The Association of Estimated Glomerular Filtration Rate With Diabetic Retinopathy and Macular Edema

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Purpose. Albuminuria, a marker of diabetic kidney disease, is closely associated with diabetic retinopathy (DR) and diabetic macular edema (DME). However, the relationship between estimated glomerular filtration rate (eGFR) with DR and DME remains unclear, particularly in type 2 diabetes. We investigated the association of eGFR with DR and DME in a sample of patients with type 2 diabetes.

Methods. We included 263 Caucasian patients with type 2 diabetes aged ≥18 years who participated in a clinic-based cross-sectional study in Melbourne, Australia. Diabetic retinopathy ($n = 140$) and DME ($n = 61$) were assessed from retinal photographs graded using the modified Airlie House classification and further confirmed with optical coherence tomography. Estimated glomerular filtration rate, assessed using the CKD-EPI formula, was analyzed continuously (per SD change) and categorically (normal renal function ≥ 90; impaired renal function, 60–89, and chronic kidney disease [CKD] < 60 mL/min/1.73 m^2).

Results. When eGFR was analyzed categorically, impaired renal function and CKD were associated with the presence of DR when compared to normal renal function in multivariable models (odds ratio [OR] with 95% confidence interval [CI] of 2.97 [1.12–7.87] and 3.77 [1.28–11.10]), respectively. In DR severity analyses, CKD showed significant associations with moderate (5.83 [1.44–23.5], *P*-trend = 0.02) and severe DR (4.91 [1.26–19.0], *P*-trend = 0.04). These associations persisted when eGFR was analyzed continuously ($P = 0.04$). No significant associations were found between eGFR and DME.

Conclusions. Our results suggest that lower levels of eGFR were associated with the presence and severity of DR, but not with DME.

Keywords: estimated glomerular filtration rate, diabetic retinopathy, urinary albumin-creatinine ratio, diabetes, diabetic kidney disease

Diabetic retinopathy (DR) is a highly specific visual complication of diabetes, and globally affects approximately two-thirds and a quarter of patients with type 1 and type 2 diabetes, respectively.[1] Chronic hyperglycemia leads to gradual changes in the retinal microvasculature, resulting in retinal nonperfusion, increased vascular permeability, and pathologic proliferation of retinal vessels.[2] Progressive microvascular alterations are also commonly observed in diabetic kidney disease (DKD).[3] Similar to DR, widespread capillary occlusion in DKD can result in podocyte death, leading first to urinary protein loss (albuminuria, defined as urinary albumin-creatinine ratio [UACR] ≥ 30 mg/g) and then eventual renal function decline (chronic kidney disease [CKD], defined as estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2).[3]

Given the similar pathophysiological features in DKD and DR, it is not surprising that previous research has established a relationship between albuminuria and DR in types 1 and 2 diabetes.[4,5] Unfortunately, the role of albuminuria as a biomarker for disease has been questioned, as recent studies have revealed that albuminuria is as likely to regress as it is to progress over time.[6–8] As eGFR is a direct measure of renal function, it also is more stable as a biomarker of disease. However, due to the increasing recognition of a dissociation between albuminuria and reduced eGFR levels in people with diabetes,[9,10] the expected relationship between reduced eGFR levels and DR also has been called into question. This is particularly evident in type 2 diabetes, where approximately a third[11,12] to half[13] of patients with normoalbuminuria have reduced eGFR levels, possibly due to nondiabetic causes[14] (e.g., hypertension, aging) and aggressive antihypertensive therapy.[12,15] The above uncertainty is supported by the limited studies conducted in type 2 diabetes patients on the relationship between eGFR and DR that have shown equivocal results.[16–19]

Studies have also found an association of albuminuria with the presence of diabetic macular edema (DME),[20,21] the most common cause of vision loss in persons with diabetes,[21]

affecting up to a quarter of those with type 2 diabetes.[22] This sight-threatening condition can occur at any stage of DR progression[23]; however, no data exist for the relationship of eGFR with DME.

In this study, we investigated the associations of eGFR and CKD with the presence and severity of DR and DME in a clinical sample of Caucasian patients with type 2 diabetes.

Methods

Study Population

The Diabetes Management Project (DMP) is a cross-sectional clinic-based study investigating the clinical, behavioral, and environmental barriers associated with optimal diabetes care in patients with diabetes with and without DR. The methodology of the DMP has been detailed in previous publications.[24–26] Briefly, we consecutively recruited a total of 609 English-speaking adults with diabetes (types 1 and 2) aged 18 years or older from the eye clinics at the Royal Victorian Eye and Ear Hospital, Victoria, Australia from February 2009 to December 2010, whether or not they were visiting the clinic for DR-related issues. All participants were free of significant hearing and cognitive impairment, and lived independently in the community (i.e., not living in assisted care facilities). Written informed consent was obtained from all participants. This study was approved by the Human Research and Ethics Committee and adhered to the tenets of the Declaration of Helsinki. In this study, we included a subset of patients with type 2 diabetes (confirmed from hospital medical records) and available renal function data (at least one UACR and eGFR measurement; $n = 274$). All study participants were consecutively recruited, and as eGFR measurements were instituted into the study protocol midway through the study, only 274 participants had renal function assessments. Of the 274 individuals, we further excluded those with missing DR severity data ($n = 11$), leaving 263 participants available for analysis.

Assessment of DR and DME

Presence of DR was graded from 2-field fundus photographs (Canon CR6–45NM; Canon, Inc., Tokyo, Japan) following the modified Airlie House classification system. We categorized the severity of DR as none (Early Treatment of Diabetic Retinopathy Study [ETDRS] level 10–15), mild (level 20), moderate (level 31–43), and severe (≥level 53). Diabetic macular edema was defined by hard exudates in the presence of microaneurysms and blot hemorrhage within 1 disc diameter from the foveal center or the presence of focal photocoagulation scars in the macular area. Presence of DME was confirmed using thickness measurements as assessed by optical coherence tomography (OCT, Stratus Model 3000 version 5.01; Carl Zeiss Meditec, Jena, Germany) using the fast macular scan protocol. Only scans with signal strength ≥ 5 were included. If present, DME was further divided into mild, moderate, or severe DME using the classification system by the American Academy of Ophthalmology.[27] Data from the worst eye were used in analyses.

Blood and Urine Chemistry

Fasting (≥8 hours) blood samples were collected for analysis of eGFR, blood glucose, glycated hemoglobin (HbA1c), and lipids (total cholesterol, high density lipoprotein [HDL] cholesterol, low density lipoprotein [LDL] cholesterol, and triglycerides). Serum creatinine was assessed using the Roche Integra 800 colorimetric assay (Roche Diagnostics Ltd., Basel, Switzerland) calibrated according to the standards set by the National Institute of Standards and Technology (NIST). Estimated glomerular filtration rate (in mL/min/1.73 m^2) was calculated from plasma creatinine using the recently developed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[28] A midstream urine sample was also collected using 50 mL specimen containers to determine UACR (in mg/g). Urinary albumin and creatinine were assessed using the Roche Integra 800 colorimetric assay (Roche Diagnostics Ltd.). Minimum detectable levels were 3.0 mg/L for albumin and 0.1 mmol/L for creatinine. All blood and urine analyses were performed at Melbourne Pathology, Melbourne, Australia, with individual results electronically delivered through a password-protected program. The laboratory is accredited to the International Standard ISO15189 (Medical Laboratories) and is certified by National Association of Testing Authorities (NATA).

Assessment of Other Risk Factors

Each participant underwent a comprehensive assessment, which included clinical, biochemical, and anthropometric measurements (height and weight). Standardized interviews were done that covered socioeconomic measures (e.g., income, education), medication use, diet, lifestyle (e.g., smoking), as well as behavioral, psychosocial, and genetic factors for poor diabetes management. Key covariables included age, sex, duration of diabetes (years), HbA1c level (%), UACR (mg/g), systolic blood pressure (SBP, mm Hg), diastolic blood pressure (DBP, mm Hg), body mass index (BMI, kg/m^2), cholesterol (mmol/L), triglycerides (mmol/L), use of antihypertensive medication, and use of insulin.

Statistical Analyses

All statistical analyses were performed using Intercooled Stata version 12.1 for Windows (StataCorp., Lake Station, TX, USA). Participants' characteristics with and without DR or DME were compared using the χ^2 statistic for proportions, and a *t*-test and/or Mann-Whitney *U* test for means or median as appropriate. Estimated glomerular filtration rate was assessed continuously (per SD change), and categorically using specific threshold values (normal renal function [eGFR > 90 mL/min/1.73 m^2], impaired renal function [eGFR 60–89 mL/min/1.73 m^2], and CKD defined as eGFR < 60 mL/min/1.73 m^2.[29] Normality was checked, and data were transformed as appropriate. Person data was used for DR and DME based on the worse eye. Binary logistic regression models were used to assess the associations of eGFR with the presence of DR and DME. Multinomial logistic regression models were performed to assess the associations of eGFR with the severity of DR (mild, moderate, and severe) and DME (mild, moderate, and severe) and ordinal logistic regression models were used to estimate the overall trend of the above associations. We developed two models, initially adjusted for age and sex (Model 1) and additionally for known risk factors of DR and DME (diabetes duration, HbA1c, UACR, SBP, BMI, cholesterol, education level, use of antihypertensive medication, and insulin use; Model 2) using stepwise selection.

Results

Of the 263 patients with type 2 diabetes included in this analysis, 140 (53%) patients had DR and 61 (25%) patients had DME. Of those with DR, 21 (15%), 58 (41%), and 61 (44%) had mild, moderate, and severe DR, respectively. Similarly, of those with DME, 20 (33%), 19 (31%), and 22 (36%) had mild, moderate, and severe DME, respectively. Compared to those

Table 1. Participant's Characteristics Stratified by Presence of DR and DME

Characteristics	Diabetic Retinopathy		Diabetic Macular Edema	
	Absent	Present	Absent	Present
N (%)	123 (46.8)	140 (53.2)	186 (75.3)	61 (24.7)
Male sex (%)	54 (46.6)	44 (33.1)*	75 (42.6)	20 (33.3)*
Current smoker (%)	12 (9.9)	13 (9.3)	17 (9.2)	5 (8.2)
Use of insulin, yes (%)	24 (19.8)	89 (63.6)†	68 (36.9)	40 (65.6)†
Use of antihypertensive, yes (%)	73 (67.6)	82 (75.2)	104 (68.9)	37 (74.0)
Education (≥14 y)	41 (50.0)	41 (50.0)	64 (35.4)	17 (28.3)
Albuminuria (%)	9 (7.3)	26 (18.6)*	18 (9.7)	13 (21.3)*
CKD (eGFR < 60, %)	28 (22.8)	54 (38.6)*	53 (28.5)	22 (36.1)
DR severity (%)				
Mild DR	–	7.9		
Moderate DR	–	22.1		
Severe DR	–	23.2		
DME severity, %				
Mild DME			–	8.1
Moderate DME			–	7.7
Severe DME			–	8.9
Mean (SD)/median (IQR)				
Age, y	67 (12.2)	64 (0.93)*	66 (11.8)	63 (10.2)
Duration of diabetes, y	9.8 (4–12)	19.8 (18–26)†	11 (6–20)	16 (12–23)†
HbA1c, %	7.4 (1.4)	8.1 (1.3)†	7.6 (1.4)	8.1 (1.4)*
Systolic BP, mm Hg	139 (20)	141 (20)	139 (18)	131 (20)
Diastolic BP, mm Hg	77 (8)	76 (10)	76 (9)	75 (9)
BMI, kg/m^2	30.2 (7.0)	30.1 (5.6)	29.8 (5.8)	30.4 (5.9)
Cholesterol, mmol/L	4.7 (1.1)	4.6 (1.3)	4.7 (1.2)	4.6 (1.4)
Triglycerides, mmol/L	1.9 (1.2)	1.7 (1.0)	1.8 (1.2)	1.8 (1.1)
HDL-cholesterol, mmol/L	1.5 (0.5)	1.4 (0.8)	1.4 (0.5)	1.5 (1.1)
LDL-cholesterol, mmol/L	2.4 (0.9)	2.4 (1.1)	2.5 (1.0)	2.5 (1.2)
UACR, mg/g	1.4 (0.6–3.5)	2.8 (1.0–16.7)†	1.7 (0.7–4.1)	3.7 (1.1–21)*
eGFR, mL/min/1.73 m^2	72 (18.4)	65.1 (20.2)†	69.5 (19.1)	65.0 (21.5)

HDL-C, high-density lipoprotein; LDL-C, low density lipoprotein.
* $P < 0.05$.
† $P < 0.001$ comparing to absent group.

without DR, participants with DR were younger, less likely to be male, had longer diabetes duration, higher HbA1c level, higher UACR, and lower serum eGFR, and more likely to be on insulin (Table 1). Similarly, compared to those without DME, participants with the condition had longer diabetes duration, were less likely to be male, had higher HbA1c and UACR levels, and were more likely to be on insulin (Table 1).

Table 2 shows the associations of renal function with the presence of DR. In age- and sex-adjusted models, lower levels of eGFR were associated with DR (odds ratio [OR], 1.54; 95% confidence interval [CI], 1.16–2.05; $P = 0.003$ per SD decrease in eGFR; Table 2, Model 1). This association remained significant after additional adjustments for duration of diabetes, HbA1c, SBP, cholesterol level, BMI, education level, UACR, use of insulin, and antihypertensive medication (Table 2, Model 2). After categorization of participants according to eGFR levels, we found that compared to individuals with normal renal function, those with impaired renal function and CKD were more likely to have DR (OR, 2.97; 95% CI, 1.12–7.87; $P = 0.028$ and OR, 3.77; 95% CI, 1.28–11.1; $P = 0.016$, respectively) after multivariable adjustments.

Table 2. Association Between eGFR and the Presence of DR

	N	DR Prevalence, %	Model 1*		Model 2†	
			OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
eGFR, mL/min/1.73m^2						
Normal, ≥90	59	37.3	Reference	–	Reference	–
Mildly impaired, 60–89	122	52.5	2.43 (1.17–5.06)	0.017	2.97 (1.12–7.87)	0.028
CKD, <60	82	74.0	4.73 (2.08–10.7)	<0.001	3.77 (1.28–11.1)	0.016
				P for trend < 0.001		*P* for trend: 0.021
Per SD decrease in eGFR	263	53.2	1.54 (1.16–2.05)	0.003	1.45 (1.01–2.11)	0.046

* Age- and sex-adjusted.
† Additionally adjusted for duration of diabetes, SBP, BMI, UACR, triglycerides, cholesterol, education, use of antihypertensive medication, HbA1c, and use of insulin.

Table 3. Associations Between eGFR and the Severity of DR

Kidney Parameters		Mild DR, $n = 21$, OR (95% CI)	Moderate DR, $n = 58$, OR (95% CI)	Severe DR, $n = 61$, OR (95% CI)	*P* for Trend
Model 1*	eGFR, mL/min/1.73 m^2				
	Normal, ≥90	Reference	Reference	Reference	–
	Mildly impaired, 60–89	1.57 (0.42–5.78)	3.05 (1.13–8.22)	2.38 (0.89–6.44)	0.013
	CKD, <60	2.32 (0.55–9.69)	4.35 (1.44–13.1)	7.31 (2.49–21.4)	<0.001
	Per SD decrease in eGFR	1.16 (0.70–1.95)	1.46 (1.02–2.07)	1.81 (1.28–2.57)	<0.001
Model 2†	eGFR, mL/min/1.73 m^2				
	Normal, ≥90	Reference	Reference	Reference	–
	Mildly impaired, 60–89	1.64 (0.27–9.66)	3.99 (0.85–18.7)	1.91 (0.53–6.92)	0.058
	CKD, <60	2.52 (0.39–16.1)	5.83 (1.44–23.5)	4.91 (1.26–19.0)	0.024
	Per SD decrease in eGFR	1.47 (0.79–2.73)	1.23 (0.79–1.92)	1.75 (1.11–2.76)	0.036

* Age- and sex-adjusted.

† Additionally adjusted for duration of diabetes, SBP, UACR, BMI, triglycerides, cholesterol, education, use of anti-hypertensive medication, HbA1c, and use of insulin.

Table 3 shows the associations of renal function with the severity of DR. In multivariable models, lower levels of eGFR were associated with severe DR (OR, 1.75; 95% CI, 1.11–2.76; $P = 0.036$, per SD decrease in eGFR), as well as an increasing trend in DR severity (P-trend = 0.034; Table 3, Model 2). When we categorized the participants according to eGFR levels, we found that CKD was associated with moderate DR (OR, 5.83; 95% CI, 1.44–23.5), severe DR (OR, 4.91; 95% CI, 1.26–19.0), as well as an increasing trend in DR severity (P-trend = 0.024; Table 3, Model 2), compared to individuals with diabetes and normal renal function.

In contrast to DR, even though decreasing eGFR was associated with the presence of DME in age- and sex-adjusted models (OR, 1.35; 95% CI, 1.01–1.81; $P = 0.047$, per SD decrease in eGFR; Table 4, Model 1), these associations were no longer apparent after multivariable adjustments (Table 4, Model 2). After categorizing participants according to eGFR levels, we also did not find any associations of mildly impaired renal function or CKD with the presence of DME compared to individuals with diabetes and normal renal function. In addition, we did not find any associations of eGFR and renal function status with the severity of DME after multivariable adjustments (all $P > 0.05$; Table 5, Model 2).

The Figure shows a bar chart of the adjusted means for eGFR values plotted against the severity of DR and DME. There was a significant decrease in mean adjusted eGFR levels as DR progresses in severity (P for trend = 0.012) after multivariable adjustments, while no significant trend was observed between eGFR levels and DME severity.

Discussion

In this sample of Caucasian patients with type 2 diabetes, we found that lower levels of eGFR were continuously associated with an increased presence and severity of DR. When eGFR was analyzed categorically, decreased eGFR levels still were associated with increased odds of severe DR, and a trend toward increasing DR severity. In contrast, no associations were found between eGFR and the presence or severity spectrum of DME.

Of the few studies investigating the association of eGFR with DR in type 2 diabetes, Chen et al.[16] and Sabanayagam et al.[19] found that lower levels of eGFR were associated with DR only in the presence of albuminuria; while Penno et al.[18] and Grunwald et al.[17] conversely demonstrated an independent inverse correlation between eGFR and DR. We found that lower levels of eGFR were associated with an increased likelihood and severity of DR in type 2 diabetic persons, independent of UACR. In addition, patients with impaired renal function (the stage before CKD) also were more likely to have DR compared to patients with normal renal function. As damage to the small vessels in the retina and glomerulus from chronic hyperglycemia, oxidative stress, and concomitant hypertension has been postulated to be the major contributor to the pathogenesis of DR and DKD,[30] our findings are expected and corroborate existing evidence that microvascular dysfunction in diabetes is the etiological mechanism that is central to these conditions.

Table 4. Association Between eGFR Rate and the Presence of DME

	N	DME Prevalence, %	Model 1*		Model 2†	
			OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
eGFR, mL/min/1.73 m^2						
Normal, ≥90	56	17.9	Reference	–	Reference	–
Mildly impaired, 60–89	116	25.0	2.10 (0.85–5.16)	0.10	1.76 (0.62–4.97)	0.28
CKD, <60	75	29.3	3.02 (1.14–7.98)	0.026	1.15 (0.37–3.54)	0.81
				P for trend: 0.028		*P* for trend: 0.99
Per SD decrease in eGFR	247	24.7	1.35 (1.01–1.81)	0.047	1.02 (0.71–1.45)	0.92

* Age- and sex-adjusted.

† Additionally adjusted for duration of diabetes, SBP, UACR, BMI, triglycerides, cholesterol, education, use of anti-hypertensive medication, HbA1c, and use of insulin.

Table 5. Association Between Renal Function and the Severity of DME

	Kidney Parameters	Mild DME, $n = 20$, OR (95% CI)	Moderate DME, $n = 19$, OR (95% CI)	Severe DME, $n = 22$, OR (95% CI)	*P* for Trend
Model 1*	eGFR, mL/min/1.73 m^2				
	Normal, ≥ 0)	Reference	Reference	Reference	–
	Mildly impaired, 60–89	6.99 (0.67–72.3)	1.11 (0.33–3.76)	2.49 (0.65–9.47)	0.11
	CKD, <60	31.3 (2.92–334.8)	0.56 (0.11–2.76)	2.38 (0.51–11.0)	0.063
	Per SD decrease in eGFR	2.25 (1.46–3.48)	0.70 (0.40–1.28)	1.24 (0.78–1.96)	0.15
Model 2†	eGFR, mL/min/1.73 m^2				–
	Normal, ≥90	Reference	Reference	Reference	–
	Mildly impaired, 60–89	3.25 (0.37–28.5)	0.89 (0.26–2.97)	1.57 (0.43–5.76)	0.30
	CKD, <60	7.55 (0.90–62.9)	0.37 (0.07–1.77)	1.05 (0.24–4.50)	0.86
	Per SD decrease in eGFR	1.47 (0.79–4.73)	1.23 (0.79–1.91)	1.75 (1.11–2.76)	0.64

* Age- and sex-adjusted.

† Additionally adjusted for duration of diabetes, SBP, UACR, BMI, triglycerides, cholesterol, education, use of anti-hypertensive medication, HbA1c, and use of insulin.

It is worth noting that the studies demonstrating no significant independent relationships between eGFR and DR in type 2 diabetes (Chen et al.[16] and Sabanayagam et al.[19]) were conducted in participants of Asian ethnicity, while studies reporting the converse[17,18] were conducted in participants of Caucasian/non-Asian ethnicity. As our study was conducted in Caucasian patients with type 2 diabetes, the significant inverse correlation between eGFR and DR demonstrated in our results appears to support the possibility of ethnic differences in the above relationship. This conjecture is further supported by data from several multiethnic population-based studies reporting differences in the prevalence and risk of developing DR and DKD in patients with diabetes of different ethnicities.[31–34] Further cohort studies to explore the temporal relationships of eGFR with DR among different ethnicities may, hence, be warranted.

In contrast, our results established that there was no relationship between eGFR and DME. Given that DME may occur at any stage of DR,[23] it is widely classified as a sight-threatening manifestation of DR[35–40] and these two conditions are assumed to share the same risk factors and underlying pathophysiological microvascular dysfunction.[2,35] However, the differential associations of eGFR with DR and with DME may suggest different pathophysiological processes between these two conditions. Caution must be taken when interpreting our findings, however, as the sample size of patients with DME is small ($n = 61$, power of 55% to detect an association between eGFR and DME at the 5% significance level), compared to patients with DR ($n = 140$, power of 83% to detect an association between eGFR and DR at the 5% significance level). Hence, it is possible that our study simply lacks the power to detect a significant association between eGFR and DME.

Strength of this study includes an objective assessment of DR from fundus images, as well as a comprehensive assessment of DR confounders. Limitations include the cross-sectional nature of this study limiting causal inferences, as well as the low number of subjects with DME ($n = 61$) as mentioned above. In addition, participants included in the analysis were consecutively recruited after eGFR assessment was implemented midway through the study. However, selection bias, if any, would not have had a major influence on our results as all subjects before and after the implementation of eGFR measurements were consecutively recruited without any

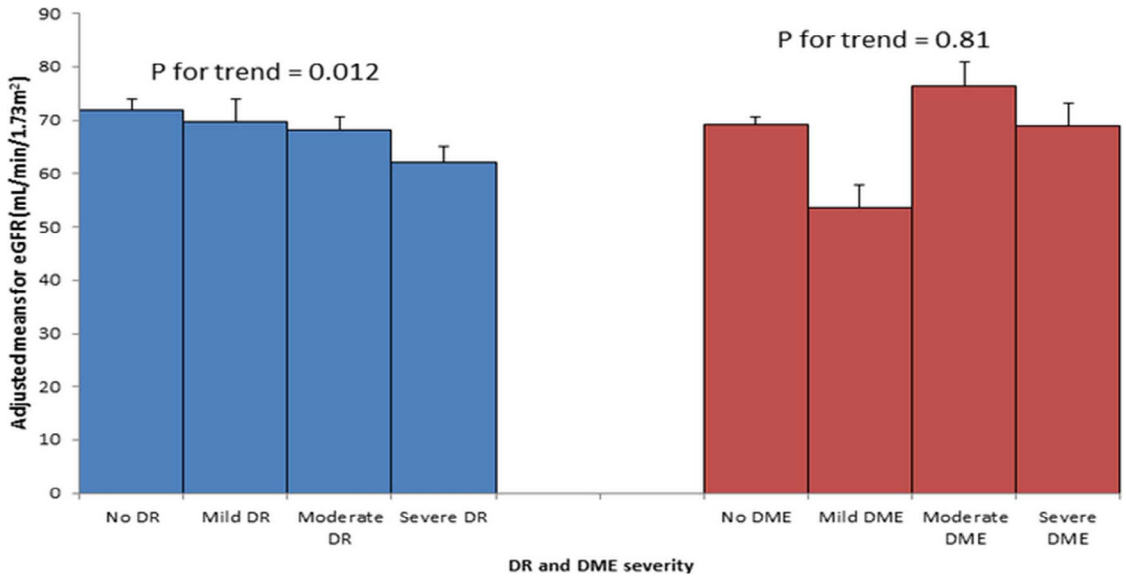

Figure. Plot of multivariable* adjusted means for eGFR against DR and DME severity. *Adjusted for age, sex, duration of diabetes, SBP, BMI, UACR, triglycerides, cholesterol, education, use of antihypertensive medication, HbA1c, and use of insulin UACR.

differences in inclusion/exclusion criteria. Moreover, our data may have limited generalizability to individuals with diabetes in the general population as our participants are derived from a clinical sample. However, our results are relevant to clinic-based diabetes population, which usually has high proportions with diabetes-related complications, including DR and DKD. Furthermore, UACR and eGFR were assessed using a single spot measurement, which could have led to nondifferential misclassification of albuminuria and CKD status, resulting in over- or under-reporting of the true prevalence of albuminuria and CKD in these subjects. Finally, 2-field fundus images were used to grade for the presence and severity of DR. This may have led to an underestimation of DR presence.

In conclusion, this study provides evidence that reduced eGFR levels were associated with the presence and severity of DR, particularly the more severe stages of DR, independent of UACR, in this sample of Caucasian patients with type 2 diabetes. Our findings suggest that patients with low GFR also can be at risk of DR progression despite the absence of albuminuria, hence, screening for diabetic eye disease in all patients with normoalbuminuric renal insufficiency should be emphasized. Additionally, we demonstrated that eGFR was not associated with DME. This disparity in associations between DR and DME warrants further investigation in larger longitudinal trials to determine if there are underlying differences in pathophysiology between these two conditions.

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