ORIGINAL ARTICLE

Clinical and pathological characteristics of non-diabetic renal disease in type 2 diabetes patients

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Abstract

Background: Renal involvement in type 2 diabetes is mainly due to diabetic nephropathy (DN). Nevertheless, a sizable proportion of diabetic patients could actually have nondiabetic renal diseases (NDRDs) or DN plus NDRDs. This study aimed to explore the pathological features of NDRD in diabetic patients and to assess the predictability of diagnosing NDRD (±DN) versus isolated DN on the basis of clinical parameters.

Methods: Medical records of type 2 diabetes patients who underwent renal biopsy under suspicion of NDRD from January 2011 through November 2015 were analyzed retrospectively.

Results: A total of 101 patients were enrolled in this study. The most frequent indication for renal biopsy was recent onset of nephrotic syndrome (41%), followed by rapidly progressive renal failure (29%) and active urinary sediment (21%). On renal biopsy, 51% of patients had isolated DN, 20% had isolated NDRD and 29% had DN plus NDRD. IgA nephropathy was the most common cause of isolated NDRD, whereas acute tubular necrosis (39%) and acute interstitial nephritis (33%) were the main causes of NDRD superimposed on DN. Male gender, short-duration diabetes (<8 years), lower glycated hemoglobin and active urinary sediment (≥10 red and white blood cells per high-power field) were independent predictors of NDRD according to multiple logistic regression analysis.

Conclusions: Judicious use of renal biopsy revealed NDRD (±DN) in nearly half of type 2 diabetes patients with atypical renal presentation, especially in male patients with well-controlled diabetes, those who have had diabetes for a short duration and those with active urinary sediment.

Key words: diabetic nephropathy, nondiabetic renal disease, renal biopsy, type 2 diabetes

Introduction

Diabetic nephropathy (DN) is a devastating complication of diabetes mellitus and is a leading cause of end-stage renal disease (ESRD) worldwide [1]. Moreover, patient survival in diabetic patients on maintenance dialysis is lower than in nondiabetic patients with ESRD due to the presence of other renal diseases [2, 3]. There is a wide variation in the prevalence of nondiabetic renal disease (NDRD) due to variable selection criteria for renal

biopsy, and geographical differences. Previous studies evaluating histological findings in renal biopsies performed in diabetic patients have shown that approximately one-third of the cases exhibit pure diabetic nephropathy, one-third a nondiabetic condition and another third diabetic nephropathy with a superimposed disease [4, 5]. The atypical clinical features that have previously been shown to predict renal involvement by NDRD in diabetic patients are sudden onset of proteinuria, proteinuria in the absence of diabetic retinopathy, active urinary sediment, rapidly decreasing renal function and short duration of diabetes [6–9]. However, due to the variability of clinical courses and the frequency of confounding medical comorbidities in this population, differentiating between DN and NDRD in individual patients without the assistance of renal biopsy remains problematic. The aim of this study is to explore the etiology of biopsy-proven NDRD in the Thai population and to determine the predictability of diagnosing NDRD with or without DN versus isolated DN in patients with type 2 diabetes, based on clinical and laboratory data.

Materials and methods

The demographic, clinical and biochemical data of patients with type 2 diabetes who underwent native renal biopsy in Srinagarind hospital from January 2011 through November 2015 were analyzed retrospectively. Data were collected from histopathological reports, requisition forms and discharge summaries. Post-transplant patients and patients with a lack of adequate clinical data or inadequate renal biopsies were excluded. The indications for renal biopsy in this cohort included the following characteristics: active urinary sediment, hematuria with dysmorphic red blood cells $\pm$ red blood cell casts; recent onset of nephrotic syndrome, sudden appearance of proteinuria >3.5 g/day with edema and/or hypoalbuminemia (serum albumin <3.0 g/dL); renal failure without significant proteinuria; acute kidney injury, increase in serum creatinine by ≥ 0.3 mg/dL within 48 h or ≥ 1.5 times baseline that is presumed to have occurred within the prior 7 days; and rapidly progressive renal failure, renal failure over weeks or months in patients with previously stable renal function. The pathologic criteria for DN included diffuse mesangial sclerosis and glomerular basement membrane thickening at the light microscopic and ultrastructural levels, with or without mesangial nodularity (Kimmelstiel–Wilson nodule). Supportive histologic features of DN included: thickening of the tubular basement membrane of nonatrophic tubules; diffuse linear staining of glomerular and tubular basement membrane for albumin and IgG; and hyalinosis of glomeruli and vessels producing fibrin caps, capsular drops and arteriolar hyalinosis. Because some degree of interstitial inflammation is commonly seen in DN, a diagnosis of acute interstitial nephritis was made only if interstitial inflammatory cell infiltrates included eosinophils-involved areas without tubular atrophy/interstitial fibrosis. A diagnosis of acute tubular necrosis was made if nonatrophic tubules displayed diffuse acute tubular injury, including epithelial simplification, loss of brush border and focal cytoplasmic shedding. Based on the kidney biopsy findings, patients were categorized as isolated DN, isolated NDRD or DN plus NDRD.

Statistical analysis included computing (i) the frequency counts and percentages for the categorical variables and (ii) the means and standard deviations for the continuous variables. One-way analysis of variance (ANOVA) and *post hoc* multiple comparisons were used to determine the significance among the means of multiple groups with the least-significant difference test for equal variances and the Dunnett test for unequal variances. The homogeneity of variance was clarified using the Levene test. Categorical data were compared by the chi-squared and Fisher's exact test. Univariate and multivariable analyses of variables considered as potential predictors of NDRD superimposed on DN versus isolated DN were performed using logistic regression. P-values <0.05 were considered statistically significant. All statistical analysis was performed using SPSS for Windows version 17.0 and STATA version 14.0.

The study was approved by Khon Kaen University Faculty of Medicine Ethics Committee.

Results

A total of 101 patients with type 2 diabetes who were suspected of having NDRD underwent renal biopsy from January 2011 through November 2015. The mean age of the cohort at biopsy was 51 ± 12 years. Approximately 57% of the patients were men. The mean duration of diabetes was 6.7 ± 4.2 years. Our study showed that most patients had notable renal dysfunction, with a mean serum creatinine of 2.8 ± 2.2 mg/dL and estimated glomerular filtration rate (eGFR) 40.4 ± 29.4 mL/min/1.73 m^2. Mean proteinuria for the entire cohort was within the nephrotic range $(5.8 \pm 3.4$ g/day). Fifty-two patients (51%) had isolated DN, 20 patients (20%) had isolated NDRD and 29 patients (29%) had DN plus NDRD. Clinical and laboratory parameters of the three groups are summarized in Table 1. Patients with isolated DN had significantly longer duration of diabetes than patients with isolated NDRD $(8.1 \pm 4.8$ versus 3.8 ± 1.5 years, $P < 0.05$). The prevalence of diabetic retinopathy was significantly higher in patients with isolated DN (84.6%) than patients with isolated NDRD (15%) and patients with DN plus NDRD (65.5%). Patients with DN plus NDRD had significantly higher serum creatinine than patients with isolated DN or isolated NDRD. Patients with isolated DN had significantly higher fasting plasma glucose, glycated hemoglobin and serum total cholesterol than patients with isolated NDRD. Patients with isolated DN had significantly higher proteinuria than patients with isolated NDRD $(6.9 \pm 3.2$ versus 3.5 ± 2.1 g/day, $P < 0.05$). More importantly, patients with NDRD ($\pm$DN) had significantly more active urinary sediment than patients with isolated DN. Neither mean systolic blood pressure, diastolic blood pressure, hemoglobin nor serum albumin appeared to differ among patients with isolated DN, those with isolated NDRD and those with DN plus NDRD.

Indications for renal biopsy (Figure 1) included recent onset of nephrotic syndrome in 41 patients (40.6%), rapidly progressive renal failure in 29 patients (28.7%), active urinary sediment in 21 patients (20.8%), acute kidney injury in 9 patients (8.9%) and renal failure without significant proteinuria in 1 patient (1.0%). Upon renal biopsy, most of the patients presenting with recent onset of nephrotic syndrome (85.4%) and rapidly progressive renal failure (44.8%) turned out to have isolated DN and DN plus NDRD, respectively. Moreover, about three-quarters of patients presenting with active urinary sediment were found to have NDRD ($\pm$DN) on renal biopsy.

The frequency of NDRD in renal biopsies on patients with type 2 diabetes was 49%. Most of these patients (29%) had NDRD concurrent with DN while the remainder (20%) had isolated NDRD. The renal histological lesions identified in patients with NDRD superimposed on DN and those with isolated NDRD are presented in Table 2. The most common NDRDs with concomitant DN were acute tubular necrosis (38.9%), acute interstitial nephritis (33.3%) and crescentic glomerulonephritis (8.3%). Glomerular diseases such as IgA nephropathy, membranous

Table 1. Demographic and clinical characteristics of the study patients at the time of renal biopsy

Characteristics	Isolated DN (N = 52)	Isolated NDRD (N = 20)	DN plus NDRD (N = 29)	P-value
Male sex, n (%)	23 (44.2)	13 (65)	22 (75.9)[a]	0.017
Age (years)	51 ± 13	50 ± 7	53 ± 12	0.72
Duration of diabetes (years)	8.1 ± 4.8	3.8 ± 1.5[b]	6.4 ± 3.1[c]	<0.001
Presence of diabetic retinopathy, n (%)	44 (84.6)	3 (15)[b]	19 (65.5)[a,c]	<0.001
Systolic blood pressure (mmHg)	149 ± 17	141 ± 10	149 ± 20	0.17
Diastolic blood pressure (mmHg)	81 ± 8	80 ± 4	83 ± 9	0.27
Hemoglobin (g/dL)	9.7 ± 1.5	10.4 ± 1.1	9.6 ± 1.5	0.16
Fasting plasma glucose (mg/dL)	183 ± 5.7	140 ± 6.7[b]	164 ± 5.3	0.002
HbA1c (%)	8.5 ± 1.0	7.3 ± 0.1[b]	8.1 ± 1.1[c]	<0.001
Serum creatinine (mg/dL)	2.69 ± 2.05	1.45 ± 0.50[b]	3.90 ± 2.06[c]	<0.001
eGFR[d] (mL/min/1.73 m^2)	38.2 ± 27.6	58.7 ± 23.9[b]	31.8 ± 31.5[c]	0.004
Serum total cholesterol (mg/dL)	300 ± 89	226 ± 42[b]	249 ± 82[a]	0.001
Serum albumin (g/dL)	2.8 ± 0.6	3.0 ± 0.4	2.7 ± 0.5	0.14
Proteinuria (g/24 h)	6.9 ± 3.2	3.5 ± 2.1[b]	5.3 ± 3.5[a]	<0.001
Urinary red blood cells/HPF	2 ± 4	12 ± 9[b]	7 ± 8[a]	<0.001
Urinary white blood cells/HPF	1 ± 1	8 ± 6[b]	6 ± 11[a]	<0.001

HPF, high-power field.
[a]Isolated DN versus DN plus NDRD (P < 0.05).
[b]Isolated DN versus isolated NDRD (P < 0.05).
[c]Isolated NDRD versus DN plus NDRD (P < 0.05).
[d]The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation.
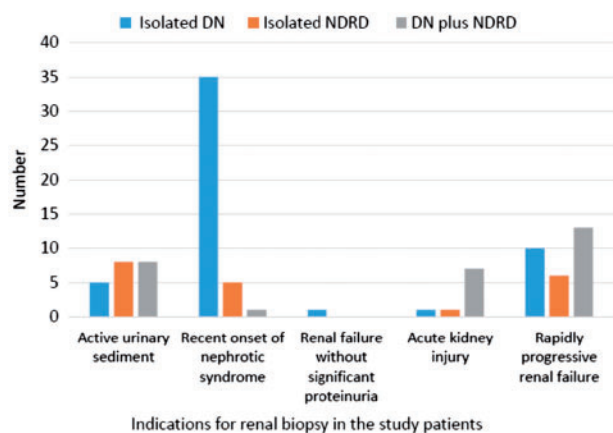

Fig. 1. Indications for renal biopsy in the study patients.

Table 2. Renal pathology of NDRD, with and without DN, in type 2 diabetes patients

Histology	NDRD superimposed on DN (N = 29)[a]	Isolated NDRD (N = 20)	P-value
Acute tubular necrosis	14 (38.9)	0 (0)	<0.001
Acute interstitial nephritis	12 (33.3)	1 (5.0)	0.007
IgA nephropathy	1 (2.8)	7 (35.0)	0.005
Membranous nephropathy	0 (0)	5 (25.0)	0.008
Lupus nephritis	2 (5.6)	4 (20.0)	0.21
Crescentic glomerulonephritis	3 (8.2)	1 (5.0)	0.64
Membranoproliferative glomerulonephritis	0 (0)	1 (5.0)	0.22
Focal segmental glomerulosclerosis	1 (2.8)	0 (0)	0.41
IgM nephropathy	2 (5.6)	1 (5.0)	1.00
Chronic interstitial nephritis	1 (2.8)	0 (0)	1.00

Values are presented as n (%).
[a]Some patients have more than one renal pathology.

nephropathy and lupus nephritis were more likely to be present in the absence of, rather than superimposed on, DN.

The results of univariate analysis indicated that male gender, short duration of diabetes, absence of diabetic retinopathy, active urinary sediment, lower cholesterol levels, glycated hemoglobin and proteinuria were significantly associated with NDRD (±DN). However, in a multivariate logistic regression model (Table 3), male gender [odds ratio (OR) 4.43, 95% confidence interval (CI) 1.39–14.15, P = 0.01] and active urinary sediment (OR 4.75, 95% CI 1.46–15.43, P = 0.01) were significantly associated with NDRD (±DN). Moreover, diabetes of long duration (>8 years) and higher glycated hemoglobin levels were significantly inversely associated with NDRD (±DN).

Discussion

DN is one of the most frequent and clinically significant complications of diabetes mellitus. It affects approximately 40% of patients who have had diabetes for >20 years and has become a major cause of ESRD worldwide [10, 11]. Interestingly, among

patients with type 2 diabetes who have undergone renal biopsy, the prevalence of NDRD varies widely from 12% to 79%, depending on the selection criteria and the population being studied [4, 7, 12–15]. Various predictive factors for NDRD have been identified in diabetic patients, including absence of diabetic retinopathy, rapid decline of renal function, abrupt onset of nephrotic syndrome and presence of active urinary sediment [7, 15, 16].

We found that the mean duration of diabetes was significantly longer in patients with isolated DN (8.1 ± 4.5 years) than in patients with NDRD with or without DN (5.3 ± 2.9 years). Similarly, Chang *et al.* reported a mean diabetes duration of 5.9 years in patients with NDRD versus 10.6 years in patients with DN alone (P < 0.001 for comparison) [17]. Furthermore, short duration of diabetes (<8 years) had a high likelihood of predicting NDRD versus isolated DN. Our results supported

Table 3. Multivariate analysis of clinical parameters in patients with NDRD with or without DN

Variables	OR	95% CI	P-value
Male gender	4.43	1.39–14.15	0.01
Duration of diabetes (>8 years)	0.15	0.04–0.49	0.002
Glycated hemoglobin (HbA1c)	0.16	0.05–0.47	0.001
Active urinary sediment[a]	4.75	1.46–15.43	0.01

[a]Active urinary sediment is defined as 10 or more red and white blood cells per high-power field.

those of the majority of previous reports suggesting that a higher degree of proteinuria is found in patients with DN than in those with isolated NDRD [7, 8, 12, 16, 18]. The prevalence of hypertension was similar in all three groups in our study, which is consistent with the findings from previous reports [7]. Recent onset of nephrotic syndrome, rapidly progressive renal failure and active urinary sediment were the most frequent indications for renal biopsy in our study. It is interesting that most of our patients presenting with rapidly increasing proteinuria actually had isolated DN on renal biopsy. A plausible explanation for this finding is that the majority of our patients had longstanding poorly controlled diabetes with established microvascular complications (e.g. diabetic retinopathy). These patients may, thus, develop progressively increasing albuminuria faster than other patients. It is worth mentioning here that about 10% of our patients with isolated DN had active urinary sediment. Okada et al. found an association between the presence of arteriolar hyalinosis in renal biopsy and persistent microscopic hematuria in type 2 diabetes patients [19]. Moreover, Matsumura et al. reported that diabetic patients with glomerular hematuria exhibited histologically advanced diffuse lesions, nodular lesions, microaneurysms, crescent formation, capsular adhesion and interstitial lesions more often than those without hematuria [20].

Our study revealed that 49% of type 2 diabetes patients who underwent renal biopsy had NDRD, either isolated or superimposed on underlying DN. Our cohort also demonstrated that acute tubular necrosis was the most common nondiabetic renal pathology superimposed on DN in type 2 diabetes patients presenting with acute kidney injury. The etiologies of acute tubular necrosis are classified as ischemic processes, nephrotoxic agents and sepsis. Diabetic patients are prone to have normotensive ischemic acute kidney injury due to atherosclerotic vasculature and impaired renal autoregulation [21]. Moreover, infectious complications are common in immunocompromised diabetic patients and are the leading cause of hospitalization. Various drugs, especially nonsteroidal anti-inflammatory drugs, and herbal remedies are also prevalent causes of nephrotoxic acute tubular necrosis and acute interstitial nephritis in diabetic patients. Taken together, this means that diabetic patients are at risk of developing acute tubular necrosis attributable to multifactorial factors. Recently, Sharma et al. also reported a high incidence of acute tubular necrosis as a superimposed disease on DN in a large cohort of type 2 diabetes patients [4]. The high prevalence of acute tubular necrosis supports the number of epidemiologic cohorts in which acute kidney injury episodes are associated with a cumulative risk for progression to ESRD, particularly in patients with diabetes. Soni et al. reported acute interstitial nephritis to be the most common concurrent nondiabetic pathology in clinical renal biopsies from type 2 diabetes patients [7]. However, it was slightly less common than acute tubular necrosis in our study. Our results support those of a

previous study by Dai et al., which showed that acute interstitial nephritis was more common in cases of DN compared with other glomerulopathies [22]. The presence of interstitial eosinophilic infiltration is the hallmark of drug-induced tubulointerstitial nephritis. However, this finding can also be seen in other conditions, including autoimmune diseases, tubulointerstitial nephritis with uveitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) and parasitic infections [23–25]. Furthermore, it is not uncommon to identify eosinophilic infiltration adjacent to disrupted tubules or chronic tubulointerstitial injury in DN. These tubulointerstitial changes in DN are thought to be related to the renal microvasculature alterations characteristic of longstanding diabetes, and it is generally held that they are due to chronic ischemia [26]. Among all cases of nondiabetic glomerulopathies in this cohort, IgA nephropathy was the most common biopsy finding. The most common nondiabetic glomerular diseases previously reported in patients with type 2 diabetes are IgA nephropathy [8, 27, 28], focal segmental glomerulosclerosis [15, 16] and membranous nephropathy [16, 29]. Interestingly, we observed three human immunodeficiency virus -negative patients (3.7% DN cases) who presented with rapidly progressive renal failure and had crescentic formation superimposed on DN in renal biopsy. The etiological linkage between diabetic glomerulosclerosis and the development of crescents has been scarcely mentioned in previous literature. Recently, Salvatore et al. also reported 26 diabetic patients (5% DN cases) with aggressive clinical courses of renal involvement whose renal biopsies showed collapsing glomerulopathy (pseudocrescent formation) presumed to be the result of extensive microvascular sclerosis/hyalinosis [30]. One critical gap in our knowledge is whether crescentic and pseudocrescent formation is associated with different outcomes in patients with type 2 diabetes. In our series, IgM nephropathy and lupus nephritis were the most common finding in nondiabetic glomerular diseases superimposed on DN, excluding crescentic glomerulonephritis. These results demonstrate that the prevalence of various types of biopsy-proven renal diseases in diabetic patients may be related to the local prevalence of renal disease in the total population of a given geographical area with similar ethnic characteristics, and the presence of NDRD in cases of type 2 diabetes may only be a coincidence. Recently, Fiorentino et al. [31] conducted a meta-analysis, combining 48 studies and 4876 participants, and it showed that the prevalence of DN, NDRD, and DN plus NDRD ranged from 6.5% to 94%, 3% to 82.9% and 4% to 45.5% of the overall diagnoses, respectively. Moreover, IgA nephropathy was the most common NDRD (3–59%). Our study complements the findings of earlier meta-analysis. We found that NDRDs are highly prevalent in patients with diabetes and clinical judgment alone can miss the correct diagnosis.

In our study, diabetic retinopathy had a close correlation with the presence of DN (±NDRD), but it was not an independent predictor by multivariate analysis. Sensitivity of diabetic retinopathy for DN (±NDRD) was 78% with a specificity of 85%, and a positive predictive value of 95% with a negative predictive value of 49%. Recently, He et al. performed a meta-analysis that demonstrated that the sensitivity and specificity of diabetic retinopathy in predicting diabetic nephropathy were 65% (95% CI 0.62–0.68) and 75% (95% CI 0.73–0.78), respectively. In addition, the pooled positive and negative predictive values of diabetic retinopathy to predict diabetic nephropathy were 72% (95% CI 0.68–0.75) and 69% (95% CI 0.67–0.72), respectively [32]. A meta-analysis by Liang et al. [33] also showed that the absence of diabetic retinopathy predicted NDRD (OR 0.15, 95% CI 0.09–0.26,

P ≤ 0.00001). However, discordance in the occurrence of the two complications has been reported and dissimilar genetic predispositions have been suggested [34]. The results of our study further support the American Diabetes Association Standards of Medical Care in Diabetes 2017 that patients with an active urinary sediment, or rapidly decreasing renal function, should be referred to a nephrologist for further diagnosis, including the possibility of kidney biopsy [35].

Our study has a number of limitations. First, biopsy-based clinicopathologic studies suffer from selection bias. As a result, our data can only be applied to those patients who have a high pre-test probability of NDRD. A second limitation is that we lack long-term follow-up data on our patients and, thus, cannot conclude whether different types of renal pathology affect future renal outcomes.

In conclusion, our data show that almost half of patients with type 2 diabetes presenting with atypical features of DN are found to have NDRD (±DN) upon renal biopsy. Male gender, short duration of diabetes (<8 years), lower glycated hemoglobin and active urinary sediment were independent predictors of NDRD (±DN). Moreover, absence of diabetic retinopathy is a good indicator of isolated NDRD. Acute tubular necrosis is the most common NDRD superimposed on DN, whereas IgA nephropathy is the most prevalent renal pathology in type 2 diabetes patients with isolated NDRD. Early diagnosis of renal disease by renal biopsy in diabetic patients is indispensable to preserving renal function in those patients with renal diseases for which the natural history can be modified by proper treatment. This is especially true in cases of primary glomerular disease or tubulointerstitial nephritis.

Funding

Conflict of interest statement

None declared.

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