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Diabetic retinopathy and renal function in Chinese type 2 diabetic patients

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Abstract
Aims To evaluate associations of diabetic retinopathy (DR) with renal function in Chinese type 2 diabetic patients.
Methods This cross-sectional study enrolled 523 type 2 diabetic patients. All patients underwent ophthalmic examination to assess DR [normal, non-proliferative DR (NPDR), proliferative DR (PDR)]. The renal function measurements were taken in urine and blood. The estimated glomerular rate (eGFR) and albumin/creatinine ratio (ACR) were calculated using standard formulas. The chronic kidney disease (CKD) was defined as eGFR < 60 mL/min/1.73 m^2, and microalbuminuria was defined as ACR > 17 for males and ACR > 25 for females. The associations of DR with renal function and CKD were assessed by regression models, without and with the adjustment of risk factors for CKD.
Results In multivariate analysis, increasing severity of DR was significantly associated with lower eGFR ($p < 0.001$), higher level of retinol-binding protein ($p < 0.001$), and larger ACR ($p < 0.0001$). The DR was significantly associated increased risk of CKD with odds ratio of 2.22 (95 % CI 1.01–4.86) for NPDR and 3.52 (1.30–9.55) for PDR.
Conclusions Among Chinese type 2 diabetic patients, increasing DR severity is significantly associated reduced kidney function and increased risk of CKD. These associations are independent of risk factors for CKD, suggesting that assessment of DR may provide useful information on the renal function and risk of kidney disease.

Keywords Diabetic retinopathy · Renal function · Chronic kidney disease

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Introduction

Diabetes is a major public health problem in China, affecting 92.4 million adults with diabetes and 148.2 million with pre-diabetes [1]. The chronic nature of the diabetes poses a significant public health burden on health care in China, due to its associated complications including macrovascular and microvascular diseases, such as cardiovascular diseases, diabetic retinopathy (DR), and chronic kidney disease (CKD). Diabetic retinopathy is a highly specific microvascular complication related to diabetes and is characterized by the gradual changes in the microvasculature, leading to retinal non-perfusion, increased vascular permeability, and pathologically intraocular proliferation of the retinal vessel. Similarly, the nephropathy is a microvascular complication from diabetes, characterized by similar pathophysiologic features in

the glomerulus as retina. Hyperglycemia plays a central role in the initiation and progression of both complications, as shown by their prevention or retardation through the intensive glycemic controls in patients with type 1 and 2 diabetes [2, 3] suggesting their common pathophysiologic mechanism. The common pathway shared by the development of retinopathy and nephropathy motivated the researches on the relationship between diabetic retinopathy and nephropathy. Several population-based epidemiological studies [4–7], conducted mostly in Western type 1 diabetic populations, found that diabetic retinopathy is closely associated with renal dysfunction, renal damage, increased risk of CKD, and microalbuminuria. Their associations are found to be dependent on the ethnicity, body mass index, hypertension status, etc. [8]. However, in type 2 diabetes, the association between diabetic retinopathy and renal disease is not yet well established, and a few studies found that their association in type 2 diabetic patients is much weaker than that in type 1 diabetic patients [9, 10].

Although China has the largest diabetic population, the data on the association between diabetic retinopathy and renal disease in type 2 diabetic patients are limited. The generalizations of findings from Western populations to Chinese populations are uncertain, due to their differences in genetic susceptibility, socioeconomic status, environmental background and lifestyle, and the association of retinopathy and renal disease is found to vary among ethnic groups [8]. The purpose of this study was to assess the association of diabetic retinopathy with renal function and kidney disease in Chinese type 2 diabetic patients.

Methods

The details on the study design and study participants have been described in the previous publication [11]. Only details related to this paper are presented here.

Study participants

Study enrolled type 2 diabetic patients from the Diabetic Clinic in the Department of Endocrinology of the First Affiliated Hospital of Zhejiang University in Hangzhou, Zhejiang Province of P. R. China, from January 2009 to December 2011. To be eligible for the study, each patient had type 2 diabetes according to the criteria of the World Health Organization [12], i.e., positive findings from any two of the following tests on different days: symptoms of diabetes mellitus plus a casual plasma glucose concentration of 200 mg/dL (11.1 mmol/L) or a fasting plasma glucose concentration of 126 mg/dL (7.0 mmol/L) or a 2 h post-test plasma glucose concentration of 200 mg/dL (11.1 mmol/L) after a 75-g oral glucose load. The exclusion criteria included patients with dialysis or renal transplantation, bladder or urinary tract infection, and chronic kidney infections or stones.

Patients were interviewed to obtain information on their age, duration of diabetes (in years), current use of diabetic, antihypertensive, and lipid-lower medications. Blood pressure was measured while the participant was seated.

The institutional review board approved the study protocol, and a written consent form was obtained from each patient.

Diabetic retinopathy determination

As a part of a comprehensive assessment of diabetic complications, the study participants underwent ophthalmic examination for DR by two experienced retinal specialists (JW, LS), masked to the renal function findings. For ophthalmic examination, 1 % tropicamide was administered to both eyes until the best possible mydriasis was achieved. Dilated ophthalmoscopy was used to assess the presence and severity of DR in each eye using standard clinical criteria [13]. Ophthalmic examination findings on DR were recorded as: (1) normal: no apparent sign of DR; (2) non-proliferative DR (NPDR): including microaneurysms, hard exudates, intraretinal hemorrhages, venous beading, or prominent intraretinal microvascular abnormality; (3) proliferative DR (PDR): including retinal or optic disk neovascularization, vitreous hemorrhage, or preretinal hemorrhage.

Assessment of renal function

Spot urine and blood samples were collected and sent for biochemical analyses of albumin, urinary creatinine (Cr), and urine proteins in the Hospital Reference Laboratory on the same day. ELISA Kits (Shanghai Debo Inc., Shanghai) were used to measure the urinary retinol-binding protein, and the measured value was adjusted by the urinary creatinine [14]. Roche automated clinical chemistry analyzers (Roche Diagnostics, Indianapolis, IN, USA) were used to measure serum creatinine.

Based on the serum creatinine concentration, the estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration equation [15]: $eGFR = 175 \times [\text{serum creatinine (milligram per deciliter)}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ for women})]$. CKD was defined by $eGFR < 60$ mL/min/1.73 m^2, representing stage 3 and above of CKD as defined by the US National Kidney Foundation Kidney Disease Outcome Quality Initiative [16]. The albumin/creatinine ratio (ACR) was calculated from assayed albumin and creatinine levels, and microalbuminuria was defined as $ACR > 17.0$ for males and $ACR > 25.0$ for females.

Table 1 The characteristics of study participants overall and by retinopathy group ($N = 523$)

Characteristics	All participants ($N = 523$) *n* (%)	No DR ($n = 317$) *n* (%)	NPDR ($n = 152$) *n* (%)	PRD ($n = 54$) *n* (%)	*p* value
Gender					0.01
Male	312 (59.7)	114 (36.0)	67 (44.1)	30 (55.6)	
Female	211 (40.3)	203 (64.0)	85 (55.9)	24 (44.4)	
Diabetic duration (years)					0.0001
≤1	90 (17.6)	82 (25.9)	7 (4.61)	1 (1.85)	
>1, ≤5	120 (23.5)	87 (27.4)	24 (15.8)	9 (16.7)	
>5, ≤10	105 (20.6)	65 (20.5)	33 (21.7)	7 (13.0)	
>10, ≤15	115 (22.5)	53 (16.7)	44 (29.0)	18 (33.3)	
>15	81 (15.9)	22 (6.94)	41 (27.0)	18 (33.3)	
Unknown	12 (2.3)	8 (2.52)	3 (1.97)	1 (1.85)	
Current use of diabetic medication					<0.0001
No	90 (17.2)	81 (25.6)	7 (4.61)	2 (3.70)	
Yes	433 (82.8)	236 (74.4)	145 (95.4)	52 (96.3)	
Hypertension					0.0005
No	185 (35.7)	133 (42.0)	33 (21.7)	19 (35.2)	
Yes	334 (64.4)	183 (57.7)	117 (77.0)	34 (63.0)	
Unknown	5 (0.9)	1 (0.32)	2 (1.32)	1 (1.85)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	58 (13)	54 (14)	61 (11)	59 (12)	<0.0001
Diabetic duration (years)	8.5 (7.3)	5.9 (6.1)	12 (7.1)	13 (7.5)	<0.0001
HbA1c (%)	9.3 (2.6)	9.4 (2.8)	9.0 (2.4)	9.7 (2.0)	0.14
Fasting insulin (mIU/L)	16 (18)	14 (14)	20 (26)	17 (10)	0.12
Fasting plasma glucose (mIU/L)	8.1 (3.4)	8.2 (3.3)	7.6 (3.3)	8.2 (3.8)	0.24
Diastolic blood pressure (mmHg)	80 (13)	80 (13)	80 (13)	79 (13)	0.80
Systolic blood pressure (mmHg)	133 (19)	130 (18)	139 (20)	137 (20)	<0.0001

SD Standard deviation, *DR* diabetic retinopathy, *NPDR* non-proliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy

Statistical analysis

The presence and severity of DR in a participant was determined based on the eye showing the worst retinopathy. The participants were grouped into three groups of DR: (1) no DR, (2) NPDR, and (3) PDR. Hypertension was defined as systolic blood pressure of 140 mmHg or more, or diastolic blood pressure of 90 mmHg or more, or the current use of antihypertensive medications. The mean, standard deviation (SD), median, and quartiles were used to summarize the continuous measures, and proportions were calculated for categorical characteristics. If the distribution of a renal function measure was not normal, the log transformation was taken for calculating the mean (SD) and statistical comparison. The mean from log-transformed data was translated back to the original unit for easy interpretation.

We assessed the association of DR with renal function measurements by comparing the mean renal function measurements among patients without DR, with NPDR, and with PDR using the analysis of variance. To assess whether the associations between DR and renal function measurements were independent of other risk factors for renal disease (age, gender, systolic blood pressure, hypertension, HBA1C, and duration of diabetes), we performed the comparisons without and with adjustment of risk factors for renal diseases.

We also assessed the associations between diabetic retinopathy with CKD, first by univariate logistic regression models, followed by multivariate logistic regression models with adjustment by age, gender, systolic blood pressure, hypertension, HbA1C, and duration of diabetes. The association between diabetic retinopathy and CKD was summarized by odds ratio (OR), and its 95 % confidence interval (CI) calculated from the logistic regression models. These analyses were performed for all patients combined and also separately for patients with and without hypertension.

All statistical analyses were performed in SAS V9.2 (SAS Institute Inc., Cary, NC, USA), and a two-tailed $p < 0.05$ was considered to be statistically significant.

Results

The study included 523 patients with type 2 diabetes, and their characteristics are summarized in Table 1. Based on eye examination by retinal specialists, 317 (60.6 %) had no sign of diabetic retinopathy, 152 (29.1 %) had non-proliferative diabetic retinopathy, and 54 (10.3 %) had proliferative diabetic retinopathy.

Their mean age of study patients was 58 years (ranging from 19 to 89 years), 60 % were male, 64 % had hypertension, and 44 % were taking antihypertensive medications. Their mean diastolic blood pressure was 80 mmHg, and their mean systolic blood pressure was 133 mmHg. Eighty-three percent of patients were using diabetic medications. The median duration of diabetes was 7 years, with 18 % <1 year, 24 % within 1–5 years, 21 % within 5–10 years, 23 % within 10–15 years, and 16 % more than 15 years. Their median HbA1c concentration was 8.8 %.

The characteristics of patients by the retinopathy group are also shown in Table 1. The patients with diabetic retinopathy were older ($p < 0.0001$), higher percentage of male ($p = 0.01$), longer diabetic duration ($p < 0.0001$), higher percentage of taking of diabetic medication ($p < 0.0001$), higher systolic blood pressure ($p < 0.0001$), and higher percentage of hypertension ($p = 0.0005$).

Among all participants, the mean (SD) of urinary creatinine was 10.1 (5.4) mmol/L, the mean of retinal-binding protein was 0.1 g/mol.Cr, the mean of ACR was 3.4, with 20 (3.82 %) patients had microalbuminuria. The mean eGFR was 107 mL/min/1.73 m^2, with 52 patients met the definition of CKD (i.e., eGFR < 60 mL/min/1.73 m^2).

Associations of diabetic retinopathy with renal function

In the univariate analysis without adjustment of risk factors for renal disease, the diabetic retinopathy was significantly associated with various renal function measurements taken from urine or blood (Table 2). The increasing severity of DR was associated with higher mean of creatinine-adjusted retinol-binding protein (0.04, 0.20, and 0.22 g/mol.Cr for no DR, NPDR, and PDR, respectively, $p < 0.0001$). The increasing severity of DR was also significantly associated with higher albumin-to-creatinine ratio (an indicator of worse renal function). The mean albumin-to-creatinine ratio was 0.63 in patients without DR, 6.4 in patients with NPDR, and 11.1 in patients with PDR ($p < 0.0001$). Finally, the DR was significantly associated with lower eGFR, with mean eGFR of 116 mL/min/1.73 m^2 in the patients without DR, and 93 mL/min/1.73 m^2 in patients with NPDR or PDR ($p < 0.0001$). In the multivariate analysis with adjustment by age, gender, systolic blood pressure, hypertension, HbA1c, and duration of diabetes, these significant associations between DR and above renal function measurements remained the same (all $p < 0.01$, Table 2).

Association of diabetic retinopathy with CKD

Among 523 patients, 52 (9.94 %) had CKD, defined as eGFR < 60 mL/min/1.73 m^2. The diabetic retinopathy was significantly associated with increased risk of CKD ($p < 0.0001$, Table 3). CKD was present in 16 (5.05 %) of 317 patients without DR, 26 (17.1 %) of 152 patients with NPDR, and 10 (18.5 %) of 57 patients with PDR. In the multivariate analysis with adjustment by age, gender, systolic blood pressure, hypertension, diabetic duration, and HbA1c (Table 3), the association between retinopathy and CKD remains significant, with OR of 2.22 (95 % CI 1.01–4.86) and 3.52 (95 % CI 1.30–9.55) for NPDR and PDR, respectively.

When the analysis for the association of DR with CKD was performed separately for patients with and without hypertension, the significant association remained the same (Table 3). In the patients with hypertension, both NPDR and PDR were significantly associated with increased risk of CKD, with OR of 4.04 (95 % CI 1.89–8.60) for NPDR, and 4.05 (95 % CI 1.45–11.4) for PDR, respectively, compared with hypertensive patients without DR. In the patients without hypertension, only PDR was significantly associated with increased risk of CKD (OR 4.80, 95 % CI 1.05–22.0). The adjustment by age, gender, HbA1c, and duration of diabetes did not change the significant association (Table 3).

Association of diabetic retinopathy with microalbuminuria

Among 523 patients, only 20 (3.82 %) participants had microalbuminuria. Diabetic retinopathy was significantly associated with microalbuminuria ($p < 0.0001$, Fisher exact test). Among 317 patients without DR, no one had microalbuminuria, while microalbuminuria was present in 13 (8.55 %) of 152 patients with NPDR and 7 (13.0 %) of 54 patients with PDR.

Discussion

This study evaluated the association of DR with renal function measurements and CKD in Chinese type 2 diabetic patients. The study found that increasing severity of diabetic retinopathy was significantly associated declined kidney function and increased risk of renal disease. These associations are independent of risk factors for renal disease, suggesting that assessment of diabetic retinopathy may provide useful information on the renal function and risk of renal disease.

Table 2 Univariate and multivariate comparison of renal function measurements among patients with and without diabetic retinopathy

Renal function measurements	Univariate analysis				Multivariate analysis[a]			
	No DR ($n = 317$) Mean (SE)	NPDR ($n = 152$) Mean (SE)	PDR ($n = 54$) Mean (SE)	p value	No DR ($n = 317$) Mean (SE)	NPDR ($n = 152$) Mean (SE)	PRD ($n = 54$) Mean (SE)	p value
Retinol-binding protein (g/mol.Cr)	0.04 (0.02)	0.20 (0.03)	0.22 (0.05)	<0.0001	0.05 (0.02)	0.18 (0.03)	0.21 (0.05)	0.0001
Albumin/creatinine ratio	0.63 (0.72)	6.36 (1.03)	11.1 (1.75)	<0.0001	1.06 (0.76)	5.60 (1.08)	10.6 (1.75)	<0.0001
eGFR (mL/min/1.73 m^2)	116 (2.34)	93.0 (3.40)	92.9 (5.74)	<0.0001	113 (2.26)	101 (3.28)	96 (5.23)	0.0004

Cr Creatinine, *DR* diabetic retinopathy, *NPDR* non-proliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy

[a] Adjusted by age, gender, systolic blood pressure, hypertension status, HBA1C, and duration of diabetes

Table 3 The association of diabetic retinopathy with CKD

	n	CKD[‡] (%)	p value	Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)
All patients ($N = 523$)			<0.0001		
No DR	317	16 (5.05 %)[a]		1.00	1.00[b]
NPDR	152	26 (17.1 %)[a]		3.88 (2.01–7.48)	2.22 (1.01–4.86)[b]
PDR	54	10 (18.5 %)[a]		4.28 (1.83–10.0)	3.52 (1.30–9.55)[b]
Patients with hypertension ($N = 334$)[d]			<0.0001		
No DR	183	11 (6.01 %)		1.00	1.00[c]
NPDR	117	24 (20.5 %)		4.04 (1.89–8.60)	2.72 (1.13–6.55)[c]
PDR	34	7 (20.6 %)		4.05 (1.45–11.4)	3.24 (1.01–10.5)[c]
Patients without hypertension ($N = 185$)[d]			0.07		
No DR	133	5 (3.76 %)		1.00	1.00
NPDR	33	2 (6.06 %)		1.65 (0.32–8.92)	0.95 (0.08–11.0)[c]
PDR	19	3 (15.8 %)		4.80 (1.05–22.0)	7.54 (1.04–54.7)[c]

OR odds ratio, *CI* confidence interval, *DR* diabetic retinopathy, *NPDR* non-proliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy

[a] CKD was defined as eGFR < 60 mL/min/1.73 m^2

[b] Adjusted by age, gender, systolic blood pressure, and hypertension status, HBA1C, and duration of diabetes

[c] Adjusted by age, gender, HBA1C, and duration of diabetes

[d] 5 Patients with hypertension status unknown were excluded

This study is one of the largest studies to comprehensively evaluate the association of diabetic retinopathy with renal function and renal disease in Chinese type 2 diabetic patients. The evaluations of renal function are very comprehensive including both markers of kidney function (eGFR), measures of renal dysfunction (microalbuminuria), and CKD. We also evaluated several renal function measurements to fully represent the renal function, including ACR (indicator of the glomerular dysfunction) and retinol-binding protein (indicator of the tubular dysfunction). The consistent associations between diabetic retinopathy and each of these of kidney function measures strengthen the plausibility of the associations between diabetic retinopathy and renal disease in type 2 diabetic patients and support the clinical practice of using these measurements to monitor the renal function in type 2 diabetic patients.

Our study found that the associations of diabetic retinopathy with renal functions are independent of hypertension and diabetes duration; this is consistent with the population-based studies in a variety of ethnic groups [8, 17–20], suggesting that the diabetic retinopathy may be both relevant to the pathogenesis of renal dysfunction and predictors of the subsequent deterioration.

Our results support the common pathogenetic mechanism of diabetic retinopathy and diabetic nephropathy in type 2 diabetic patients. The microvascular changes in both the retina and glomerulus are thought to be initiated by the chronic hyperglycemia, followed by the progressive narrowing and eventual occlusion of vascular lumina, subsequently leading to inadequate perfusion of affected tissues. In the glomerulus, the widespread capillary occlusion and podocyte loss caused urinary protein loss and renal function decline. In the retina, this induces programmed cell

death of Muller and ganglion cells, the losses of endothelial cells in capillaries, together with the losses of pericytes, and eventually leads to the development of retinal microvascular signs including microaneurysms, cotton-wool spots, hemorrhage, arteriovenous nicking, and focal and generalized narrowing.

Several studies reported that the correlation between eGFR and albuminuria was lower in type 2 diabetic patients than in type 1 diabetic patients [10, 21, 22]. Consistent with these studies, our study found the eGFR was only moderately correlated with urine albumin (Spearman correlation coefficient $= -0.28$, $p < 0.0001$), and the concordance between microalbuminuria and CKD (eGFR < 60 mL/min/1.73 m^2) was lower. In our study, among 52 patients with CKD, 39 (75 %) patients were normoalbuminuric, as compared to 67 % in the UK Prospective Diabetes Study of type 2 diabetes, and 60 % in the renal insufficiency and cardiovascular event Italian multicenter study [10, 21]. Conversely, in type 1 diabetic patients, only 24 % patients with CKD were normoalbuminuric in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study [22].

In spite of the association between diabetic retinopathy and renal disease has been well studied, mostly in Western diabetic population, the data on their association among Chinese type 2 diabetic patients are very limited. A study on the risk factors for diabetic retinopathy among diabetic and pre-diabetic (either type 1 or type 2) subjects in Shanghai found that the urinary albumin-to-creatinine ratio and albuminuria are associated with diabetic retinopathy [23]. Another study in Hong Kong evaluated the diabetic retinopathy with resistance index of the kidney (a novel biomarker of kidney function) among the Chinese type 2 diabetic patients and found that increased intrarenal arterial resistance is associated with diabetic retinopathy [24]. Although our study differs from these studies in either the study population or the renal outcome measures, our results are consistent with these studies and support that the diabetic retinopathy is associated with renal dysfunction and increased risk of kidney disease.

Our study had several limitations. First, the study determined the DR from clinical examination by senior retinal specialists using ophthalmoscopy rather than from the standard grading of fundus photographs. Ophthalmoscopy may mis-classify DR status. However, because DR was determined by senior retinal specialists who were masked to the renal function measurements, we believe the mis-classification of DR from ophthalmoscopy was not dependent on renal function and thus was unlikely to bias the association between DR and renal function. Second, this was a cross-sectional study of in-patients in a clinical center and suffered from the limitation in generalization of such single-center study. This study only allows us to evaluate the cross-sectional association of diabetic retinopathy with renal function and will not allow us to assess their causal association or prediction of DR on CKD. Future prospective cohort studies are needed to determine how the diabetic retinopathy can predict the development and progression of renal diseases in Chinese type 2 diabetic patients. Finally, the study only had small number of patients with diabetic retinopathy (either NPDR or PDR), and CKD was relatively uncommon; thus, the study may not have provided sufficient power to evaluate the association of each severity of DR with renal disease.

In summary, our study supports that increasing severity of diabetic retinopathy is associated with decreased renal function and increased risk of CKD in type 2 diabetic patients. These associations are independent of the risk factors for renal diseases. Future population-based cohort studies are needed to evaluate the prediction of diabetic retinopathy on the development and progression of CKD.

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Conflict of interest None.

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