negative impact of dyslipidemia on the retina, a phenomenon previously suggested in sub-analyses of major European observational studies (Siguier and Guillausseau, 2021; Kang et al., 2019).

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Study strengths and limitations

The primary strength of this study lies in its real-world clinical validity and large sample size, providing a highly reliable reflection of the diabetic population. By moving away from the strict, artificial constraints of randomized controlled trials, this cohort exposes the real-world effectiveness of clinical care and the diagnostic tools available for preventing visual impairment in patients with diabetes.

However, several limitations inherent to the design must be acknowledged. As a retrospective observational study, we cannot establish a strict temporal causality between the onset of HTN or fluctuations in HbA1c and the exact onset of DR. Furthermore, data on potential confounding variables, such as exact duration since diabetes diagnosis or treatment adherence rates, were unavailable; these parameters typically refine regression models in microvascular pathology. Similarly, a notable limitation is the lack of laboratory data on renal function, specifically regarding albuminuria or the urinary albumin-to-creatinine ratio. Given the tight pathophysiological links between nephropathy and retinopathy as parallel microvascular manifestations of systemic damage, including these parameters would have allowed us to evaluate target-organ interactions and adjust the independent risk of retinal progression with greater precision.

CONCLUSION

Chronic glycemic control, measured via HbA1c levels, is consolidated as the primary independent and modifiable predictor of both the presence and severity of diabetic retinopathy in the studied cohort. Additionally, the presence of HTN and advanced patient age is confirmed as an independent clinical cofactors that significantly increase the risk of developing this condition. Furthermore, a diagnosis of type 1 diabetes is independently associated with a higher likelihood of developing retinopathy and a higher frequency of advanced stages compared to type 2 diabetes. Conversely, patient sex and a concurrent diagnosis of dyslipidemia did not show a statistically significant association with either the presence or severity of diabetic retinopathy in this population.

AUTHOR'S CONTRIBUTION

Conceptualization, J.M.G., D.A.M., F.J.G.C. and J.M.C.; data curation, J.M.G., D.A.M., F.J.G.C. and J.M.C.; formal analysis, J.M.G., D.A.M., F.J.G.C. and J.M.C.; funding acquisition, J.M.G., D.A.M., F.J.G.C. and J.M.C.; investigation, J.M.G., D.A.M., F.J.G.C. and J.M.C.; methodology, J.M.G., D.A.M., F.J.G.C. and J.M.C.; project administration, J.M.G., D.A.M., F.J.G.C. and J.M.C.; resources, J.M.G., D.A.M., F.J.G.C. and J.M.C.; software, J.M.G., D.A.M., F.J.G.C. and J.M.C.; supervision, J.M.G., D.A.M., F.J.G.C. and J.M.C.; validation, J.M.G., D.A.M., F.J.G.C. and J.M.C.; visualization, J.M.G., D.A.M., F.J.G.C. and J.M.C.; writing – original draft, J.M.G.; writing – review & editing, J.M.G.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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