Characteristics of diabetic nephropathy patients without diabetic retinopathy
A retrospective observational study

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Abstract

The purpose of the current study was to investigate the characteristics of patients with diabetic nephropathy (DN) without diabetic retinopathy (DR).

One hundred four patients with biopsy-proven DN, and 52 patients with diabetes mellitus (DM) without DR who were diagnosed as membranous nephropathy by renal biopsy were retrospectively included. We compared the clinical and laboratory parameters of DN patients with and without DR. Furthermore, among the DM patients without DR, we compared those with DN and with membranous nephropathy.

Among patients with DN, including those with pure DN and DN coexisting with nondiabetic renal disease, compared with patients with DR, those without DR had significantly higher levels of serum albumin and hemoglobin (31.72 ± 7.97 vs 28.49 ± 6.30 g/L, $P = .023$; 128.11 ± 21.87 vs 113.06 ± 22.03 g/L, $P = .001$, respectively), and significantly lower level of serum creatinine and prevalence of diabetic neuropathy (148.56 ± 99.19 vs 203.75 ± 145.36 μmol/L, $P = .028$; 7.30% vs 32.70%, $P = .001$, respectively). Among patients with pure DN, compared with patients with DR, those without DR had significantly higher level of serum albumin (33.91 ± 5.79 vs 29.32 ± 5.42 g/L, $P = .012$). Among DM patients without DR, patients with membranous nephropathy had significantly lower levels of serum albumin and serum creatinine, and significantly higher levels of high-density lipoprotein and cholesterol than those with DN.

In conclusion, DN patients without DR may have less serious renal damage and less diabetic complication than those with DR. In the absence of DR, there is still a lack of effective indicators suggesting diabetic nephropathy or nondiabetic glomerulopathy, and renal biopsy is indispensable for diagnosis in such circumstances.

Abbreviations: CRP = C-reaction protein, DM = diabetes mellitus, DN = diabetic nephropathy, DR = diabetic retinopathy, ESR = erythrocyte sedimentation rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NDRD = nondiabetic renal disease, TG = triglyceride.

Keywords: diabetes mellitus, diabetic nephropathy, diabetic retinopathy

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1. Introduction

Diabetes mellitus (DM) is characterized by chronic hyperglycemia and disturbances in carbohydrate, lipid, and protein metabolism resulting from defects in insulin secretion and/or insulin action. It was estimated that if no urgent action is taken, the number of patients with DM will rise from 415 million in 2015 to 642 million by 2040.[1] About 20% to 40% of patients with DM have diabetic nephropathy (DN).[2] DN is the leading cause of end-stage renal disease in USA, Europe, and Japan.[3] Approximately 4.1 million US adults over 40 years old have diabetic retinopathy (DR).[4] A number of studies showed that DR may be helpful in distinguishing DN in patients with type 2 diabetes mellitus (T2DM) and renal diseases.[5–7] However, the results of these studies are sometimes inconsistent, and DN and DR can appear independently.[8] Characteristics of diabetic nephropathy patients without diabetic retinopathy have not been fully investigated except for a few studies.[8]

DR is a useful indicator for the clinical diagnosis of DN. However, for diabetes patients with proteinuria, if DR is absent, it is sometime difficult to differentiate DN or other glomerulopathy without renal biopsy. To be more specific, membranous nephropathy, the most common type of primary glomerulopathy, has some similar features to DN, including chronic course of the disease, proteinuria with few red blood cells in the urine, and more common in the elderly.

Table 1

General data of the patients with DN (n=104).

	Mean and SD	Range
HbA1c, %	6.58±1.35	3.90–12.40
Hemoglobin, g/L	121.03±23.10	70.00–182.00
Albumin, g/L	30.20±7.38	16.00–47.00
Serum creatinine, μmol/L	174.56±125.59	59.00–651.00
FPG, mmol/L	6.98±3.00	2.20–20.92
TG, mmol/L	2.34±1.58	0.73–8.77
Total cholesterol, mmol/L	5.67±2.66	1.90–23.30
HDL, mmol/L	1.02±0.30	0.45–2.16
LDL, mmol/L	3.25±1.55	0.77–10.36
ESR, mm/1h	53.31±36.14	0–140.00
CRP, mg/L	7.36±13.61	1.00–95.00
Urinary protein, g/24h	6.41±5.15	0.10–27.00

CRP = C-reaction protein, DN = diabetic nephropathy, ESR = erythrocyte sedimentation rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, LDL = low-density lipoprotein, TG = triglyceride.

Therefore, in the current study, we compared the clinical and laboratory parameters of DN patients with and without DR; furthermore, among the DM patients without DR, we compared the clinical and laboratory parameters of those with biopsy-proven DN and with membranous nephropathy.

2. Patients and methods

2.1. Patients

One hundred four cases with T2DM in the Department of Nephrology, Peking University First Hospital from September 2005 to December 2015, who were diagnosed as diabetic nephropathy by renal biopsy, were retrospectively recruited in the current study. Renal specimens were evaluated using direct immunofluorescence, light, and electron microscopy by experienced renal pathologists. Classification of DN and pathological scores were evaluated according to the criteria of Tervaert et al.[9] Meanwhile, 52 patients with T2DM without DR, who were diagnosed as membranous nephropathy by renal biopsy in the same period, were recruited. All these patients fulfilled the WHO (1999) type 2 diabetes diagnostic criteria and classification.[10]

Diagnosis of DR was made by trained ophthalmologists according to the International Clinical DR guidelines issued by International Department of Ophthalmology Conference.[11] The results were defined as no apparent retinopathy, nonproliferative diabetic retinopathy, and proliferative diabetic retinopathy.

2.2. Data collection

Clinical data were extracted from the electronic medical records of our hospital, including age, gender, duration of diabetes, duration of hypertension, diabetic neuropathy, diabetic vascular diseases, 24-hours urinary protein excretion, fasting plasma glucose (FPG), HbA1c, hemoglobin, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), albumin, creatinine, triglyceride (TG), total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Diabetic complications included diabetic neuropathy and vascular diseases. Peripheral neuropathy was assessed using the validated Toronto Clinical Scoring System (Score >5).[12] For this study, we defined "peripheral vascular disease" as arterial sclerosis of the carotid arteries, upper extremities, abdominal aorta, and other first-order aortic branches. As a method to diagnose peripheral atherosclerosis, ultrasonography of carotid or lower limb arteries was performed to detect the presence of thickening or plaque on the wall of those blood vessels. The research was in compliance with the Declaration of Helsinki and was approved by the ethics committees of Peking University First Hospital. Informed consent was obtained from each patient at renal biopsy.

2.3. Statistical analysis

Variables were represented as means ± SD. Continuous variables were compared by t test or Mann–Whitney U test, while differences of qualitative results were compared using χ^2 test, as appropriate. All P values were 2-tailed and considered significant at $P < .05$. Analyses were performed using SPSS 13.0 (Chicago, IL).

3. Results

3.1. General data

Among the 104 patients with DN, 82 (78.85%) were males and 22 (21.15%) were females, with an age of 50.12 ± 11.65 years old at renal biopsy. The duration of diabetes and hypertension was 8.72 ± 6.58 and 6.22 ± 8.40 years, respectively. Twenty of 104 (19.23%) patients had diabetic neuropathy, 38/104 (36.54%) patients had diabetic vascular diseases. The clinical and laboratory parameters are shown in Table 1.

Among these 104 patients with DN, 43 patients had pure DN revealed by renal histopathology, including 26 patients with DR and 17 patients without DR; 61 patients had DN coexisting with nondiabetic kidney disease (NDRD) revealed by renal histopathology, including 23 patients with DR and 38 patients without DR. The coexistence of NDRD is listed in Table 2.

3.2. Comparisons between DN patients with and without DR

For a DM patient with renal disease who receives renal biopsy, there are 3 possibilities for the renal histopathology, that is, DN, NDRD, and DN coexisting with NDRD.

Table 2

The coexistence of nondiabetic renal disease in patients with diabetic nephropathy.

Coexistence of other kidney diseases	Patients with diabetic retinopathy (n=23)	Patients without diabetic retinopathy (n=38)	P
Membranous nephropathy	5 (21.74%)	10 (26.32%)	.687
Mesangial proliferative glomerulonephritis	5 (21.74%)	10 (26.32%)	.687
Focal segmental glomerulosclerosis	2 (8.70%)	4 (10.53%)	1.000
Membranous proliferative glomerulonephritis	2 (8.70%)	4 (10.53%)	1.000
Other glomerular disease	4 (17.39%)	4 (10.53%)	.447
Renal tubular interstitial lesion	5 (21.74%)	6 (15.79%)	.733

Table 3

Comparisons between DN patients (including those with pure DN and DN coexisting with NDRD) with and without DR.

	With DR (n=49)	Without DR (n=55)	*P*
Age, y	48.00±11.20	52.02±11.82	.079
Gender, men	75.50%	81.80%	.432
Duration of diabetes, y	9.68±7.02	7.86±6.10	.164
Duration of hypertension, y	4.55±7.50	7.70±8.94	.054
Diabetic neuropathy	32.70%	7.30%	.001
Diabetic vascular diseases	36.70%	36.40%	.969
HbA1c, %	6.59±1.80	6.57±0.81	.943
Hemoglobin, g/L	113.06±22.03	128.11±21.87	.001
Albumin, g/L	28.49±6.30	31.72±7.97	.023
Serum creatinine, μmol/L	203.75±145.36	148.56±99.19	.028
FPG, mmol/L	6.48±2.91	7.43±3.04	.106
TG, mmol/L	2.07±1.08	2.58±1.91	.095
Total cholesterol, mmol/L	5.58±1.75	5.76±3.29	.737
HDL, mmol/L	1.05±0.27	1.00±0.32	.400
LDL, mmol/L	3.18±1.21	3.31±1.82	.684
CRP, mg/L	4.59±3.08	9.88±18.02	.094
ESR, mm/1h	62.54±31.79	45.66±38.04	.030
Urinary protein, g/24h	7.21±5.13	5.71±5.11	.141

CRP = C-reaction protein, DN = diabetic nephropathy, DR = diabetic retinopathy, ESR = erythrocyte sedimentation rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NDRD = nondiabetic renal disease, TG = triglyceride.

Table 4

Comparisons between pure DN patients with DR and without DR.

	With DR (n=26)	Without DR (n=17)	*P*
Age	45.96±11.09	52.71±10.66	.055
Gender, male	73.07%	100%	.019
Duration of diabetes, y	8.55±6.61	7.29±5.18	.511
Duration of hypertension, y	3.97±7.95	8.90±8.87	.064
Diabetic neuropathy	30.77%	11.76%	.149
Diabetic vascular diseases	42.31%	29.41%	.329
HbA1c, %	6.24±1.35	6.37±0.81	.764
Hemoglobin, g/L	113.60±21.20	124.82±21.05	.099
Albumin, g/L	29.32±5.42	33.91±5.79	.012
Serum creatinine, μmol/L	210.50±162.05	196.22±133.45	.764
FPG, mmol/L	5.82±1.67	7.60±3.22	.047
TG, mmol/L	1.98±1.02	2.80±2.21	.106
Total cholesterol, mmol/L	5.78±1.88	5.25±1.95	.377
HDL, mmol/L	1.05±0.31	0.92±0.21	.142
LDL, mmol/L	3.34±1.29	3.05±1.28	.468
CRP, mg/L	4.30±3.22	6.20±7.66	.397
ESR, mm/1h	60.10±27.03	42.60±26.39	.062
Urinary protein, g/24h	6.53±4.45	6.03±4.37	.721

CRP = C-reaction protein, DN = diabetic nephropathy, DR = diabetic retinopathy, ESR = erythrocyte sedimentation rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, LDL = low-density lipoprotein, TG = triglyceride.

In the total cohort of DN patients, including those with pure DN and DN coexisting with NDRD, we compared characteristics of patients with and without DR. Patients without DR had significantly lower levels of serum creatinine at renal biopsy (148.56±99.19 vs 203.75±145.36 μmol/L, *P*=.028) than those with DR. The prevalence of diabetic neuropathy in patients without DR was significantly lower than that in patients with DR (7.30% vs 32.70%, *P*=.001). Compared with patients with DR, those without DR had significantly higher levels of albumin and hemoglobin (31.72±7.97 vs 28.49±6.30 g/L, *P*=.023; 128.11± 21.87 vs 113.06±22.03 g/L, *P*=.001, respectively) (Table 3).

Then, we compared pure DN patients, that is, without the coexistence of NDRD, with DR and without DR. Compared with DN patients with DR, those without DR had significantly higher prevalence of male (100% vs 73.07%, *P*=.019), and significantly higher levels of albumin and FPG (33.91±5.79 vs 29.32±5.42 g/L, *P*=.012; 7.60±3.22 vs 5.82±1.67 mmol/L, *P*=.047, respectively) (Table 4). We also compared the renal pathological characteristics between DN patients with and without DR, and found no significant difference between these 2 subgroups of patients, including classification of renal pathology, tubular atrophy, interstitial fibrosis, podocyte injury and deposition of immunoglubulins, and complements in immunofluorescence.

3.3. Comparisons between patients with pure DN and patients with membranous nephropathy among DM patients without DR

As mentioned above, for diabetes patients with proteinuria and without DR, if renal histology is not available, it is sometime difficult to differentiate DN or other glomerulopathy, especially membranous nephropathy. Therefore, we further compared these 2 groups of patients, expecting to find some clues for differential diagnosis. It was found that the prevalence of male in patients with DN was significantly higher than that in patients with membranous nephropathy (100% vs 55.77%, *P*=.001). Compared with patients with membranous nephropathy, those

with DN had significantly higher levels of albumin and serum creatinine at renal biopsy (33.91±5.79 vs 26.74±8.46 g/L, *P*=.002; 196.22±133.45 vs 76.86±33.83 μmol/L, *P*=.002, respectively), and significantly lower levels of total cholesterol and HDL (5.25±1.95 vs 6.72±2.35 mmol/L, *P*=.023; 0.92± 0.21 vs 1.32±0.76 mmol/L, *P*=.039, respectively) (Table 5).

4. Discussion

DN and DR are the 2 most important diabetic microvascular complications, and they have similar pathological basis. Previous

Table 5

Comparisons between patients with pure DN and with membranous nephropathy among DM patients without DR.

	DN (n=17)	Membranous nephropathy (n=52)	*P*
Age	52.71±10.66	58.88±11.33	.052
Gender, men	100%	55.77%	.001
Duration of diabetes, y	7.29±5.18	5.72±5.02	.271
Duration of hypertension, y	8.90±8.87	5.82±7.62	.169
Diabetic neuropathy	11.76%	1.90%	.084
Diabetic vascular diseases	29.41%	32.70%	.801
HbA1c, %	6.37±0.81	6.70±1.22	.392
Hemoglobin, g/L	124.82±21.05	134.08±22.90	.145
Albumin, g/L	33.91±5.79	26.74±8.46	.002
Serum creatinine, μmol/L	196.22±133.45	76.86±33.83	.002
FPG, mmol/L	7.60±3.22	6.56±2.34	.157
TG, mmol/L	2.80±2.21	3.04±2.39	.713
Total cholesterol, mmol/L	5.25±1.95	6.72±2.35	.023
HDL, mmol/L	0.92±0.21	1.32±0.76	.039
LDL, mmol/L	3.05±1.28	3.79±1.72	.106
CRP, mg/L	6.20±7.66	3.92±3.37	.177
ESR, mm/1h	42.60±26.39	52.31±30.83	.279
Urinary protein, g/24h	6.03±4.37	7.36±5.36	.358

CRP = C-reaction protein, DM = diabetic mellitus, DN = diabetic nephropathy, DR = diabetic retinopathy, ESR = erythrocyte sedimentation rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, LDL = low-density lipoprotein, TG = triglyceride.

studies found that DR is an important predictor for DN.[13] However, there were still many conditions that DN was not associated with DR, and the incidence of fundus lesions was inconsistent in different studies.[14–18] Characteristics of DN patients without DR are not fully clear yet.

In this study, we analyzed the clinical and laboratory feature of DN patients without DR, in comparison with the "classical" DN, that is, those with DR. Compared with patients with DR, patients without DR had a lower level of serum creatinine and lower prevalence of diabetic neuropathy, suggesting that patients without DR had less serious renal damage and less diabetic complications. It was consistent with the study by Katulanda et al,[19] who found that in DM patients, peripheral neuropathy was associated with DR. We also found that the level of albumin in patients without DR was significantly higher than that in patients with DR. Although the difference in proteinuria was not significant, DR was associated with the duration of diabetes [19]; chronic metabolic disorder of diabetes would accelerate the decomposition of albumin resulting in lower level of albumin.

Another clinically relevant issue is that for diabetes patients with proteinuria, if DR is absent, it is sometime difficult to differentiate DN from other glomerulopathy, especially membranous nephropathy, without renal biopsy. In particular, DN and membranous nephropathy have some similar clinical characteristics, as mentioned above. Therefore, we compared the clinical and laboratory parameters of those with DN and membranous nephropathy in DM patients without DR, expecting to find some clues for differential diagnosis of these 2 circumstances in the case that renal biopsy is unavailable. We found that among DM patients without DR, compared with DN patients, patients with membranous nephropathy had significantly higher levels of HDL and cholesterol, which was consistent with the characteristics of membranous nephropathy. Meanwhile, the level of creatinine in patients with DN was significantly higher than that in patients with membranous nephropathy. However, these differences were relatively minor despite the statistical difference, and not robust enough to provided effective indicators for the differential diagnosis of these 2 entities.

The main limitation of our study was the selection bias. In the routine clinical practice in our center, we often made the diagnosis of diabetic nephropathy clinically when DM patients had diabetic retinopathy and proteinuria, and therefore this subgroup of patients seldom received renal biopsy. Patients with DM usually received renal biopsy when they were suspected to have NDRD. Therefore, our results should be confirmed by a larger prospective study.

In conclusion, DN patients without DR may have less serious renal damage and less diabetic complication than those with DR.

In the absence of DR, there is still a lack of effective indicators suggesting DN or nondiabetic glomerulopathy, and renal biopsy is indispensable for diagnosis in such circumstances.

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