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ORIGINAL RESEARCH

Evaluation of the Relationship Between Diabetic Macular Edema and Renal Function in a Latino Population

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ABSTRACT

Introduction: Diabetic macular edema (DME) is one of the leading causes of vision impairment. The relationship between DME and estimated glomerular filtration rate (eGFR) has not been clearly evaluated in Hispanic or Latino populations. The objective of this study was to evaluate the eGFR in a Latino population with DME.

Methods: A cross-sectional, observational, and descriptive study was carried out on the basis of a multicenter phase III clinical trial.

Results: A total of 82 subjects diagnosed with DME (36 women and 46 men) were included in the study. The mean age was 61.93 ± 6.71 years. Mean values of the blood chemistry parameters glycated hemoglobin and eGFR were 7.20 ± 0.95% and 74.42 ± 26.82 mL/min/1.73 m^2, respectively. The time elapsed since diagnosis of diabetes mellitus was 15.30 ± 7.35 years, while the duration of DME was 1.41 ± 1.75 years. Mean values for central macular thickness (CMT) and total macular volume (TMV) were 440.99 ± 132.22 µm and 11.97 ± 2.11 mm^3, respectively. DME duration had a negative correlation with TMV (Rho − 0.26, $p < 0.05$) and a positive correlation with mean arterial pressure (Rho 0.26, $p < 0.05$). CMT was correlated with TMV (Rho 0.43, $p < 0.0001$) and visual acuity (Rho 0.26, $p < 0.05$). No significant correlations were observed between eGFR and CMT, TMV, or any demographic variable ($p > 0.05$). Chronic kidney disease (CKD) was associated with hypertension (OR 9.32, $p = 0.035$), elevated intraocular pressure (IOP) (OR 0.03, $p = 0.011$), and advanced age (OR 0.45, $p = 0.011$). CMT was significantly associated with TMV ($\beta = 27.69$, $p < 0.0001$).

Conclusions: We did not find a correlation between eGFR and DME. Our findings suggest that the presence of hypertension is associated with a decrease in the GFR < 60 mL/min/1.73 m^2, and CKD may be associated with advanced age and elevated IOP which may increase the risk for the development of glaucoma.

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Keywords: Central macular thickness; Total macular volume; Diabetes mellitus; Diabetic macular edema; Glomerular filtration rate

Key Summary Points
The relationship between diabetic macular edema (DME) and estimated glomerular filtration rate (eGFR) has been not clearly evaluated in Hispanic or Latino populations.
The principal objective of this study was to evaluate the eGFR in a Latino population with DME.
Hypertension was associated with a decrease in glomerular filtration rate.
There was no association between glomerular filtration rate and diabetic macular edema.
A reduced glomerular filtration rate may be associated with advanced age and elevated intraocular pressure, which increases the risk of developing glaucoma.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia, associated with long-term damage of different organs, particularly the eyes, kidneys, peripherical nervous system, heart, and blood vessels [1, 2]. Diabetes can be classified into type 1 diabetes; type 2 diabetes, which appears to be due to a non-autoimmune progressive loss of adequate β-cell insulin secretion; and specific types of diabetes due to other causes or gestational diabetes mellitus [3]. The resulting complications are grouped under microvascular or macrovascular disease. Microvascular complications include diabetic retinopathy (DR) and diabetic macular edema (DME) [4]. DME is one of the most common causes of visual loss in patients with DM. The prevalence of DME in patients with DR varies from 2.7% to 11% [5–7]. DR prevalence is high between Latinos of primarily Mexican ancestry. DME has been observed in 10.4% and clinically significantly DME in 6.2% of a diabetic population cohort in the USA [8]. Several risk factors have been identified, such as diabetes duration, elevated glycosylated hemoglobin (HbA1c), hypertension, and age [5, 6]. The pathophysiology of DME involves dilated capillaries, retinal microaneurysms, and loss of pericytes, with eventual impairment of the blood-retinal barrier, resulting in fluid leakage into the extracellular space, altering macular structure, function at the cellular level, and the main morphological alteration—central macular thickness (CMT) leading to impaired of visual acuity (VA).

Vascular endothelial growth factor (VEGF) promotes neovascularization and angiogenesis. When VEGF is overproduced, conditions such as DME, aged-related macular degeneration, or DR can occur. The severity of vascular leakage in DME correlates with the level of VEGF produced and therefore anti-VEGF agents, such as ranibizumab (Lucentis, Genentech Inc., South San Francisco, CA, USA), bevacizumab (Avastin, Genentech Inc, South San Francisco, CA, USA), PRO-169 (anti-VEGF monoclonal antibody for intravitreal administration, Laboratorios Sophia, S.A. de C.V., Zapopan, Jalisco, Mexico), are used to inhibit it [9–12]. Nevertheless, it has been suggested that the use of anti-VEGF agents may result in systemic absorption, leading to further reduction in plasma VEGF activity, which turn produces accelerated hypertension, worsening proteinuria, glomerular disease, and possible chronic renal function decline [2, 13].

The diagnosis of macular edema is clinical [14–16]. Optical coherence tomography (OCT) is the most widely used imaging method in the diagnosis and follow-up of DME [17]. In OCT, DME is generally seen as an area of retinal thickening that is often accompanied by loss of the foveal depression [18].

Furthermore, diabetes and hypertension are the main causes of chronic kidney disease (CKD). The former accounts for 30–50% of all

CKD and affects 285 million (6.4%) adults worldwide [19], and more than a quarter of the adult population was estimated to have hypertension in 2000, although this proportion is projected to increase by approximately 60% by 2025 [20]. CKD is defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or markers of kidney damage, or both, of at least 3 months' duration. The best available indicator of overall kidney function is glomerular filtration rate which equals the total amount of fluid filtered through all the functioning nephrons per unit of time [19].

There is little evidence of the relationship between eGFR and DME. It has been observed that low levels of eGFR are associated with the presence and state of the DR [21, 22]. Although eGFR has been used as a marker of renal function to assess the impact of renal status in subjects with DME, eGFR was not associated with DME severity or macular thickness, and it was concluded that it is not a useful marker for prediction of DME severity or pattern [23].

The objective of this study was to evaluate the association between DME and renal function measured by eGFR in a Latino population. In addition, it was possible to evaluate the relationship between DME and some risk factors.

METHODS

Study Design

A cross-sectional, observational, and descriptive study was carried out on the basis of a multicenter phase III clinical trial (ClinicalTrials.gov Identifier NCT05217680). The population of the main study consisted of volunteer patients who met the inclusion criteria and who signed the letter of informed consent for the performance of all the procedures involved. The sample analyzed is a subset of those patients included before they were randomized to any intervention (screening visit). This protocol was performed in accordance with the principles of the Declaration of Helsinki of 1964 and according to ICH guidelines and current local legislation.

Participants

The inclusion criteria required for the participants to present a diagnosis of DM (defined by use of insulin or oral hypoglycemic agents as treatment and according to the criteria established by the World Health Organization or the American Diabetes Association), older than 18 years, both genders, with an HbA1c value < 8.5%, and eGFR > 15 mL/min/1.73 m^2. The ocular inclusion criteria included a corrected visual acuity Early Treatment Diabetic Retinopathy Study (ETDRS) < 78, diagnosis of DME with clinical evidence of central macular thickening or DME present on spectral domain OCT (criterion of central macular thickness > 300 µm for men and > 290 µm for women). The exclusion criteria were CKD in renal failure (eGFR < 15 mL/min/1.73 m^2), requiring glycemic control with insulin, poorly controlled blood pressure (systolic ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg), history of myocardial infarction or another cardiovascular event and non-diabetic macular edema, intraocular pressure (IOP) > 21 mmHg, lens opacities, evidence of external ocular infections or significant ocular surface disease, evidence of macular traction and hyaloid thickening on OCT. For more information about inclusion and exclusion criteria, see the supplementary material (Table S1).

Patient's age, sex, weight, body mass index (BMI), waist circumference, heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure, and respiratory rate (RR) were registered. Also, a brief questionnaire was applied to obtain information about their lifestyle and medical history, such as hypertension, duration of diagnosis of DM and DME. Mean arterial pressure (MAP) was estimated as (SBP + 2 × DBP)/3 [23].

Assessment of DME and Ophthalmological Evaluation

Patients underwent a complete ophthalmologic examination, which included best corrected visual acuity (BCVA) test according to ETDRS guidelines, biomicroscopy for detailed

examination of ocular structures and media transparency analysis, measurement of IOP with Goldmann tonometer, as well as indirect ophthalmoscopy for detailed retinal examination. Subsequently, an OCT (Heidelberg Engineering, Heidelberg, Germany) was performed to assess total macular volume (TMV) and CMT.

Blood Chemistry

For the assessment of HbA1c and eGFR, a blood sample was obtained by venipuncture. Whole blood HbA1c testing was made by Variant II Turbo HbA1c analyzer (Bio-Rad Laboratories, Hercules, CA, USA) with the Variant II Turbo HbA1c kit from the same manufacturer which uses cation exchange high-performance liquid chromatography. Enzymatic creatinine was quantified with the Roche Cobas analyzer, and the CKD-EPI equation was used to calculate eGFR. The samples were processed in the local laboratory through a standardized process.

Statistical Analysis

Statistical analyses were carried out with a specialized statistical package, R statistical software package (The R Foundation for Statistical Computing; http://www.R-project.org). The Kolmogorov–Smirnov test was applied to determine the distribution of the numerical variables. Quantitative variables were reported as means ± standard deviation (SD). Qualitative variables were reported as frequency and percentage. Spearman's correlations were used to evaluate the association between the variables [24]. The variables that presented a significant correlation were used as a reference for the construction of the regression models. To measure the association of eGFR with other covariates, a binary logistic regression model was used. The model took eGFR as the dependent variable, divided into two groups: > 60 mL/min/1.73 m^2 and CKD < 60 mL/min/1.73 m^2 [23, 25]; the remaining covariates were treated as independent variables. The results of the regression models were presented as odd ratios (ORs), a 95% confidence interval (95% CI), and the p value. The relationships between the CMT (dependent variable) and the other covariates (as independent variable) were studied with a multiple linear regression model.

RESULTS

Characteristics of the Participants

A total of 82 subjects (36 female and 46 male) were included in the study. All participants were diagnosed with type 2 DM (T2DM) and DME. The mean age of the included subjects was 61.93 ± 6.71 years. The mean duration of DM and DME was 15.30 ± 7.35 and 1.41 ± 1.75 years, respectively. Several patients were under treatment 4 months prior to the start of the study. A total of 23 patients had panretinal photocoagulation laser (28%), 15 patients were injected previously with anti-VEGF agents (18.3%), and 44 patients were newly diagnosed with DME (53.7%). The mean values of eGFR and HbA1c were 74.42 ± 26.82 mL/min/1.73 m^2 and 7.20 ± 0.95%, respectively. The mean CMT value measured by OCT was 440.99 ± 132.22 μm and the mean TMV was 11.97 ± 2.11 mm^3. Other characteristics of the study participants are shown in Table 1. Most patients were users of concomitant medications (98%), such as antidiabetic (biguanides), 82.9%; antihypertensives (angiotensin II receptor antagonists), 62.1%; hypolipidemic (statins), 17.0%; or diuretics (hydrochlorothiazide), 14.6%.

Spearman's Correlation

A Spearman's rank correlation analysis was computed to assess the strength, statistical significance, and direction of variables associated with DME. Thus, variables correlated positively or negatively were included in models (see below). We detected a moderate positive correlation between waist circumference and BMI (Rho 0.59, $p < 0.0001$), CMT and TMV (Rho 0.43, $p < 0.0001$), as well as TMV and VA–logMAR (Rho 0.39, $p < 0.001$). The correlation of RR with VA–logMAR was weak and positive (Rho 0.35, $p < 0.01$), as were those of

HbA1c with waist circumference (Rho 0.30, $p < 0.01$) and HbA1c with MAP (Rho 0.28, $p < 0.05$). Other variables with weak and positive correlations were VA–letters score and waist circumference, CMT and VA–logMAR, duration of DME and MAP, and HbA1c with VA–letters score, and eGFR with MAP (see supplementary Table S2). As expected, there was a significant, very strong, negative correlation between VA–letters score and VA–logMAR (Rho − 0.99, $p < 0.0001$), TMV and VA–letters score correlation was moderate and negative (Rho − 0.41, $p < 0.001$), RR and VA–letters score correlation was weak and negative (Rho − 0.34, $p < 0.01$), like those of age and sex, duration of DME and TMV, as well as VA–letters score and CMT, among others. The correlation analysis of all significant variables is shown in Fig. 1.

Table 1 Clinical characteristics and demographic data of patients in this study (n = 82)

Characteristic	Mean ± SD
Age (years)	61.93 ± 6.71
Sex[a]	
Female	36 (43.90%)
Male	46 (56.10%)
BMI (kg/m^2)	27.47 ± 3.96
Waist circumference (cm)	92.10 ± 13.62
Systolic blood pressure (mmHg)	131.27 ± 11.60
Diastolic blood pressure (mmHg)	79.20 ± 7.01
Mean arterial pressure (mmHg)	96.55 ± 7.24
Heart rate (beats pm)	74.54 ± 8.71
Respiratory rate (breaths pm)	16.50 ± 1.72
Hypertension diagnosis[a]	62 (75.6%)
GFR (mL/min/1.73 m^2)	74.42 ± 26.82
Glycosylated hemoglobin (%)	7.20 ± 0.95
Duration of DM (years)	15.30 ± 7.35
Duration of DME (years)	1.41 ± 1.75
Intraocular pressure (mmHg)	14.23 ± 2.14
Central macular thickness (μm)	440.99 ± 132.22
Total macular volume (mm^3)	11.97 ± 2.11
VA–letters score	55.09 ± 13.49
VA–logMAR	0.59 ± 0.27

BMI body mass index, *DM* diabetes mellitus, *DME* diabetic macular edema, *GRF* glomerular filtration rate, *pm* per minute, *SD* standard deviation, *VA* visual acuity
[a]Data reported as frequency (%)

Association Between eGFR and OCT Parameters and Clinical Factors

After the exploratory and correlation analysis, data of 82 patients with diagnosis of DME were included to adjust three logistic regression models for eGFR and three linear regression models for CMT. For eGFR, ORs were used, and their 95% CI was used to predict values below 60 mL/min/1.73 m^2, considered suggestive of kidney damage. To assess the performance of logistic models, overdispersion and parsimonies (Akaike's information criterion [AIC] and Bayesian information criterion [BIC]) were evaluated (supplementary Table S3).

Logistic Regression Modeling for eGFR

Model 1 (M1) included HbA1c, hypertension, IOP, and age as predictors of eGFR values < 60 mL/min/1.73 m^2. Model 2 (M2) included HbA1c, TMV, hypertension, IOP, and age. Model 3 (M3) included HbA1c, hypertension, age, and CMT as predictors of kidney damage (see supplementary Fig. S1). We compared the models to obtain the significant variables and their ORs, based on AIC, BIC, log likelihood, and deviance metrics, without differences among models ($p > 0.05$). The incidence of hypertension had an OR of 9.32 (95% CI 1.95–75.49), IOP had an OR of 0.03 (95% CI 1.41e−03 to 0.04), age had an OR of 0.45 (95% CI 0.23–0.79), and the interaction between IOP and age had an OR of 1.05 (95% CI 1.01–1.10). Additionally, we included the HbA1c that was not significant ($p = 0.061$) but presented an OR of 0.03 (95% CI 6.75e−04 to 1.07), which is acceptable for $p < 0.10$. The model's metrics are shown in Table 2 and Fig. S1.

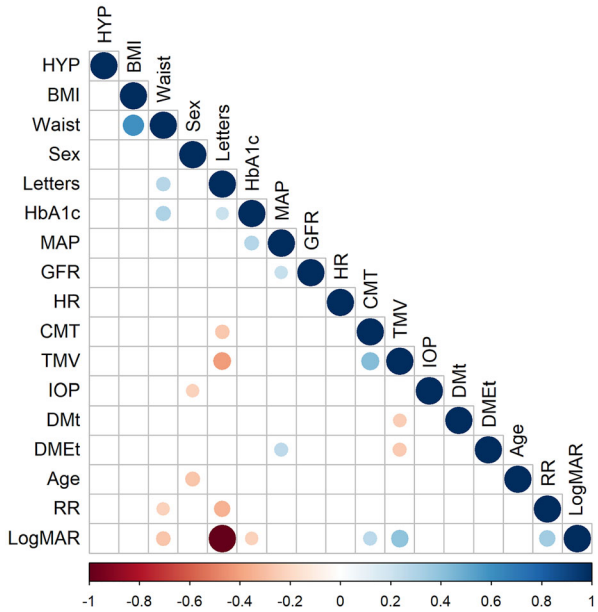

Fig. 1 Correlation matrix of all significant variables

Table 2 Risk of CKD using binary logistic regression analysis

Variable/level	Estimate	Std. error	*p* value
Intercept	76.44	25.56	0.003
HbA1c	− 3.45	1.84	0.061
TMV	− 1.79	1.04	0.085
Hypertension–yes	2.23	0.91	0.014
IOP	− 3.51	1.38	0.011
Age	− 0.80	0.31	0.011
HbA1c/TMV	0.25	0.15	0.086
IOP/age	0.05	0.02	0.015

Multivariate model. Goodness-of-fit: AIC 99.60, deviance 83.60, null deviance 106.50

CDK chronic kidney disease, *CI* confidence interval, *HbA1c* glycated hemoglobin, *IOP* intraocular pressure, *TMV* total macular volume

Association Between CMT and Total Macular Volume

The linear relationship, autocorrelation among residuals, multicollinearity, and heteroscedasticity were checked in all linear models for CMT. Data from 82 patients were included to adjust three linear regression models, all of them valid for the analysis. M1 included the age, total macular volume, and VA–letters score as predictors of CMT. The fitted regression for M1 was CMT = 372.62 + 27.66 × TMV − 2.92 × age − 1.48 × VA–letters score. The overall regression was statically significant (multiple $R^2 = 0.27$, $F_{(3,78)} = 9.75$, $p < 0.0001$); however, only 24% of the variance in CMT was predicted by M1. TMV significantly predicted CMT ($\beta = 27.66$, $p < 0.001$). M2 included total macular volume, age, VA–letters score, and hypertension as predictors. The fitted regression for M2 was CMT = 399.21 + 27.69 × TMV − 41.69 × hypertension − 2.91 × age − 1.42 × VA–letters score. M2 was statistically significant ($R^2 = 0.29$, $F_{(4,77)} = 7.91$, $p < 0.0001$), and 25% of the variance in CMT was predicted by M2. TMV significantly predicted CMT ($\beta = 27.69$, $p < 0.0001$). M3 included total macular volume, MAP, and hypertension as predictors. The fitted regression for M3 was CMT = − 151.33 + 31.73 × TMV + 2.56 × MAP − 45.74 × hypertension. M3 was statistically significant (multiple $R^2 = 0.28$, $F_{(5,69)} = 6.52$, $p < 0.0001$), 25% of the variance in CMT was predicted by M3, and once again TMV significantly predicted CMT ($\beta = 31.73$, $p < 0.0001$). Finally, the metrics were similar for the three models, showing adequate parsimonies (Table 3 and supplementary Table S4, and Figs. S2–S5).

DISCUSSION

To the best of our knowledge this is the first study reporting the relationship between DME and renal function in a Latino population, as well as the relationship with other risk factors.

The relationship between renal function parameters and microvascular complications of the eye in patients with diabetes has been reported in several studies [23, 26, 27]. Subjects with a moderate decrease in eGFR (30–54.9 mL/min/1.73 m^2) are at increased risk of developing treatment-requiring diabetic eye diseases

(hazard ratio 1.90, 95% CI [1.11–3.23], $p = 0.019$) [28].

Although most of the studies indicate a lack of significant relation between renal parameters and the presence or severity of DME [23], there are a few reports of a possible association; however, most of these studies found a greater association with proteinuria than with decreased eGFR [26, 29]. Though both nephropathy and retinopathy have a similar pathology, i.e., microangiopathy, the precise impact of renal factors and proteinuria on DR and DME remains elusive [23].

In accordance with previously published results, in this sample of Latino patients with T2DM and DME, we did not find significant correlations between eGFR and OCT parameters (CMT or TMV, $p > 0.05$). In addition to comparisons among Latinos in several studies, contradictory results were found in those comparing Latinos to non-Hispanic whites [2, 8, 30]. However, the data consistently confirm the high rates of DR observed among Latinos of primarily Mexican ancestry [8].

We also analyzed additional variables and found an association of CKD with hypertension, with elevated IOP and advanced age. In this regard, it has been reported that prevalence of CKD increases rapidly with age. In the USA, the CKD prevalence in adults 30 years of age or older is estimated to be 16.7% in 2030 [31]. Although the relationship between CKD and glaucoma appears to be inconsistent in population-based studies, there is some evidence that the prevalence of glaucoma is higher in patients with known CKD, with a prevalence of 7.6% [31–33]. In this study we did not perform diagnostic tests for glaucoma; however, we found an association with increased IOP which is known to be the only modifiable risk factor for developing glaucoma [34, 35]. The exact mechanism by which CKD might be associated with higher IOP is not known. Possible mechanisms that could explain it include a breakdown in the homeostasis of body fluids leading to fluid overload, accumulation of toxic metabolites, and impaired aqueous outflow through the trabecular meshwork [36].

Another correlation found in this study was between CMT and visual acuity which supports

Table 3 Linear regression models for CMT

Model	Multiple R^2, p value	VA–letters score estimate (95% CI)	TMV estimate (95% CI)	Age estimate (95% CI)	Hypertension estimate (95% CI)	MAP estimate (95% CI)	Intercept estimate (95% CI)	RSE
M1 ($n = 82$)	0.27, < 0.0001	− 1.48 (− 3.55, 0.59)	27.66 (14.45, 40.87)	− 2.92 (− 6.76, 0.91)	–	–	372.62 (38.91, 748.18)	114.9
M2 ($n = 82$)	0.29, < 0.0001	− 1.42 (− 3.48, 0.64)	27.69 (14.57, 40.83)	− 2.91 (− 6.72, 0.90)	− 41.69 (− 100.22, 16.84)	–	399.21 (65.49, 732.93)	114.2
M3 ($n = 82$)	0.28, < 0.0001	–	31.73 (19.53, 43.92)	–	− 45.74 (− 104.54, 13.05)	2.56 (− 0.99, 6.11)	− 151.33 (− 545.29, 242.64)	114.7

CI confidence interval, *CMT* central macular thickness *MAP* mean arterial pressure, *RSE* residual standard error, *TMV* total macular volume, *VA* visual acuity

the findings of previous studies. Sakata et al. found a significant positive correlation (Rho 0.64, $p = 0.001$) between retinal thickness at the central fovea and BCVA in patients with diabetes [37]. Li et al. studied 39 patients with DME and found a positive correlation between central foveal thickness and VA–logMAR (Rho 0.58, $p < 0.001$) [38]. This can be explained by histopathologic reports of eyes with macular edema wherein retinal swelling initiates the intracellular swelling of Müller cells, especially in the outer plexiform layer of the neurosensory retina, and continuous retinal swelling can lead to visual impairment in patients with DME [37].

Duration of diabetes is a clinically accepted marker for overall diabetic health status. In the eye, longer duration of diabetes is a risk factor for the development of DR and DME [30, 39]. There was a negative and weak correlation between duration of diabetes mellitus and TMV (Rho − 0.24, $p = 0.028$), like that between duration of DME and TMV (Rho − 0.26, $p = 0.019$). TMV tends to move in the opposite direction to the duration of DM and the duration of DME. We believe this may be attributed to the degeneration of retinal neurons and glial cells, which has been previously described as playing an important role in the pathogenesis of DR [40]; also, it has been described that choroidal thickness tends to increase in the early stages of DR, and then to decrease as DR progresses [41]. On the other hand, ganglion cell–inner plexiform layer thickness has been found to get thinner in eyes with resolved DME after treatment for macular edema. This suggests that inner retinal alterations occur in patients with DME and DR including vascular changes and primary neuronal degeneration [42].

We also found a positive correlation between HbA1c and waist circumference, in agreement with Veiby et al.'s study (Rho 0.17, $p < 0.01$) [43], which reported that waist circumference was strongly associated with diabetes progression: higher waist circumference likely reflects better a high level of HbA1c cumulatively over many years.

Lastly, we found a correlation between MAP and eGFR. In the study conducted by Yang et al., it was demonstrated that with increasing MAP, the vascular resistance and elasticity increase, the arteries become progressively stiffer, and finally eGFR is decreased [44].

Our current study has some limitations. First, the study's cross-sectional nature does not allow us to assess the temporal sequence of these associations. Second, the sample size was relatively small. Third, measurement of eGFR was assessed at only one point in time and another renal function biomarker was not measured. Fourthly, we did not include subjects with chronic kidney disease in renal failure (GFR < 15 mL/min/1.73 m^2). Lastly, we did not include subjects with a poor glycemic control who required insulin treatment within 4 months prior the study which may limit the sample of subjects.

Our findings constitute an important contribution to the understanding of the relationship not only between DR and DME but also between additional risk factors. The fact that we have not identified a relationship between eGFR and changes in macular OCT may constitute an additional guideline for the evaluation of renal function in patients with DME using other biomarkers such as proteinuria. This in turn highlights the importance of the need for multidisciplinary approaches and follow-up in patients with DM in order to reduce or modulate risk factors as hypertension and elevated waist circumference or to identify those patients who are at a higher risk for developing complications such as ocular hypertension in patients with renal function impairment. Further exploration is warranted.

CONCLUSION

A correlation between eGFR and DME was not found in this sample of patients with type 2 diabetes and DME. Our findings suggest that the presence of hypertension is associated with a decrease in glomerular filtration rate < 60 mL/min/1.73 m^2, and CKD may be associated with advanced age and elevated intraocular pressure which may increase the risk for the development of glaucoma.

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Author Contribution. José María Torres-Arellano, Andrea Tornero-Jimenez, Alejandra Sánchez-Ríos, Oscar Olvera-Montaño, and Patricia Muñoz Villegas all contributed substantially to the conception and design, data acquisition, or their analysis and interpretation; participated in the drafting of the article or critically reviewed it of important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All named authors collaborated in the drafting of the article, and all read and approved the final article.

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Data Availability. In addition to the summary statistics, the supplementary material shows the proof of principles for each model performed openly in the Open Science Framework (https://osf.io) as https://doi.org/10.17605/OSF.IO/3HEVN.

Ethical Approval. This protocol was performed in accordance with the principles of the Declaration of Helsinki of 1964 and according to ICH guidelines and current local legislation. The study protocol and informed consent form were approved by their respective Institutional Review Boards, chosen by the research center or principal investigator as follows: Comité Ética en Investigación del Instituto Mexicano de Trasplantes, Comité de Ética en Investigación de Medical Care and Research, Comité de Ética en Investigación del Centro de Investigación Clínica Acelerada, S.C, Comité de Ética de Investigación del Hospital de la Misión, Comité de Ética en Investigación de la Clínica de Investigación en Reumatología y Obesidad, Comité de Ética en Investigación del Hospital Christus Muguerza del Parque S.A de C.V, Comité de Ética en Investigación del Antiguo Hospital Civil de Guadalajara Fray Antonio Alcalde. The Original Study Group comprised members from 28 sites in Mexico where the trial is currently conducted.

Conflict of Interest. All named authors confirm that they have no competing financial interests or conflicts of interest to declare.

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