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Prevalence of diabetic nephropathy complicating non-diabetic renal disease among Chinese patients with type 2 diabetes mellitus

Li Zhuo, Guming Zou, Wenge Li*, Jianhua Lu and Wenwen Ren

Abstract

Background: The incidence of diabetes mellitus (DM) and diabetic nephropathy (DN) have risen rapidly in the past few decades and have become an economic burden to the healthcare system in China. DN is a major complication of DM and is a leading cause of end-stage renal disease (ESRD). The occurrence of non-diabetic renal disease (NDRD) in diabetic patients has been increasingly recognized in recent years. It is generally believed that it is difficult to reverse DN, whereas some cases of NDRD are readily treatable and remittable. However, DN is known to co-exist with NDRD in a poorly defined population of patients with type 2 diabetes mellitus (T2DM). This study estimated the prevalence of co-existing DN and NDRD in Chinese patients.

Methods: Data were retrospectively analyzed from 244 patients with T2DM who had undergone a renal biopsy between January 2003 and December 2011 at the Nephrology Department, China-Japan Friendship Hospital, China. Male patients numbered 151 (61.9%) of the study population. The biopsies were performed because urinary abnormalities or renal function were atypical of a diagnosis of DN. Biopsy samples were examined using light, immunofluorescence (IF) and electron microscopy (EM). Clinical parameters were recorded for each patient at the time of biopsy.

Results: Nineteen of 244 diabetic patients (7.8%) had co-existing DN and NDRD. These patients showed clinical features and pathologic characteristics of DN, including a high prevalence of diabetic retinopathy (89.5%), a long duration of diabetes, increased thickness of the glomerular basement membrane (GBM) and mesangial expansion. However, they also presented with clinical findings which were inconsistent with DN, such as hematuria, rapidly progressive renal failure and marked proteinuria. Immunoglobulin A (IgA) nephropathy was apparent in 10 out of the 19 patients (52.6%), tubulointerstitial lesions were found in four patients (21.1%), membrano-proliferative glomerulonephritis (MPGN) in three patients (15.8%) and membranous nephropathy (MN) in two patients (10.5%).

Conclusion: Retrospective analysis of biopsy data suggests that approximately 8% of Chinese patients with T2DM may have co-existing DN and NDRD. The most common histological diagnosis in our small series was IgA nephropathy.

Keywords: Diabetic nephropathy, Non-diabetic renal disease, Diabetes mellitus, Renal biopsy, Renal histopathology

Background

The incidence of diabetes mellitus (DM) and diabetic nephropathy (DN) have risen rapidly in the past few decades and have become an economic burden to the healthcare system in China. DN, also known as diabetic glomerulosclerosis or diabetic kidney disease, is a major complication of DM and is a leading cause of end-stage renal disease (ESRD). Persistent and slowly progressive

proteinuria is a characteristic of DN and diabetic renal failure [1-5]. The diagnosis of DN is usually inferred in cases where renal biopsy has not produced definitive results. These are usually patients with a 7 to 10-year history of type I DM, who have demonstrable diabetic retinopathy and a history of microalbuminuria. These patients present no evidence of a sudden onset of marked proteinuria, hematuria, abnormal kidney size, or other renal disease [5-8]. Renal biopsy in this setting will not be diagnostically useful, while it will be inferred as DN.

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Most of our knowledge with respect to the nature of kidney disease in patients with type 2 diabetes mellitus (T2DM) is derived from studies of patients with type I DM [5]. However, biopsy data from patients with T2DM with renal disease or proteinuria show that these patients have a more heterogeneous group of renal lesions than patients with type I DM [3-5,7-9]. Based on these findings the occurrence of non-diabetic renal disease (NDRD) in diabetic patients has been increasingly recognized in recent years. However, the prevalence of NDRD varies widely in different regions of the world and is reported to range from 15.7% to 82.9% [10-27].

It is generally believed that it is difficult to reverse DN, whereas some cases of NDRD are readily treatable and remittable. However, in some diabetic patients, DN and NDRD co-exist. Based on data published between 1983 and 2012 (Table 1), the prevalence of DN complicating NDRD ranges between 3.0% and 45.8% [6,10,12,13,15-17,19,21,22,28-30].

The present retrospective, single center, analysis was undertaken to estimate the prevalence of DN complicating NDRD in Chinese patients with T2DM. The pathogenic mechanism of DN that complicates NDRD is thought to be different to the mechanisms that underlie either DN or NDRD alone [10,18,21,22,27]. We, therefore, also studied the correlations between the clinical and pathologic features in these patients.

Methods

Patient selection

The study included data from 244 patients with T2DM who underwent renal biopsy between January 2003 and December 2011 at the Nephrology Department, China-Japan Friendship Hospital, China. Male patients numbered 151 (59.4%) of the study population. Patients with known DN were excluded from the study as renal biopsy was not routinely performed in these patients at this institution. Patients with current acute illness including infectious disease were also excluded from entry. The existence of immunologic diseases, malignancy and infections was also investigated prior to inclusion into the study.

The study protocol was approved by the Human Ethics Review Committee of the China-Japan Friendship Hospital and a signed consent form was obtained from each patient before biopsy.

Assessments

DM was diagnosed using the criteria of the American Diabetes Association [31]. The clinical and demographic parameters were recorded for each patient at the time of renal biopsy. These included duration of diabetes, blood pressure, electrocardiogram, echocardiogram, kidney ultrasound and fundoscopic findings. Laboratory studies included fasting blood sugar, glucose

Table 1 Diabetic nephropathy (DN) with non-diabetic renal disease (NDRD) in diabetic patients: literature summary

Pathological types	Number of cases (%)	References
Glomerular diseases		
IgA nephropathy	31 (14.1%)	[10,15,16,21,28,30]
Mesangial proliferative glomerulonephritis	22 (10%)	[12,15,19,28,30]
Post-infectious glomerulonephritis	22 (10%)	[12,29,30]
Membranous nephropathy	15 (6.8%)	[6,10,15,17,21,28]
Immune complex-trapping glomerulonephritis	12 (5.5%)	[13,29,30]
Crescentic glomerulonephritis	8 (3.6%)	[12,13,16]
Focal segmental glomerulosclerosis	7 (3.2%)	[10,12,13,15,16]
Minimal change glomerulopathy	3 (1.4%)	[12,19]
Membrano-proliferative glomerulonephritis	3 (1.4%)	[10,16,29]
Lupus glomerulonephritis	2 (1.0%)	[29]
Fibrillary glomerulonephritis	1 (0.5%)	[16]
Necrotizing focal glomerulonephritis	1 (0.5%)	[29]
Hepatitis-related nephritis	1 (0.5%)	[17]
Vascular		
Hypertensive changes and arterionephrosclerosis	19 (8.6%)	[12,16,17,22,30]
Atheroembolic renal disease	2 (1.0%)	[12]
Thrombotic microangiopathy	1 (0.5%)	[13]
Tubulointerstitial		
Tubulointerstitial nephritis	50 (22.7%)	[6,10,12,16,22,30]
Pyelonephritis	5 (2.3%)	[12,16,22]
Toxemia of pregnancy	1 (0.5%)	[28]
Other	14 (6.4%)	[10,30]
Total	220	

DN, diabetic nephropathy; IgA, immunoglobulin A; NDRD, non-diabetic renal disease.

tolerance test, glycated hemoglobin (HbA1c), urinalysis, urine osmotic pressure, 24-hour protein excretion, total protein, albumin, blood urea nitrogen, serum creatinine levels and creatinine clearance.

Nephrotic syndrome was defined as proteinuria (>3.5 g/day) accompanied by edema, hyperlipidemia, hypoproteinemia, or other metabolic disorders [32]. Nephritic syndrome was defined as pathologically diffuse inflammatory changes in the glomeruli accompanied by hematuria with red blood cell casts, mild proteinuria, and, often, hypertension, edema and azotemia. Renal failure was diagnosed in patients with blood urea nitrogen >20 mg/dl and serum creatinine >1.4 mg/dl. Hypertension was defined as a systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.

Biopsy assessment

In all cases renal biopsy was performed because urinary abnormalities or renal function was inconsistent with the clinical expression or the natural history of DN. Percutaneous renal biopsy were performed as described by Veiga [33].

Renal tissue submitted for diagnosis was divided into three portions. One portion was fixed in buffered formalin and processed onto paraffin blocks for light microscopy examination. Sections were stained with hematoxyline and eosin, periodic acid-Schiff (PAS), silver methanamine and Masson's trichrome. The second portion of tissue was frozen for direct immunofluorescence (IF) studies using fluorescein isothiocyanate (FITC) conjugated antibodies for immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), C3, C1q and fibrinogen (FIB). The third tissue portion was fixed in Trump's electron microscopy (EM) fixative and processed into resin blocks. Ultrathin sections were stained with uranyl acetate and lead citrate, and examined using a transmission electron microscope.

Renal lesions were classified according to the Chinese classification criteria for renal diseases [34]. Each biopsy

was reviewed by two pathologists, both dedicated to renal pathology.

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 for Windows (IBM SPSS Statistics, Armonk, NY, USA). Data were expressed as mean \pm SD. The Spearman rank correlation test was used to determine the associations between clinical parameters and histopathological findings. Values of $P < 0.05$ were considered statistically significant.

Results

Data were retrospectively analyzed from 244 patients with T2DM. Male patients numbered 151 (61.9%) of the study population. There were 20 cases (8.2%) with a pathologic diagnosis of DN, 205 cases (84%) with NDRD and 19 cases (7.8%) had DN complicating NDRD. The proportion of males was 65% in DN, 59% in NDRD and 89.5% in DN complicating NDRD, respectively. The clinical features and laboratory data are summarized in Table 2. The population included 17 men and two women between 28 and 64 years of age, with only one

Table 2 The clinical data of diabetic nephropathy (DN) with non-diabetic renal disease (NDRD) in patients with type 2 diabetes mellitus (T2DM)

Case	Age (years)/ sex	Duration of T2DM (years)	Diabetic retinopathy	Fasting blood sugar (mmol/l)	HbA1c (%)	Clinical manifestations	Hematuria	Urinary protein (g/day)	BUN (mg/dl)	Serum creatinine (mg/dl)	History of hypertension
1	41/M	12	+	7.9	7.0	CRF	2+	3.8	23.2	1.5	+
2	31/M	NA	-	6.3	5.4	NG	+	0.9	6.8	1.0	-
3	45/M	7	+	10.6	8.6	NS	2+	3.0	18.9	1.0	+
4	31/M	3	+	4.6	5.7	CRF	-	0.3	20.5	1.5	-
5	53/M	20	+	3.3	5.2	NG	+	6.3	16.9	1.1	+
6	58/M	11	+	7.0	6.5	CRF	+	8.0	62.3	6.9	-
7	64/M	10	+	4.4	7.5	ARF	+	7.0	21.5	3.4	+
8	28/M	5	+	9.0	7.8	NG	+	1.3	13.5	0.6	-
9	48/F	14	+	8.9	4.8	CRF	2+	4.9	21.7	1.4	+
10	39/M	9	+	6.2	5.3	CRF	2+	5.4	29.3	2.5	+
11	58/M	15	+	4.8	6.4	NG	2+	5.6	17.8	1.2	+
12	44/F	16	+	8.3	10.6	NS	-	5.4	23.2	0.7	+
13	54/M	2	+	9.5	7.3	NG	2+	1.7	17.3	1.1	+
14	55/M	13	+	7.2	7.9	NS	2+	10.0	20	1.1	+
15	46/M	15	+	19.2	11.5	CRF	2+	3.2	22.2	1.4	+
16	47/M	5	+	5.1	6.0	NS	+	7.0	17.4	0.9	-
17	54/M	10	+	5.9	6.4	CRF	-	4.4	46.0	2.9	+
18	57/M	2	+	5.0	5.0	ARF	-	10.9	40.2	2.9	+
19	52/M	6	-	5.1	5.6	NG	3+	6.6	42.5	1.3	+

ARF, Acute renal failure; BUN, Blood urea nitrogen; CRF, chronic renal failure; DN, diabetic nephropathy; HbA1c, glycated hemoglobin; NA, not available; NDRD, non-diabetic renal disease; NG, nephritic syndrome; NS, nephrotic syndrome; T2DM, type 2 diabetes mellitus.

patient older than 60 years. All patients had T2DM; the duration of diabetes at the time of renal biopsy ranged from 2 to 20 years. Diabetic retinopathy was present in 17 patients and the majority of patients had hematuria (15 cases, 78.9%). Fourteen patients had hypertension, four patients had nephrotic syndrome, six patients had nephritic syndrome and nine patients had renal dysfunction.

Patients with a longer history of diabetes had higher urinary protein levels than those with a shorter duration of diabetes ($r = 0.67, P < 0.05$). However, there was a poor correlation between disease duration and fasting blood sugar ($r = 0.116, P > 0.05$) and HbA1c ($r = 0.256, P > 0.05$).

Renal pathology findings are summarized in Table 3. All patients had diabetic renal lesions complicated with NDRD. The most common NDRD finding was IgA nephropathy (Figure 1), which was present in 10 patients (52.6%). Four patients had tubulointerstitial lesions (Figure 2), three patients had membranoproliferative glomerulonephritis (MPGN) (Figure 3) and two patients had membranous nephropathy (MN) (Figure 4).

Discussion

The occurrence of NDRD in diabetic patients is well recognized. A variety of renal lesions can occur in diabetic patients, such as IgA nephropathy, MN, mesangial proliferative glomerulonephritis, hypertensive renal disease and focal segmental glomerular sclerosis. In some diabetic patients, DN is complicated by co-existing NDRD. We summarize the relevant studies published between 1983 to 2012 [6,10,12,13,15-17,19,21,22,28-30], which indicated that glomerular disease (58.2%) remains the most common renal complication in diabetic patients with co-existing DN and NDRD. The review showed that the three most common forms of glomerular disease were IgA nephropathy (14.1%), mesangial proliferative glomerulonephritis (10%) and post-infectious glomerulonephritis (10%). Tubulointerstitial lesions (25.5%) and vascular lesions (10%) also existed in such patients.

In the present study, we found a high incidence of DN complicating NDRD (7.8%). These patients all had pathologic hallmarks of DN, including increased thickness of the glomerular basement membrane (GBM) and mesangial expansion. According to the new classes of glomerular lesions in DN, the degree from light to

Table 3 The histology of diabetic nephropathy (DN) with non-diabetic renal disease (NDRD)

Case	IgA	IgM	IgG	C3	C1q	FIB	Diabetic renal lesion	NDRD
1	2+	2+	2+	+	±	-	Diffuse and nodular glomerulosclerosis	IgA nephropathy
2	2+	2+	-	2+	-	3+	Diffuse glomerulosclerosis	IgA nephropathy
3	-	-	-	-	-	-	Diffuse and nodular glomerulosclerosis	Membrano-proliferative glomerulonephritis
4	2+	±	+	3+	-	2+	Diffuse and nodular glomerulosclerosis	IgA nephropathy
5	±	3+	2+	3+	2+	-	Diffuse and nodular glomerulosclerosis	Membranous nephropathy
6	±	+	-	-	-	-	Diffuse glomerulosclerosis	Membrano-proliferative glomerulonephritis
7	-	2+	-	3+	+	-	Diffuse and nodular glomerulosclerosis	Tubulointerstitial lesion
8	3+	+	2+	2+	-	2+	Diffuse glomerulosclerosis	IgA nephropathy
9	2+	+	3+	3+	-	±	Diffuse and nodular glomerulosclerosis	IgA nephropathy
10	-	2+	2+	-	-	+	Diffuse and nodular glomerulosclerosis	Tubulointerstitial lesion
11	2+	+	+	±	-	2+	Diffuse and nodular glomerulosclerosis	IgA nephropathy
12	2+	+	2+	3+	-	2+	Diffuse glomerulosclerosis	IgA nephropathy
13	2+	-	2+	-	-	+	Diffuse and nodular glomerulosclerosis	IgA nephropathy
14	2+	2+	+	2+	-	-	Diffuse glomerulosclerosis	IgA nephropathy
15	2+	+	2+	-	-	-	Diffuse and nodular glomerulosclerosis	IgA nephropathy
16	2+	-	3+	3+	-	-	Diffuse glomerulosclerosis	Membranous nephropathy
17	±	-	2+	-	-	-	Diffuse glomerulosclerosis	Tubulointerstitial lesion
18	-	3+	3+	2+	-	2+	Diffuse and nodular glomerulosclerosis	Tubulointerstitial lesion
19	2+	2+	3+	-	±	-	Diffuse and nodular glomerulosclerosis	Membrano-proliferative glomerulonephritis

The fluorescent staining was graded as follows: - negative, ± doubtful, + weak, 2+ moderate, 3+ bright. DN, diabetic nephropathy; FIB, fibrinogen; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; NDRD, non-diabetic renal disease.

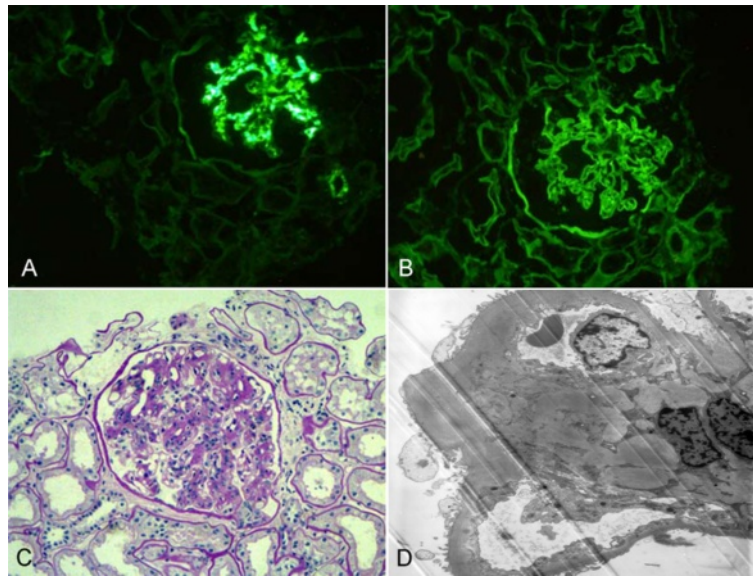


Figure 1 A case with immunoglobulin A (IgA) nephropathy and diabetic nephropathy (DN). (A) Typical mesangial absorbance pattern after labeling with anti-IgA antibody (IF, 200x). (B) The deposits of mainly IgG collected in the basement membrane and appeared in the linear pattern as shown by immunofluorescence (IF, 200x). (C) Mesangial cellularity and matrix increased, and there was a thickening of the glomerular basement membrane (GBM) (PAS, 200x). (D) The electron micrograph demonstrated an increase in small dense deposits in the mesangium and the mesangial matrix. The basement membrane was diffusely thickened due to diabetic involvement (EM, 5000x). DN, diabetic nephropathy; EM, electron microscopy; GBM, glomerular basement membrane; IF, immunofluorescence; IgA, immunoglobulin A; IgG, immunoglobulin G; PAS, periodic acid-Schiff.

severe are presented as follows: I. Mild or nonspecific light microscopy changes and electron microscopy-proven glomerular basement membrane thickening. IIa. Mild mesangial expansion. IIb. Severe mesangial expansion. III. Nodular sclerosis (Kimmelstiel-Wilson lesion). IV. Advanced diabetic glomerulosclerosis [35,36]. In our study, most patients' glomerular lesions in DN were IIb or III.

The most common NDRD in our patients was IgA nephropathy, which accounted for 52.6% of all cases, followed by tubulointerstitial lesion (21.1%) and MPGN

(15.8%). The high prevalence of IgA nephropathy was in accordance with findings from the aforementioned literature review, which showed prevalence rates ranging from 7.1% to 44.8% [10,15,16,21,28,30]. The disease spectrum of DN complicating NDRD in China might be thought to be different from that in other parts of the world. Our findings are in accordance with those of other studies, which have reported IgA nephropathy to be the most common NDRD pathology in Asian diabetic patients [7,15,37].

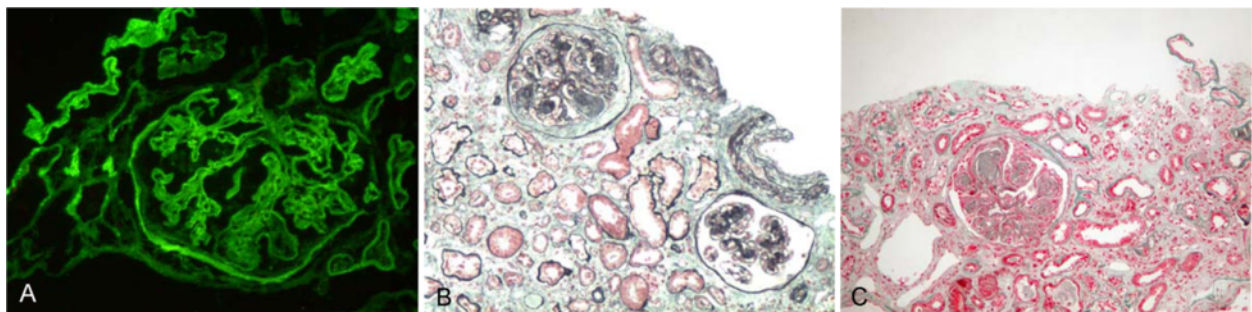


Figure 2 A case with chronic tubular interstitial nephritis (TIN) and diabetic nephropathy (DN). (A) Deposits of mainly IgG collected in the basement membrane and appeared in a linear pattern as viewed by immunofluorescence (IF, 200x). (B) (PAS, 100x) and (C) (Masson, 100x) show severe mesangial expansion (Kimmelstiel-Wilson nodules) and severe tubular injury with only minimal cell infiltration in the interstitial area. DN, diabetic nephropathy; IF, immunofluorescence; IgG, immunoglobulin G; PAS, periodic acid-Schiff; TIN, tubular interstitial nephritis.

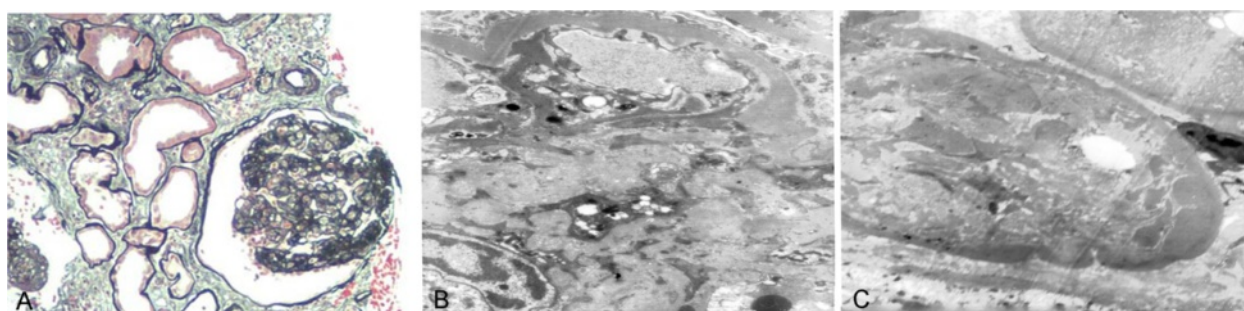


Figure 3 A case with membranoproliferative glomerulonephritis (MPGN) and diabetic nephropathy (DN). (A) This silver staining demonstrated a double contour of many basement membranes, with 'tram-tracking', which is characteristic of type I MPGN (PAS, 200 \times). (B) Prominent subendothelial deposits and mesangial interposition are seen (EM, 5000 \times) and (C) the basement membrane was thickened due to diabetic involvement (EM, 5000 \times). DN, diabetic nephropathy; EM, electron microscopy; MPGN, membranoproliferative glomerulonephritis; PAS, periodic acid-Schiff.

There was a high prevalence (89%) of diabetic retinopathy among our 19 cases of co-existing DN and NDRD. The mean duration of diabetes was more than 7 years, and there was a direct association between duration of diabetes and the severity of proteinuria. The poor correlation between disease duration, fasting blood sugar and HbA1c does not necessarily indicate that DN is the only factor affecting disease progression, since the poor correlation coefficients may have been the consequence of the diversity of other types of NDRD. It is possible, however, that is in the small population. The other surprising finding of this study was the high frequency of hypertension (14 cases, 73.7%), especially as some workers report absence of hypertension in DM as one of the differential diagnostic features of NDRD [28]. These findings indicate that blood pressure control is of primary importance in the prevention of progressive renal disease.

Our results indicate that there are distinct clinical and pathologic features in diabetic patients with DN complicating

NDRD. These patients have some of the clinical and pathologic features of DN, which include a high prevalence of diabetic retinopathy, a long duration of diabetes, increased thickness of the GBM and mesangial expansion. Other clinical findings are inconsistent with the natural history of DN, including the presence of hematuria, rapidly progressive renal failure and severe proteinuria. These diverse clinical manifestations might be the direct consequence of a different pathologic diagnosis within the population. IgA nephropathy was the most common histological diagnosis in patients undergoing renal biopsy. However, the pathologic types of NDRD in DN complicating NDRD in diabetic patients are no different to those in non-diabetic patients in previous studies [28].

Conclusions

In this study, retrospective analysis of biopsy data suggests that approximately 8% of Chinese patients with T2DM may have co-existing DN and NDRD. The most common

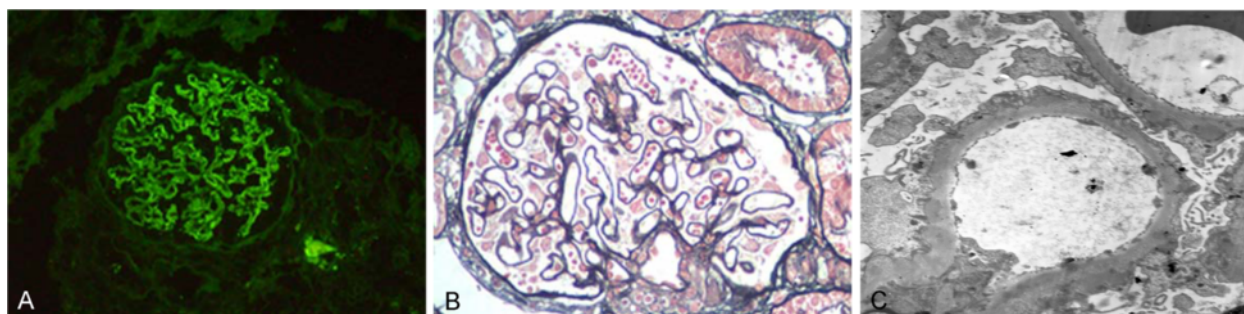


Figure 4 A case with membranous nephropathy (MN) and diabetic nephropathy (DN). (A) Deposits of mainly IgG collected in the basement membrane and appeared as a diffuse granular pattern as shown by immunofluorescence (IF, 200 \times). (B) Light microscopy showing membranous glomerulonephritis in which the capillary loops were thickened and prominent. Numerous granular dense deposits were located in subepithelial areas (PAS, 200 \times). (C) Thickened glomerular basement membrane (GBM) with numerous granular, dense deposits located in subepithelial areas (EM, 5000 \times). DN, diabetic nephropathy; GBM, glomerular basement membrane; IF, immunofluorescence; IgG, immunoglobulin G; MN, membranous nephropathy; PAS, periodic acid-Schiff.

histological diagnosis in our small series was IgA nephropathy. However, it is single-center study with a small number of patients. Larger, multicenter randomized prospective studies are, therefore, required to confirm these preliminary findings.

Abbreviations

ARF: Acute renal failure; BUN: Blood urea nitrogen; CRF: Chronic renal failure; DM: Diabetes mellitus; DN: Diabetic nephropathy; EM: Electron microscopy; ESRD: End-stage renal disease; FIB: Fibrinogen; FITC: Fluorescein isothiocyanate; GBM: Glomerular basement membrane; HbA1c: Glycated hemoglobin; IF: Immunofluorescence; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; MN: Membranous nephropathy; MPGN: Membrano-proliferative glomerulonephritis; NDRD: Non-diabetic renal disease; NG: Nephritic syndrome; NS: Nephrotic syndrome; PAS: Periodic acid-Schiff; T2DM: Type 2 diabetes mellitus; TIN: Tubular interstitial nephritis.

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

LZ conceived the study and drafted the manuscript. WL participated in the study design and coordination, and helped draft the manuscript. GZ carried out the renal pathology. JL carried out the immunoassays. WR performed the statistical analysis. All authors read and approved the final manuscript.

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