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ORIGINAL RESEARCH

Risk Factors Associated with Diabetic Retinopathy with and without Macular Edema in Recently Diagnosed Patients with Type 2 Diabetes

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Purpose: To evaluate the risk factors associated with diabetic macular edema (DME) in patients with a recent type 2 diabetes mellitus (T2DM) diagnosis.

Patients and Methods: We conducted a case-control study at a third-level hospital in Mexico City. We enrolled patients ≥18 years old, with T2DM less than five years of diagnosis, without disabling complications, and non-smokers. The control group was patients with diabetic retinopathy and without macular edema (DR-DME). Cases were patients with DR+DME. We measured fasting glucose, creatinine, lipid profile, urinary albumin/creatinine ratio (ACR), and HbA1c. An ophthalmological examination consisted of visual acuity measurement, digital three-field fundus photography with an automatic non-mydriatic camera, slit lamp, and Optical coherence tomography (OCT) examination.

Results: 183 and 61 patients with DR-DME and DR+DME, respectively, were included in the analysis. The prevalence of mild DR was higher in the DR-DME group, but the frequencies of moderate and severe retinopathy were higher in the DR+DME group. Patients in the DR-DME group had better vision than those in the DR+DME group. Logistic regression analysis revealed that age (OR, 1.07), HbA1c (OR, 1.19), and Albumin-to-Creatinine Ratio (ACR) > 30 mg/g (OR, 3.37) were associated with an increased possibility of DME compared to DR-DME.

Conclusion: Our study provides insights into the association between risk factors and DME. We found a statistically strong association between HbA1c levels, age, and ACR. Patients with poor metabolic control should undergo an extensive medical examination to screen for DME, which may be related to the chronicity of DM and renal damage.

Keywords: macular edema, recent diagnosis, diabetes mellitus, metabolic control

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease associated with various degrees of peripheral insulin resistance and progressive beta-cell fatigue, leading to a constant hyperglycemic state.[1] Control of morbidity and mortality in this population is highly associated with early therapeutic interventions and strict glycemic and overall metabolic control.[2] Regardless, the spectrum of clinical manifestations is wide. Even when patients have a recent diagnosis, many already have chronic complications due to long-term progression and time with metabolic dysregulation before a diagnosis of diabetes.[2]

Since the time of diagnosis is often years after the pathogenesis has begun, it is paramount to understand that complications seen in patients with T2DM result from intertwined metabolic reactions between conditions, such as obesity, non-alcoholic fatty liver disease (NAFLD), and kidney damage.[3] The 2021 Health and Nutrition Survey in Mexico found that 72.4% of the

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population was overweight or obese.[4] Individuals older than 60 have experienced a rapid increase in their prevalence. This population already experiences the greatest burden of chronic kidney disease (CKD), cardiovascular disease, and metabolic derangement based on age, all of which are further complicated by obesity.[5] Dysregulation of adipose tissue correlates with the degree of multiple complications such as proteinuria, CKD, and atherosclerotic artery disease.[6,7]

Current guidelines recognize dyslipidemia as a risk factor for diabetic microangiopathic complications, including diabetic retinopathy (DR). Diabetic macular edema (DME) is a part of the spectrum of non-proliferative diabetic retinopathy.[8] DME can present at any stage of DR and is the main cause of chronic diminishment of visual acuity.[9] Its presence requires aggressive therapeutic intervention, as it is associated with the development of blindness.[10] The American College of Cardiology (ACC) and the American Heart Association (AHA) recommend statin therapy for all people with diabetes between the ages of 40 and 75 years who have low-density lipoprotein (LDL) cholesterol levels of 100 mg/dL and above.[11] Furthermore, the ACCORD-Eye Study evaluated the effects of fenofibrate and simvastatin on DR, showing that dual therapy slowed the progression of DR in patients with T2DM at four years.[12]

This study aimed to evaluate the characteristics and factors associated with DME in patients with a recent diagnosis of T2DM attending a multidisciplinary care center.

Materials and Methods

This case-control study was conducted at the Center of Comprehensive Care for Patients with Diabetes (CAIPaDi) at the National Institute of Medical Sciences and Nutrition Salvador Zubirán.[13] We enrolled patients aged >18, with T2DM within five years, without disabling chronic complications, non-smokers, and who agreed to participate in the multidisciplinary program.

CAIPaDi Model

CAIPaDi is a multidisciplinary center. This model seeks to prevent the chronic complications of diabetes. Nine different healthcare professionals, including endocrinology, psychiatry, odontology, ophthalmology/optometrist, diabetes educators, dietitians, psychologists, nurses, and physical therapists, participated in the study. Medical notes and general laboratory results were recorded during each visit and were included in each patient's chart.

By the Helsinki Declaration, all subjects were informed about the study objectives and provided written consent to participate.

Procedures

The patients arrived at the Center for Laboratory and Anthropometric Tests. Fasting glucose, creatinine, lipid profile, urinary albumin/creatinine ratio (ACR) (colorimetric technique with Synchron CX System), and HbA1c (HPLC method with Bio-Rad Variant II Turbo HbA1c Kit 2) levels were assessed at each visit. Body composition was assessed using bioimpedance (Body Composition Analyzer, JAWON Medical ioi353).

At every visit, specialists registered the main indicators for each intervention. Endocrinologists specified the pharmacological treatment and made the required changes following algorithms for glucose, lipids, and blood pressure control.[14,15]

Ophthalmological Evaluation

A standardized examination was performed for all subjects, consisting of visual acuity measurements (M&S Technologies Inc. Smart System 20/20, Ilinois), digital three-field fundus photography with an automatic non-mydriatic camera (Centervue, DRS, Padova, Italy), slit lamp, and OCT examination (Spectralis Heidelberg Engineering).

Clinical detection using slit lamps, photographs, and OCT was performed to classify the patients to establish the final DME diagnosis. Certified optometrists and ophthalmologists performed all ophthalmological examinations. The criteria for DR and DME were based on the Scottish Diabetic Retinopathy Grading (SDRG) scale. Diabetic retinopathy was classified as R0 (no DR); the presence of DR includes R1 (mild non-proliferative DR), R2 (observable non-proliferative-DR), R3 (referable non-proliferative DR), and R4 (proliferative retinopathy). DME was classified as M0 (no DME), and the presence of DME included M1 (observable DME) and M2 (referable DME). Both eyes were evaluated and classified. Patients with visually

significant cataracts, high myopia, and anterior segment opacity that could mislead to DR or ME diagnosis were excluded. No other cause of exclusion was identified.

Glaucoma or suspected glaucoma was evaluated according to the ophthalmologic evaluation using a slit-lamp and nervous fibers with OCT analysis.

Groups

We included all patients diagnosed with recent T2DM diagnosis attending the CAIPaDi program (convenience sampling) from October 2013 to June 2022.

The controls included patients with DR-DME. Patients with DM+DME were included in the study. Cases and controls were matched in a 1:3 ratio according to sex to adjust for possible confounding variables. The patients were divided into the following groups:1) patients with DR and without DME (DR-DME) and 2) patients with DR and DME (DR+DME).

Statistical Analysis

The distribution was assessed using the Kolmogorov–Smirnov test for continuous variables. Data are presented as median and standard deviation (SD) or median with interquartile ranges (IQR; 25–75) according to normality in distribution. The Paired *t*-test was used to compare quantitative variables between the two groups (DR-DME vs DR+DME) with a normal distribution. The Wilcoxon matched-pairs signed-rank test compared two paired groups with a nonparametric distribution. Frequencies and percentages were used for categorical values and analyzed using the chi-square test.

We included the DR-DME (control) and DR+DME (cases) groups in the multiple logistic regression analysis and excluded patients without DR because it could underestimate the magnitude of the differences. The model evaluated the association between DME and metabolic risk factors. We reported the Odds Ratio and its 95% IC. Model fits were tested by Hosmer-Leme to show the goodness of fit after interactions and evaluation of possible confounders.

All statistical analyses were performed using the Stata Version 14 (Stata et al. Station, TX, USA). Statistical significance was set at $P < 0.05$.

Results

From October 2013 to June 2022, 2163 patients with diabetes underwent ophthalmological evaluation. We eliminated four (0.18%) patients for the analysis because they were not classifiable by OCT or ophthalmological evaluation. These cases corresponded to mature cataracts. Sixty-one patients had DME (prevalence, 2.91%). After pairing the sexes (49.1% women), we included 183 patients with DR-DME and 61 patients with DR+DME. The DR+DME group was older and had more years of diabetes diagnosis, higher blood pressure, and higher HbA1c and ACR levels than the DR-DME group. Body Mass Index (BMI), fat mass, and lean mass were lower in the DR+DME group. Table 1 presents the characteristics of each group.

When considering pharmacological treatment (Supplemental Material), a higher percentage of patients with DR +DME were on sulfonylureas (16.3% vs 30%, p=0.001), iDPP-IV (13.6% vs 10.9%, p=0.002), insulin (7.1% vs 10.3%, p=0.31), and beta-blockers (1.6% vs 6.5%, p=0.03). Supplementary Table 1 shows the pharmaceutical treatments administered to the groups.

Ophthalmologic Measurements

The global prevalence of DR was 11.2%. Table 2 shows the classification of ophthalmologic characteristics of the groups. Mild DR was the most frequent presentation in both groups, representing 94.2% in the DR-DME group and 40% in the DR+DME group (p<0.001). The frequency of moderate and severe retinopathy was higher in the DR+DME group. Patients with DR-DME have better vision (0.06 logMAR, 20/25 in Snellen notation) compared to the DR+DME group (0.16 logMAR, 20/30), p<0.001. The frequency of glaucoma or suspicion of glaucoma did not differ between groups.

Table 1 Characteristics Between Healthy, DR and No DME, and Macular Edema Groups

	DR-DME n=183	DR +DME n=61	p-value
Age (years)	55.36±9.63	59.93±8.19	0.001
Time since diagnosis (years)	2 (0–3)	3 (1–4)	0.008
Systolic blood pressure Diastolic blood pressure	127.74±15.79 77.6±7.26	135.34±19.82 80±8.42	0.002 0.03
Hypertension (%)	36 (19.67)	28 (45.90)	<0.001
Triglycerides (mg/dl)	165.5 (119–229)	200 (127–292)	0.40
Cholesterol-LDL (mg/dl)	116.19 ±32.28	128.85 ±37.33	0.01
Glucose (mg/dl)	151 (117–216)	171 (124–243)	0.054
HbA1c (%)	8.94±2.33	9.92±2.34	0.004
Creatinine (mg/dl)	0.74±0.19	0.79±0.20	0.04
Uric acid (mg/dl)	5.26±1.33	5.18±1.18	0.69
Albumin/creatinine ratio (mg/g)	10.9 (5.8–24.04)	50 (10–192)	<0.001
Body mass index (kg/m2)	28.83±4.63	25.93±3.46	<0.001
Fat mass (%)	33.86±6.40	30.74±7.30	0.001
Lean mass (kg)	45.24±9.75	42.60±7.22	0.053

Abbreviations: DR, Diabetic Retinopathy; DME, Diabetic Macular Edema.

Table 2 Ophthalmologic Characteristics of Patients

	DR-DME n=183	DR+DME n=61	p-value
Diabetic Retinopathy, n (%) Mild Moderate Severe and proliferative	 165 (94.29) 8 (4.57) 2 (1.14)	 22 (40) 17 (30.91) 16 (29.09)	<0.001
Glaucoma or suspect, n (%)	7 (3.83)	2 (3.33)	0.86
Visual Acuity, logMAR	0.06±0.14	0.16±0.15	<0.001

Abbreviations: DR, Diabetic Retinopathy; DME, Diabetic Macular Edema; logMAR, Logarithm of the Minimum Angle of Resolution.

Logistic Regression Analysis

In the multiple logistic regression analysis, we included the variables age, diastolic blood pressure (>90 mmHg), LDL-cholesterol (>100 mg/dl), HbA1c (continuous), ACR (>30 mg/g), and lean mass (continuous). There was a significant association between age (OR, 1.07/year; 95% CI, 1.02–1.11, p=0.001), HbA1c (OR, 1.19, per unit; 95% CI, 1.03–1.37, p=0.01), ACR > 30 mg/g (OR, 3.37; 95% CI, 1.74–6.54; p<0.001), and an increased possibility of DME. The model was statistically significant (p<0.001), with R2=0.15, the area under the ROC Curve (AUC-ROC) 0.77, and Hosmer-Lemeshow = 0.68 (Table 3).

Table 3 Logistic Regression Model for Risk Factors Associated with DR +DME

Predictors	Adjusted OR	*p*-value	95% CI
Age, years	1.07	0.001	1.02–1.11
Diastolic blood pressure >90mmHg	2.68	0.10	0.82–8.70
Cholesterol-LDL >100	1.05	0.15	0.51–2.18
HbA1c, %	1.19	0.01	1.03–1.37
Albumin/creatinine ratio >30 mg/g	3.37	<0.001	1.74–6.54
Lean mass (kg)	0.98	0.34	0.94–1.02

Abbreviations: DR, Diabetic Retinopathy; DME, Diabetic Macular Edema.

In a sub-analysis of the albumin/creatinine ratio (ACR), we found that a cut-off value of > 35 mg/gr provided a maximum sensitivity of 65% and a specificity of 75% to predict the presence of DME.

Discussion

Our study found a prevalence of DR and DME like that described in the literature. We found a prevalence close to the global estimate of 3.1% for DME in subjects with less than ten years of DM diagnosis.[16] This similarity was unexpected since our study population had less than five years of T2DM diagnosis. However, this could be explained by using a high-sensitivity diagnostic test OCT for DME diagnosis, which would identify patients who may miss out on conventional, less sensitive diagnostic workouts.[17]

Likewise, we did not find a significant difference in the values of the workup for dyslipidemia, particularly triglyceride levels, which we originally hypothesized would show a high degree of difference among the groups. This could be explained by the fact that most of our patient population was already receiving some form of lipid-lowering therapy, particularly statin therapy. Likewise, regardless of efficient metabolic control, most patients had undergone nutritional assessment at some point in their clinical workup in our clinic. Table 1 also shows that the distribution of total cholesterol and triglyceride levels remained homogeneous regardless of metabolic control, which would reduce the chances of finding significant differences.

We found that patients with worse metabolic control at diagnosis also had the most severe clinical presentation, concordant with published literature.[16] Our patients with a higher degree of DME also had lower BMI, higher ACR, and worse HbA1c. This finding could be related to disease chronicity and waste. These metabolic derangements act in concert and by various mechanisms, leading to DME.[18] Worse HbA1c levels are associated with microvascular damage, leading to non-enzymatic glycosylation of blood vessel walls that results in extravasation of intravascular content, including cholesterol- and lipid-derived products. The retinal and macular microvasculature results in extravasation and deposition of high amounts of lipid-rich content, further contributing to the inflammatory microenvironment and degenerated macular cells.[19]

Diabetes-related visual derangements exist in a spectrum that considers both DR and DME as complications that share an underlying pathophysiological mechanism but can be distinguished by characteristic findings in the diagnostic workout of patients. However, because they exist within this spectrum, one condition often shares the characteristics of the other.[20] DME is a common cause of visual loss in patients with T2DM, and although some may share features of DR, the presence of DME over the severity of DR is identified as the driving factor leading to blindness.[21]

Our results showed that visual acuity was significantly worse in the group with DR+DME (0.06 logMAR) than in the group with DR-DME, where vision was the same (0.16 logMAR). This finding further contributes to the idea that both conditions coexist within a spectrum and that both create an inflammatory microenvironment that further reduces the visual quality of patients. Lent-Schochet et al reported that patients with DME with a visual acuity of 20/25 or better,[22] but worse DR severity, have an increased risk of visual loss, concordant with our findings. In addition, we found that approximately one-third of cases of DR-DME have non-proliferative severe DR or proliferative DR, which means that these patients must be monitored closely to prevent further visual loss due to the progression of either DME or DR complications.

Our study provides insights into the metabolic profiles of patients with a recent diagnosis of DM2. In a comprehensive care program, we evaluated patients with recent diagnoses to detect complications promptly. The strength of this study is that all patients received multidisciplinary attention, including a comprehensive ophthalmological evaluation. This improves the sensitivity at diagnosis. We also provided complete information from all specialties for the analysis. In this analysis, we compared the patients with and without DME. Most published articles present factors associated with DR without separating patients with DR-DME. In our study, we separated patients with DR-DME and DR+DME to identify DME-associated factors.

Some limitations of our study are that it was a cross-sectional evaluation of patients and that we could not perform serial measurements over time. Likewise, our population was evaluated by a specialized center, and their metabolic profile does not necessarily correlate with the general population with a longer duration of diabetes. Further research could benefit from using patients without DR as the reference group to develop a multimodal regression, where we evaluated the risk for both DR-DME and DR+DME. DME data were not adjusted according to severity, which also opens an opportunity for follow-up research.

Conclusion

Although multiple factors are involved, it is important to study the association between these factors and the development of complications in patients with T2DM. Our study provides insight into how risk factors for the development of DME in people living with diabetes are related to HbA1c and ACR. Patients with a higher degree of albuminuria and worse metabolic control should undergo an extensive ophthalmological examination to screen for DME and DR, which causes preventable visual loss in this population.

Abbreviations

ACC, American College of Cardiology; ACR, Albumin/creatinine ratio; AHA, American Heart Association; AUC-ROC, Area under the ROC Curve; BMI, Body Mass Index; CAIPaDi, Centro de Atención Integral del Paciente con Diabetes; CKD, Chronic kidney disease; DME, Diabetic Macular Edema; DR, Diabetic Retinopathy; NAFLD, Non-alcoholic fatty liver disease; LDL, Low-density lipoprotein; LogMAR, Logarithm of the Minimum Angle of Resolution; OCT, Optical coherence tomography; SDRG, Scottish Diabetic Retinopathy Grading; T2DM, Type 2 Diabetes Mellitus.

Data Sharing Statement

Data will be available upon request. Interested parties may request access to this data by sending a letter to the corresponding author outlining their specific data needs and research intentions. Authors are committed to facilitating data sharing in the spirit of collaboration and transparency. The provided data will be de-identified and will remain accessible for five years following the publication of the manuscript. This information will be made available through digital registries to ensure convenient and efficient access, enabling researchers to harness the valuable insights generated from clinical trials for further scientific exploration and advancement.

Ethics Approval and Informed Consent

The Institutional Ethics approves the CAIPaDi model and Research Committees of the National Institute of Medical Sciences and Nutrition Salvador Zubirán (Ref 1198, reapproved January 2023) and registered at the website ClinicalTrials.gov (NCT02836808). According to the Helsinki Declaration, all subjects were informed about the study's objectives and provided written consent to participate.

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Disclosure

The authors report no conflicts of interest in this work.

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