• Clinical Research •

Risk evaluation for diabetic retinopathy in Chinese renal-biopsied type 2 diabetes mellitus patients

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Abstract

● **AIM:** To investigate diabetic retinopathy (DR) prevalence in Chinese renal-biopsied type 2 diabetes mellitus (T2DM) patients with kidney dysfunction, and to further evaluate its relationship with diabetic nephropathy (DN) incidence and the risk factors for DR development in this population.

● **METHODS:** A total of 84 renal-biopsied T2DM patients were included. Fundus and imaging examinations were employed for DR diagnosis. Demographic information and clinical measures along with renal histopathology were analyzed for comparisons between the DR and non-DR groups. Risk factors on DR development were analyzed with multiple logistic regression.

● **RESULTS:** DR prevalence was 50% in total. The incidences of DN, non-diabetic renal disease (NDRD) and mixed-type pathology were 47.6%, 19.0% and 33.3% in the DR group respectively, while 11.9%, 83.3% and 4.8% in the non-DR group. Systolic blood pressure, ratio of urinary albumin to creatine ratio, urinary albumin, 24-hours urinary protein, the incidence and severity of DN histopathology were found statistically increased in the DR group. Multiple logistic regression analysis showed histopathological DN incidence significantly increased the risk of DR development [odds ratio (OR)=21.664, 95% confidential interval (CI) 5.588 to 83.991, *P*<0.001 for DN, and OR=45.475, 95%CI 6.949 to 297.611, *P*<0.001 for mixed-type, respectively, in reference to NDRD)], wherein DN severity positively correlated.

● **CONCLUSION:** Renal histopathological evidence indicates DN incidence and severity increases the risk of DR development in Chinese T2DM patients inexperienced of regular fundus examinations.

● **KEYWORDS:** diabetic retinopathy; diabetic nephropathy; vision threatens; renal biopsy; vision screening

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INTRODUCTION

As a common complication of diabetes mellitus (DM) manifested in eye, diabetic retinopathy (DR) is recognized as a ocular microvascular disorder, which can be observed directly with fundus examination and other optical visualization techniques[1-2]. DR has become a leading cause of visual impairment in adults around the world, and been also shown to grow markedly in prevalence in China[3].

Given the notorious detrimental consequences of DR if not noticed and treated at early stage, timely ophthalmic examination, especially of the fundus, is necessary for DM patients to reveal preventable development or progressing of DR, which is also significant for the remission of public health burden in long term. Since the classification of DM mainly consists of type 1 and type 2, more than 90% of all patients fall into the type 2 category[4-5]. Correspondingly, type 2 DM (T2DM) patients appear to be the majority of subgroup among DR patients, comprising the most concerned population in the public health affairs of DR screening[6]. However, the imbalance of regional distribution of medical resources and the huge population base as well as the rapid increase of DM population have contributed to the growing unmet needs of DR prophylaxis and treatment in China[4,7-8]. Such inadequacy may lead to delay of DR treatment and irreversible impairment of visual function in many T2DM patients, who are going through regular treatment and follow-up for endocrine events as well as other noticed systemic complications, but unaware of the possible asymptomatic DR at early stage[9-10].

Among the various complications of DM, DM-related renal disease, or diabetic nephropathy (DN), shares similar pathogenesis with DR as due to microvascular disorders[11-12].

Patients may be more familiar with and educated about the clinical measures of renal function during their regular follow-up with endocrinologists or nephrologists, but may pay less attention to the probability of DR occurrence due to lack of perceivable visual symptoms or absence of frequent specialized fundus examination.

Given the forementioned fact that in China the imbalance of distribution of medical service resources may impede timely diagnosis and treatment of DR in many T2DM patients, who are already clinically diagnosed as DN but have no idea of the possibility of vision-threatening DR development. Therefore, it is never too late to emphasize the importance of DR screening in T2DM patients, especially in the DN population that have no precedent fundus examination. And study work on the risk evaluation of DR development in the context of existing diabetic renal disease should be boosted.

In the current study we aimed to find out clues about the risk for DR development in T2DM patients with renal disorder evidenced by biopsied histopathology, along with other clinical indicators and laboratory tests but without experience of standard fundus examination, trying to contribute to the gap filling and set preliminary basis for further investigation.

SUBJECTS AND METHODS

Ethical Approval The present study complied with the Declaration of Helsinki, and inform consents were obtained from all participants. The protocol was approved by the Ethics Committee Review Board of Ruijin Hospital Affiliated School of Medicine, Shanghai Jiao Tong University (Reference Number: 2016-132).

Study Population This study is a retrospective observational review of medical records, involving a total of 84 T2DM patients (according to the criteria of WHO[13]), who underwent renal biopsies due to clinical necessity in diagnosis and treatment for suspicion of non-DN in the Department of Nephrology of Ruijin Hospital Affiliated School of Medicine Shanghai Jiao Tong University, and were referred to the Department of Ophthalmology in advance for ophthalmic examination from December 2018 to October 2023. As various non-diabetes factors can contribute to kidney injury and dysfunction, which may turn out to be non-diabetic renal disease (NDRD) or otherwise superposed on DN in DM patients. Whether the patients will benefit from their treatment regimens largely depends on the consistency between the clinical diagnosis and the pathological nature. Thus, the indication of renal biopsy for the selected T2DM patients was mainly based on atypical signs of renal disorders that might confuse with the diagnosis of DN, which included: albuminuria or proteinuria without DR, rapid decrease of estimated glomerular filtration rate (eGFR), rapid deterioration of albuminuria or proteinuria, hematuria accompanying kidney dysfunction, and suspicion of other types of nephropathy (such as nephrotic syndrome, glomerulonephritis, amyloidosis, vasculitis, systemic diseases other than DM, *etc.*). Patients with ocular disorders other than DR that may affect eye circulation (such as glaucoma, uveitis, retinal vascular occlusion, age-related macular degeneration, ocular trauma, *etc.*) or severe systemic diseases were excluded. The qualified subjects were divided into two groups as DR group and non-DR group.

Evaluation of Diabetic Retinopathy and Renal Biopsy Histopathology DR was confirmed or excluded with combined diagnostic tools as direct fundus examination under slit lamp, fundus photography, optical coherence tomography (OCT) and fundus fluorescence angiography (FFA) or OCT angiography (OCTA), and the integrated results were evaluated by trained ophthalmologists and finally reviewed by a fundus expert in accordance with the standard of acknowledged guideline[6]. All renal biopsy samples routinely went through procedures of light microscopy, immunofluorescence analysis and electron microscopy, and the results were interpreted by two experienced nephrology pathologists. The histopathological diagnosis of DN complied with the acknowledged criteria[14]. Accordingly, results of renal histopathology were categorized into three types: DN only, DN mixed with NDRD, and NDRD only, while DN was further classified into four hierarchical levels as grade I, II (IIa, IIb), III, and IV in line with the severity of glomerular lesions, along with a separate evaluation for presence of interstitial or vascular involvement.

Data Collection The medical information of enrolled patients was acquired from electronic medical records and reviewed, including age, gender, height, weight, calculated body mass index (BMI), systolic/diastolic blood pressure (SBP/DBP), T2DM duration, antidiabetic dosage type, hypertension history/duration, antihypertensive medication history, chronic heart disease (CHD) history (including coronary heart disease, myocardial dysfunction and other chronic heart disorders), peripheral vascular disease (PVD) history, diabetic neuropathy history, anticoagulant history and educational level. Parameters of laboratory tests included urine indicators: 24-hour volume, 24-hour proteinuria, urinary microalbumin, 24-hour urinary microalbumin, urinary α-1 microglobulin, 24-hour urinary α-1 microglobulin, urinary albumin/creatine ratio (UACR), hematuria; blood biochemical indicators: eGFR, glycated hemoglobin, fasting glucose, albumin, urea, creatinine, uric acid, potassium; blood lipid profile: triglyceride, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), apolipoprotein A1 (APOA1), apolipoprotein B (APOB), apolipoprotein E (APOE); complete blood cell analysis: white blood cell (WBC) count, neutrophil count, lymphocyte count, red blood cell (RBC) count,

hemoglobin, hematocrit value, platelet (PLT) count. Data of carotid artery ultrasound were also collected, including intima-media thickness (IMT), resistance index (RI) and peak systolic velocity (PSV) of both right and left common carotid artery (CCA).

According to classical consensus, kidney dysfunction level was categorized on the basis of eGFR value, in terms of chronic kidney disease (CKD) level, into stage 1 (more than 90 mL/min per 1.73 m^2), stage 2 (60-89 mL/min per 1.73 m^2), stage 3 (3a: 45-59 mL/min per 1.73 m^2, 3b: 30-44 mL/min per 1.73 m^2), stage 4 (15-29 mL/min per 1.73 m^2) and stage 5 (less than 15 mL/min per 1.73 m^2)[15]; or on the basis of UACR value, in terms of albuminuria severity, as normal or mild (less than 3 mg/mmol·L), moderate (3-30 mg/mmol·L) and severe (more than 30 mg/mmol·L)[16].

Statistical Analysis We calculated the mean±standard deviation (SD) for normally distributed variables, median (the 25th and 75th percentiles) for non-normally distributed variables, and number (percentage) for categorical variables. The normality of the data distribution was examined by using the Shapiro-Wilk test. The independent two sample test for normally distributed variables, Mann-Whitney *U* test for non-normally distributed variables, and Chi-square or Fisher's exact test for categorical variables were used to compare the characteristics between the patients with DR and the patients without. The univariate and multiple variate logistic regression models were used to evaluate the impact of potential risk factors on DR development, the odds ratio (OR) and 95% confidential interval (CI) were calculated accordingly. The multiple variable models adjusted for age, gender and BMI. A two-sided *P*-value of <0.05 was regarded as statistically significant. Data management and statistical analyses were conducted using the Statistical Product and Service Solution software (SPSS, Version 27.0; IBM, Armonk, NY, USA).

RESULTS

Clinical Characteristics of the Included Subjects A total of 84 renal-biopsied T2DM patients (65 males and 19 females) were qualified and included, as shown in the summary in Table 1. The median of the subjects ages was 59y (ranged from 32 to 85y). The median of durations after the diagnosis of T2DM was 48mo (ranged from 0.5 to 360mo). Among the total subjects there were 42 patients diagnosed DR for the first time, with a prevalence of 50%.

As shown in Table 1 regarding demographic characteristics of the included subjects, SBP in the DR group was almost statistically greater than the one in the non-DR group (*P*=0.05), while the proportion of CHD in the non-DR group was nearly statistically greater than the one in the DR group (*P*=0.049). However, there was no obvious difference in age, gender, BMI, DBP, DM/hypertension duration, hypoglycemic/antihypertensive medication and education level between the DR group and the non-DR group, neither was any marked difference observed in terms of PVD, diabetic neuropathy and drinking or smoking history between the two groups.

As the laboratory parameters (Table 2) of kidney function, blood glucose, blood lipid and hemacytometry demonstrated, significant differences between the DR and non-DR groups were observed in UACR, 24-hour urinary protein and urinary albumin (*P*=0.030, 0.041 and 0.025, respectively), along with a *P* value close to 0.05 of difference in 24h urinary albumin. However, there was no else significant difference observed in other parameters.

The carotid artery ultrasound results in terms of both right and left CCA structure and dynamic were collected and analyzed as shown in Table 3. There was no obvious difference observed in carotid artery wall thickness and blood dynamics between the DR group and the non-DR group (all *P*>0.05).

Evaluation of Kidney Function and Histopathology of the Included Subjects As shown in Table 4, according to the CKD staging classification system based on eGFR values, CKD grading of the involved patients showed no obvious difference between the DR and non-DR groups. With respect to the assessment of severity of albuminuria, employing the classification system based on UACR values, there were neither any significant difference observed between the two groups. On the other hand, following the renal-biopsied histopathological evidence, the incidence of DN and mixed type was found to be markedly greater in the DR group (47.6% and 33.3%, respectively) in comparison with the non-DR group (11.9% and 4.8%, respectively), while the incidence of NDRD was lower in the DR group (19.0%) in comparison with the non-DR group (83.3%). The distribution of renal pathology types was significantly different between the two groups (*P*<0.001).

Further data analysis into the comparison of renal pathology severity in DN subpopulation between the two groups were shown (Table 5). Based on the degree of glomerular lesions, the difference of the DN severity distribution between the two groups was statistically significant (*P*=0.038), which was considered worthy of further evaluation of its impact on the risk of DR development with the following logistic regression analysis. However, whether being accompanied with interstitial or vascular lesions showed no obvious difference between the DR and non-DR groups.

Evaluation of Risk Factors for DR Development in the Included Subjects Parameters that demonstrated obvious differences between the DR and non-DR groups were selected, and went through binary logistic regression analysis for further risk evaluation regarding DR development (Table 6). The results showed that incidence of DN increased the risk of DR

Table 1 Demographic characteristics in DR group and non-DR group median (25th and 75th percentiles), *n* (%)

Characteristics	Total (*n*=84)	DR (*n*=42)	Non-DR (*n*=42)	*P*
Age, y	59.00 (48.00, 68.00)	55.00 (45.50, 65.25)	61.00 (49.00, 68.25)	0.100
Female	19 (22.6)	10 (23.8)	9 (21.4)	0.794
BMI, kg/m^2	25.03 (23.28, 27.45)	24.78 (22.79, 27.65)	25.20 (23.59, 27.32)	0.761
SBP, mm Hg, mean±SD	140.17±23.31	145.14±26.20	135.19±19.04	0.050
DBP, mm Hg	78.00 (70.00, 88.00)	79.00 (70.75, 89.00)	74.00 (67.75, 84.00)	0.245
DM duration, mo	48.00 (10.00, 120.00)	60.00 (11.50, 120.00)	36.00 (7.25, 111.00)	0.375
Hypoglycemic				0.244
Non	4 (4.8)	0	4 (9.5)	
Oral	48 (57.1)	24 (57.1)	24 (57.1)	
Insulin	18 (21.4)	10 (23.8)	8 (19.0)	
Oral+insulin	14 (16.7)	8 (19.0)	6 (14.3)	
Hypertension history	65 (81.0)	35 (83.3)	33 (78.6)	0.578
Hypertension duration, mo	22.00 (1.00, 120.00)	16.00 (1.00, 96.00)	39.00 (0.50, 120.00)	0.503
Antihypertensive	65 (77.4)	33 (78.6)	32 (76.2)	0.794
CHD history	42 (50.0)	16 (38.1)	26 (61.9)	0.049
PVD history	15 (17.9)	8 (19.0)	7 (16.7)	1.000
Diabetic neuropathy history	14 (16.7)	9 (21.4)	5 (11.9)	0.380
Anticoagulant	22 (26.2)	9 (21.4)	13 (31.0)	0.321
Education level				0.750
Primary or less	12 (14.3)	5 (11.9)	7 (16.7)	
Secondary	42 (50.0)	23 (54.8)	19 (45.2)	
Undergraduate	25 (29.8)	11 (26.2)	14 (33.3)	
Postgraduate	5 (6.0)	3 (7.1)	2 (4.8)	
Smoking history				0.425
Never	68 (81.0)	36 (85.7)	32 (76.2)	
Quit	4 (4.8)	2 (4.8)	2 (4.8)	
Persistent	12 (14.3)	4 (9.5)	8 (19.0)	
Drinking history				0.294
Never	74 (88.1)	39 (92.9)	35 (83.3)	
Quit	4 (4.8)	2 (4.8)	2 (4.8)	
Persistent	6 (7.1)	1 (2.4)	5 (11.9)	

DR: Diabetic retinopathy; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; DM: Diabetes mellitus; CHD: Chronic heart disease; PVD: Peripheral vascular disease.

development in the biopsied patients who never experienced specialized fundus examination (in reference to NDRD: OR=21.664, 95%CI 5.588 to 83.991, *P*<0.001 for DN; OR=45.475, 95%CI 6.949 to 297.611, *P*<0.001 for mixed pathology type). The degree of DN severity also appeared to be positively related to DR development (in reference to non-DN: OR=18.442, 95%CI 4.005 to 84.911, *P*<0.001 for Grade I-II DN; OR=37.238, 95%CI 8.107 to 171.037, *P*<0.001 for Grade III-IV DN). On the other hand, in terms of indicators for proteinuria/albuminuria, 24-hour urinary protein, 24-hour urinary albumin and urinary albumin showed no significant impact on DR development (*P*=0.089, 0.105 and 0.531, respectively), while UACR showed statistical significance but minor OR impact (OR=1.002, 95%CI 1.000 to 1.003, *P*=0.034). SBP also presented some statistical significance but either no obvious OR impact on DR development (OR=1.023, 95%CI 1.002 to 1.045, *P*=0.031). The negative impact of CHD history on DR development was also diminished after adjustment (OR=0.437, 95%CI 0.173 to 1.104, *P*=0.080).

DISCUSSION

The present observational study assessed the DR prevalence as well as its risk factors in kidney-biopsied patients with clinical suspicion of NDRD. We found in this population who lacked previous experience of special ophthalmic examinations that the DR prevalence was 50%. With concrete evidence of renal-biopsied histopathology, a distribution of 47.6% DN, 19.0% NDRD and 33.3% mixed-type was observed in the DR group, while the corresponding distribution in non-DR group was 11.9% DN, 83.3% NDRD and 4.8% mixed-type, which showed marked statistical significance. Given

Table 2 Laboratory results in DR group and non-DR group median (25th and 75th percentiles), *n* (%)

Characteristics	Total (*n*=84)	DR (*n*=42)	Non-DR (*n*=42)	*P*
UACR, mg/mmol•L	229.19 (79.16, 506.92)	316.07 (174.52, 556.70)	155.35 (56.02, 412.92)	0.030
Urine volume (24h), L	1.80±0.60	1.73±0.57	1.87±0.63	0.283
Urinary protein (24h), mg	3803.50 (1636.00, 8154.00)	4678.00 (2469.25, 8644.50)	2628.50 (1214.75, 7081.00)	0.041
Urinary albumin, mg/dL	142.93 (61.87, 270.26)	185.01 (132.35, 313.60)	92.78 (42.53, 244.57)	0.025
Urinary albumin (24h), mg	2347.78 (934.61, 4968.40)	3221.28 (1801.24, 5193.08)	1959.00 (778.56, 4619.97)	0.053
Urinary α-1 microglobulin, mg/dL	2.57 (1.36, 5.19)	2.82 (1.37, 5.50)	2.31 (1.24, 4.69)	0.232
24h urinary α-1 microglobulin, mg	43.81 (25.96, 79.68)	48.91 (24.72, 97.09)	42.93 (26.35, 72.20)	0.426
Hematuresis	22 (26.2)	10 (23.8)	12 (28.6)	0.620
eGFR	53.9 (31.93, 79.25)	51.30 (30.63, 76.70)	54.00 (32.60, 84.40)	0.463
Glycated hemoglobin, %	6.60 (5.93, 7.40)	6.65 (5.90, 7.83)	6.50 (5.98, 7.10)	0.420
Fasting glucose, mmol/L	5.33 (4.59, 7.19)	5.81 (4.67, 7.93)	5.16 (4.58, 6.21)	0.150
Albumin, g/L	33.00 (25.25, 37.00)	31.50 (25.00, 35.25)	34.50 (25.75, 38.00)	0.244
Urea, mmol/L	9.05 (6.73, 12.33)	9.60 (6.18, 13.10)	8.85 (6.88, 11.95)	0.816
Creatinine, μmol/L	124.50 (86.00, 178.75)	132.50 (91.00, 185.25)	122.00 (81.75, 173.00)	0.403
Uric acid, μmol/L	395.23±80.67	403.79±84.95	386.67±76.21	0.334
Blood potassium, mmol/L	3.87 (3.63, 4.14)	3.90 (3.62, 4.29)	3.87 (3.66, 4.05)	0.477
Triglyceride, mmol/L	1.95 (1.39, 2.85)	2.01 (1.35, 3.04)	1.88 (1.41, 2.82)	0.971
Total cholesterol, mmol/L	4.86 (4.12, 6.11)	4.79 (4.20, 6.21)	4.90 (3.84, 6.03)	0.792
HDL, mmol/L	0.98 (0.83, 1.26)	0.98 (0.84, 1.28)	0.98 (0.82, 1.20)	0.588
LDL, mmol/L	2.89 (2.23, 3.82)	2.94 (2.22, 3.66)	2.74 (2.25, 3.89)	0.986
APOA1, g/L	1.23 (1.07, 1.47)	1.23 (1.07, 1.50)	1.24 (1.08, 1.44)	0.737
APOB, g/L	0.98 (0.79, 1.19)	0.98 (0.80, 1.18)	0.98 (0.79, 1.21)	0.925
APOE, mg/dL	4.30 (3.70, 5.20)	4.40 (3.70, 5.23)	4.20 (3.60, 5.05)	0.600
Lipoprotein a, g/L	0.26 (0.10, 0.71)	0.26 (0.11, 0.84)	0.26 (0.09, 0.52)	0.778
WBC, 10^9/L	6.50 (5.38, 7.98)	6.68 (5.60, 8.58)	6.29 (5.18, 7.34)	0.248
Neutrophil, 10^9/L	4.05 (3.23, 4.95)	4.18 (3.41, 4.95)	3.67 (3.08, 5.01)	0.388
Lymphocyte, 10^9/L	1.69 (1.20, 2.11)	1.69 (1.28, 2.47)	1.67 (1.20, 2.03)	0.410
RBC, 10^{12}/L	4.08±0.75	3.97±0.81	4.20±0.68	0.156
Hemoglobin, g/L	122.92±22.97	118.69±24.57	127.14±20.68	0.092
Hematocrit value	0.37±0.06	0.35±0.07	0.38±0.06	0.062
PLT, 10^9/L	194.18±54.78	198.76±52.99	189.60±56.78	0.447

DR: Diabetic retinopathy; UACR: Urinary albumin/creatine ratio; eGFR: Estimated glomerular filtration rate; HDL: High density lipoprotein; LDL: Low density lipoprotein; APOA1: Apolipoprotein A1; APOB: Apolipoprotein B; APOE: Apolipoprotein E; WBC: White blood cell; RBC: Red blood cell; PLT: Platelet.

Table 3 Carotid artery ultrasound results in DR group and non-DR group median (25th and 75th percentiles)

Characteristics	Total (*n*=84)	DR (*n*=42)	Non-DR (*n*=42)	*P*
Right CCA				
IMT, mm	0.70 (0.60, 0.80)	0.70 (0.60, 0.80)	0.70 (0.60, 0.90)	0.456
RI	0.73±0.05	0.72±0.05	0.73±0.06	0.722
PSV, cm/s	70.00 (58.25, 80.00)	70.5 (62.25, 80.00)	66.00 (55.75, 85.75)	0.747
Left CCA				
IMT, mm	0.65 (0.60, 0.80)	0.60 (0.60, 0.80)	0.70 (0.60, 0.90)	0.354
RI	0.72±0.06	0.72±0.06	0.72±0.06	0.817
PSV, cm/s	69.50 (59.00, 85.75)	71.00 (60.75, 82.00)	67.50 (57.50, 87.00)	0.516

DR: Diabetic retinopathy; CCA: Common carotid artery; IMT: Intima-media thickness; RI: Resistance index; PSV: Peak systolic velocity.

the mixed-type renal pathology to be designated into the DN category, the DN incidences would be modified as 80.9% in DR group and 16.7% in non-DR group, respectively. As further shown with logistic regression analysis, the risk for

Table 4 Kidney function evaluation and renal histopathology results in the DR group and non-DR group *n* (%)

Characteristics	Total (*n*=84)	DR (*n*=42)	Non-DR (*n*=42)	*P*
Grade of CKD				0.826
I	15 (17.9)	6 (14.3)	9 (21.4)	
II	18 (21.4)	10 (23.8)	8 (19.0)	
IIIa	16 (19.0)	8(19.0)	8 (19.0)	
IIIb	19 (22.6)	8 (19.0)	11 (26.2)	
IV	8 (9.5)	5 (11.9)	3 (7.1)	
V	8 (9.5)	5 (11.9)	3 (7.1)	
Severity of albuminuria				0.245
Normal or mild	6 (7.1)	1 (2.4)	5 (11.9)	
Moderate	5 (6.0)	3 (7.1)	2 (4.8)	
Severe	73 (86.9)	38 (90.5)	35 (83.3)	
Pathology of biopsy				<0.001
NDRD	43 (51.2)	8 (19.0)	35 (83.3)	
Mixed	16 (19.0)	14 (33.3)	2 (4.8)	
DN	25 (29.8)	20 (47.6)	5 (11.9)	

DR: Diabetic retinopathy; CKD: Chronic kidney dysfunction; NDRD: Non-diabetic renal disease; DN: Diabetic nephropathy.

Table 5 Degree of DN severity in DR group and non-DR group *n* (%)

Characteristics	Total (*n*=41)	DR (*n*=34)	Non-DR (*n*=7)	*P*
Degree of DN severity				0.038
Grade I	4 (9.8)	1 (2.9)	3 (42.9)	
Grade IIa	4 (9.8)	4 (11.8)	0	
Grade IIb	8 (19.5)	7 (20.6)	1 (14.3)	
Grade III	16 (39.0)	15 (44.1)	1 (14.3)	
Grade IV	9 (22.0)	7 (20.6)	2 (28.6)	
With interstitial lesions	15 (36.6)	13 (38.2)	2 (28.6)	1.000
With vascular lesions	22 (53.7)	20 (58.8)	2 (28.6)	0.219

DR: Diabetic retinopathy; DN: Diabetic nephropathy.

Table 6 Analysis of risk factors for DR in renal-biopsied patients using binary logistic regression method OR (95%CI)

Characteristics	Crude model	*P*	Adjusted model	*P*
Pathology of biopsy		<0.001		<0.001
NDRD	Reference		Reference	
Mixed	30.625 (5.772, 162.498)	<0.001	45.475 (6.949, 297.611)	<0.001
DN	17.500 (5.038, 60.783)	<0.001	21.664 (5.588, 83.991)	<0.001
Degree of DN severity		<0.001		<0.001
Without DN	Reference		Reference	
Grade I-II	13.125 (3.343, 51.529)	<0.001	18.442 (4.005, 84.911)	<0.001
Grade III-IV	32.083 (7.677, 134.073)	<0.001	37.238 (8.107, 171.037)	<0.001
SBP	1.020 (1.000, 1.040)	0.055	1.023 (1.002, 1.045)	0.031
CHD history	0.379 (0.157, 0.914)	0.031	0.437 (0.173, 1.104)	0.080
Urinary protein (24h)	1.000 (1.000, 1.000)	0.102	1.000 (1.000, 1.000)	0.089
Urinary albumin (24h)	1.000 (1.000, 1.000)	0.112	1.000 (1.000, 1.000)	0.105
Urinary albumin	1.000 (0.999, 1.002)	0.604	1.000 (0.999, 1.002)	0.531
UACR	1.001 (1.000, 1.003)	0.082	1.002 (1.000, 1.003)	0.034

DR: Diabetic retinopathy; CI: Confidential interval; OR: Odds ratio; NDRD: Non-diabetic renal disease; DN: Diabetic nephropathy; SBP: Systolic blood pressure; CHD: Chronic heart disease; UACR: Urinary albumin/creatine ratio.

DR development was much greater in patients with DN compared to the ones with NDRD, along with the observation of a positive correlation between the DR incidence and DN severity. However, other demographic features and clinical measures, such as age, educational level, alcohol consumption, DM duration, glycometabolism, hypoglycemic medications,

kidney function, lipid profile and hematology profile, as described in previous publications as risk factors for DR, did not appear to be significantly associated with the risk of DR development in these subjects, including the fact that SBP and UACR presented some statistical significance but little OR impact[17-19]. The inconsistency was probably due to the selection specificity of the patients biopsied and involved in the present study. These subjects were under particular pathological conditions warranting further renal biopsy in accordance with nephrologists' judgement and clinical guidelines. Therefore, the demographic distribution of this population was totally different from the previous studies, contributing to the differences in conclusions and applications.

As reflected from the results, DR and DN respectively took place in nearly half of the involved patients who were renal-biopsied for suspicion of NDRD, with a parallel tendency between the two clinical events. Although the selection of the subjects was clinically limited by the biopsy indication, this finding raised a concern that more attentions should be paid to the unrecognized visual threatens in T2DM patients who were currently focusing on diagnosis and treatment of renal disorders.

It has been acknowledged that DR and DN, as common microvascular complications of DM, shared analogous pathogenesis[11,20-21]. Most studies as well as ours are consistent upon the conclusion that DR and DN were closely associated in T2DM patients, although there are still some inconsistencies, such as which event precedes earlier, how the severities of the two disorders correlate and whether the risk factors of the two events differed from each other[22-28]. However, DR is relatively more often designated as a potential predictor for DN development and progression, frequently combined with renal biopsy histopathology as the final diagnostic criteria for kidney disease assessment in various clinical researches. For risk evaluation of DR development using DN as a predictor, clinical parameters of kidney function were usually employed as indicators for DN, rarely with histopathological evidence. In the present study, we analyzed risk factors for DR development with parameters of clinical measures combined with histopathology of renal biopsy, which would undoubtedly strengthen the theoretical evidence and make the conclusion more convincing.

Kidney function has always been the most concerned issue in clinical practice dealing with DN in T2DM patients. Proteinuria, microalbuminuria and eGFR values are common indicators for kidney function evaluation. As previous studies reported, the impairment of kidney function reflected from clinical measures was significantly associated with DR development and proved to be predictive risk factors for DR progression[29-34]. As shown in results of the present study, UACR, 24-hour urinary protein and urinary albumin were found to be significantly increased in the DR group, however, further risk evaluation for DR development with logistic regression method demonstrated some statistical significance in UACR but with little OR impact. This inconsistency might be attributed to the selection bias of the present study design, considering most of the renal-biopsied patients were of clinically significant kidney dysfunction or highly suspicious for NDRD. Similar results might be reasonable in interpreting the indifference between the two groups in terms of obesity, lipid profile and glucose level, which are acknowledged risk factors for both DR and DN[35-40]. Furthermore, it's worth noting that the incidence of NDRD was 19.0% in the DR group of our study, indicating that there may be different underlying mechanisms between the two types of microvascular complications in DM, as also noticed by other researchers[41-42].

Our finding through this study emphasized the importance of screening retinopathy in T2DM patients who are aware of their kidney dysfunction and already under regular clinical supervision from nephrologists, but having no idea of the potential visual impairment threatens. Considering the inconvenience caused by visual impairment especially for the kidney dysfunction patients who require routine peritoneal dialysis or hemodialysis, timely detection and treatment of DR at early stage in this population will be definitely meaningful in terms of improving prognosis and life quality[34].

There are certain limitations in our present study. First is the retrospective nature of the study design, along with obvious selection bias mainly due to the invasive feature of renal biopsy and its strict indication in clinical practice. Then, the sample size is small and needs to be augmented in future expansion of the study, where the severity and detailed parameters of DR should be considered.

In conclusion, the present study proved the association between DR development and DN incidence, and confirmed the severity of DN lesions positively correlated with the risk of DR in T2DM patients. The conclusions were better supported by histopathological evidence from renal biopsy. The findings partly indicate the current implementation of screening for DR in kidney dysfunction T2DM patient is inadequate in China.

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