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CLINICAL STUDY

Clinical Predictors of Non-diabetic Renal Disease and Role of Renal Biopsy in Diabetic Patients with Renal Involvement: A Single Centre Review

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is reportedly the leading cause of end-stage renal disease (ESRD) worldwide. However, non-diabetic renal diseases (NDRD) are not uncommon among T2DM patients with renal involvement. Our study aimed to examine the prevalence of NDRD in T2DM and clinical markers for diabetic nephropathy (DN) and NDRD and to determine the role of renal biopsy in T2DM patients and its impact on clinical practice. *Methods*: We conducted a retrospective analysis of T2DM patients in whom renal biopsies were performed from January 2004 to March 2008 ($n = 110$). *Results*: Biopsy results were divided into three groups: group I/pure DN (62.7%), group II/isolated NDRD (18.2%), and group III/mixed lesions (19.1%). The causes of NDRD in decreasing order of frequency were acute interstitial nephritis, glomerulonephritides, hypertensive renal disease, and acute tubular necrosis. Significant clinical markers for DN are presence of diabetic retinopathy and longer duration of diabetes. For NDRD, useful clinical markers include the presence of acute renal failure and microscopic hematuria. In the DN subgroup, Indians had significantly shorter duration of diabetes on biopsy compared with Malays and Chinese. *Conclusions*: NDRD is prevalent in T2DM patients, and given its potentially treatable nature, renal biopsy should be considered in T2DM patients with nephropathy, especially in those with atypical features.

Keywords: diabetic nephropathy, epidemiology, non-diabetic renal disease, renal biopsy, type 2 diabetes mellitus

INTRODUCTION

Diabetic nephropathy (DN) is reportedly the leading cause of chronic kidney disease and end-stage renal disease (ESRD) worldwide.[1,2] In the United States, the overall adjusted rate of ESRD due to diabetes was 155 per million population, contributing to 54% of new patients in 2007.[3] In other parts of the world including Europe and Asia, diabetes remains the leading cause of ESRD, contributing to 20–30% of the incident ESRD patients in Europe and up to 40–55% in certain parts of Asia.[4–7]

While it is widely acceptable that the cause of chronic kidney disease in most type 1 diabetics is usually DN by the time they develop microalbuminuria,[8–11] the routine presumption that DN is the cause of renal impairment in type 2 diabetes mellitus (T2DM) patients may not be correct given that a substantial minority may have non-diabetic renal disease (NDRD) or mixed lesions.[9,12–15] The prevalence of NDRD in T2DM from the literature review of renal biopsy studies varies from 27% to 79%,[16–18] depending on the selection criteria, threshold of biopsy, and population studied.

Despite the fact that NDRD is not uncommon and renal biopsy may correctly identify these patients, the role of renal biopsy in T2DM patients with renal disease remains controversial and is an issue regularly debated by nephrologists. In practice, most patients with T2DM are not formally evaluated with a renal biopsy. The

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diagnosis of DN is frequently based on clinical grounds, and patients with NDRD are often overlooked and potentially erroneously classified as having DN.

In order to determine the indication and justification of renal biopsy in these patients, we carried out a retrospective study on T2DM patients who underwent renal biopsies in our center to evaluate the prevalence of NDRD and the possible clinical markers or predictors suggestive of NDRD. This valuable information would assist clinicians in identifying patients for kidney biopsy leading to timely and disease-specific treatment.

SUBJECTS AND METHODS

Patients and Data Collection

We performed a retrospective analysis on all T2DM patients in whom renal biopsies were performed from January 2004 to March 2008 in the University Malaya Medical Centre. Indications for renal biopsy in T2DM patients in our division include uncertain cause of acute renal failure (with no obvious prerenal or obstructive disorders), acute on chronic renal failure, chronic renal failure with relatively short duration of diabetes or without retinopathy, heavy proteinuria (>1 g/day), and microscopic hematuria. All patients were >18 years old. Patients with small kidneys (<9 cm) were excluded. Altogether 110 biopsies were available for analysis. All biopsies were reviewed and validated by two experienced renal histopathologists based on light microscopy and immunofluorescence. Electron microscopy was not routinely performed in our center. DN was diagnosed by the presence of mesangial expansion and diffuse glomerulosclerosis (with or without nodular Kimmelstiel–Wilson nodule), basement membrane thickening, and hyalinization of the renal arterioles.

Based on the biopsy findings, the patients were divided into three groups: group I patients had only pure DN or diabetic glomerulosclerosis, group II patients had isolated NDRD while group III had mixed lesions (NDRD superimposed on underlying DN). The demographic, clinical, and laboratory data were gathered by reviewing medical case records.

Clinical data such as age, gender, duration of diabetes, serum creatinine, serum albumin, glycosylated hemoglobin (HbA1c), erythrocytes sedimentation rate (ESR), kidney size, presence or absence of microscopic hematuria, diabetic retinopathy, and degree of proteinuria at the time of renal biopsy were collected. Degree of proteinuria was quantified using 24-hour urine protein collection. Ultrasound findings of kidney size were based on departmental ultrasound scan. The information on diabetic retinopathy was retrieved from the records of ophthalmology clinic.

Statistical Analysis

The collected data were systematically analyzed using PASW Statistics 18 (version 18.0, SPSS Inc. Chicago, IL, USA). Data were expressed as mean ± SEM where applicable. The differences between groups were examined using analysis of variance test or Pearson's chi-square test as appropriate. Post hoc analysis was performed using Scheffe's test. Significance was evaluated using a two-sided p-value <0.05.

RESULTS

Pathological Findings

Biopsy results were divided into three groups based on the reported pathological findings: pure DN (group I) was the most common at 62.7% ($n = 69$), followed by mixed lesions (group III, 19.1%, $n = 21$) and isolated NDRD (group II, 18.2%, $n = 20$).

Table 1 show the causes of NDRD with or without DN. Acute interstitial nephritis is the most common NDRD (48.8% of NDRD ± DN) in our biopsied population, accounting for 45% of the isolated NDRD and 52.4% of the mixed lesions. The other causes of NDRD in decreasing order of frequency include glomerulonephritides (40%), hypertensive renal disease (10%), and acute tubular necrosis (5%). Twenty-one patients had mixed lesions. The most common nondiabetic lesions found in patients with mixed lesions were acute interstitial nephritis (52.4%), followed by hypertensive renal disease (38.1%) and chronic pyelonephritis (9.5%). Minimal change disease is the most common glomerulonephritis (3/8 or 37.5%) in our biopsied population.

Clinical and Laboratory Parameters

Mean age at biopsy was 53.8 ± 9.7 years and 58.2% were male. The majority (39.1%) of the biopsied patients were Malays, 32.7% were Chinese, and 28.2% were Indians. Patient demographics and laboratory data are summarized in Table 2.

Patients with pure DN had longer duration of diabetes (13.6 ± 0.91 vs. 8.2 ± 1.44 years, $p = 0.017$)

Table 1. NDRD with or without DN.

	Isolated NDRD (*n*/%)	Mixed lesions (*n*/%)	NDRD ± DN (%)
Acute interstitial nephritis	9/45.0	11/52.4	48.8
Glomerulonephritides			
Minimal change disease	3		7.3
IgA nephropathy	2		4.9
Diffuse proliferative glomerulonephritis	1		2.4
Focal segmental glomerulosclerosis	1		2.4
Lupus nephritis	1 (8/40.0)		2.4 (19.4)
Acute tubular necrosis	1/5.0	0	2.4
Chronic pyelonephritis	0	2/9.5	4.9
Hypertensive nephrosclerosis	2/10.0	8/38.1	24.4
Total	20	21	100.0

Note: NDRD, non-diabetic renal diseases; DN, diabetic nephropathy.

Table 2. Patient demographics and laboratory data between three groups of patients.

	Pure DN (Group I)	Isolated NDRD (Group II)	Mixed lesions (Group III)	*p*-Value
n (%)	69 (62.7%)	20 (18.2%)	21 (19.1%)	
Age (years)	52.0 ± 1.1	57.5 ± 2.1	56.0 ± 2.4	NS
Sex (M/F)	44/25	12/8	8/13	
Race				
Malay	19	9	15	
Chinese	25	7	4	
Indian	25	4	2	
Duration of diabetes (years)	13.6 ± 0.91[a]	8.2 ± 1.44[a]	10.6 + 1.44	0.017[a] (I vs. II)
24-hour urine protein (g/day)	7.5 ± 0.66	6.8 ± 1.64	5.9 ± 1.12	NS
Serum albumin (g/L)	26.4 ± 1.10	25.0 ± 2.10	28.1 ± 1.57	NS
Serum creatinine (μmol/L)	254.6 ± 21.32[b]	425.9 ± 80.64[b]	309.9 ± 41.9	0.013[b] (I vs. II)
HbA1c (%)	8.2 ± 0.27	7.5 ± 0.48	7.9 ± 0.41	NS
ESR (mm/h)	67.3 ± 4.56	91.7 ± 13.50	62.5 ± 10.07	NS
Kidney size (cm)	10.6 ± 0.14	10.8 ± 0.24	10.4 ± 0.23	NS

Data are mean ± SEM. [a,b]Significant *p*-value between group I and group II.
Note: NDRD, non-diabetic renal diseases; DN, diabetic nephropathy.

and lower serum creatinine at the time of biopsy (254.6 ± 21.32 vs. 425.9 ± 80.64 μmol/L, $p = 0.013$) compared with those with isolated NDRD (Table 2). These differences were not observed between the DN versus mixed lesions group. ESR appeared to be higher in the NDRD group, but did not reach statistical significance (II vs. I, $p = 0.12$ and II vs. III, $p = 0.11$). There were no significant differences in terms of mean age, observed serum albumin, 24-hour urine protein excretion, HbA1c, and kidney size between the three groups of patients (Table 2).

Duration of diabetes of >10 years predicts the possibility of DN ($p = 0.002$, OR 4.99 for group I vs. group II) (Table 3). Apart from the duration of diabetes, the presence of diabetic retinopathy is also strongly associated with DN ($p < 0.0001$, OR 16.67 for group I vs. II; and $p = 0.003$, OR 6.36 for group I vs. III) (Table 3). Diabetic retinopathy was found in 84% (61/73) of patients with DN. On the other hand, the presence of acute renal failure and microscopic hematuria is strongly associated with NDRD (OR 27.41, group II vs. I and OR 16.36, group II vs. III for acute renal failure; OR 5.71, group II vs. I and OR 4.4, group II vs. III for microscopic hematuria, respectively) (Table 3).

Table 3. Association between clinical markers and renal pathology.

	Pure DN (group I)	Isolated NDRD (group II)	Mixed lesions (group III)	*p*-Value	OR (95% CI)
Duration of diabetes					
>10 years ($n = 63$)	47	6	10	0.002 (I vs. II)	4.99 (1.69–14.71)
≤10 years ($n = 47$)	22	14	11	NS (I vs. III or II vs. III)	
Acute renal failure					
Present ($n = 12$)	2	9	1	<0.0001 (I vs. II)	II vs. I 27.41 (5.21–144.09)
Absent ($n = 98$)	67	11	20	0.03 (II vs. III)	II vs. III 16.36 (1.83–146.67)
				NS (I vs. III)	
Microscopic hematuria					
Present ($n = 54$)	28	16	10	0.002 (I vs. II)	II vs. I 5.71 (1.73–18.92)
				0.03 (II vs. III)	II vs. III 4.4 (1.10–17.68)
Absent ($n = 55$)	40	4	11	NS (I vs. III)	
Diabetic retinopathy					
Present ($n = 67$)	50	6	11	<0.0001 (I vs. II)	I vs. II 16.67 (4.25–65.41)
Absent ($n = 22$)	5	10	7	0.003 (I vs. III)	I vs. III 6.36 (1.70–23.83)
				NS (II vs. III)	

Note: NDRD, non-diabetic renal diseases; DN, diabetic nephropathy; OR, odd ratio; CI, confidence interval.

Among DN subgroup, Indian patients had shorter duration of diabetes on biopsy compared with Malays and Chinese (9.7 ± 7.0, 15.1 ± 7.1, 16.2 ± 7.0 years, respectively, $p = 0.004$). Mean HbA1c at the time of biopsy was significantly higher among Indians compared with Chinese (9.03 ± 2.41 vs. 7.25 ± 1.47%, $p = 0.016$), although there was no significant difference between Indian and Malay or Chinese and Malay. Female patients with DN were found to have shorter duration of diabetes, as compared with male patients (10.4 ± 5.8 years vs. 15.3 ± 7.9 years, $p = 0.009$).

We further evaluated the sensitivity and specificity of each of these significant clinical markers (diabetic retinopathy, acute renal failure, microscopic hematuria, and duration of diabetes) for the prediction of DN or NDRD. The results were shown in the Table 4. The presence of diabetic retinopathy has high sensitivity (84%) in predicting DN, with specificity of 63%. Duration of diabetes >10 years predicts DN with sensitivity of 63% and specificity of 70%, respectively. Regarding NDRD, the presence of microscopic hematuria is highly sensitive in predicting NDRD (80%), while the occurrence of acute renal failure has high specificity of 97%, but with low sensitivity of 45%.

DISCUSSION

Common indications for renal biopsy in diabetic patients include acute renal failure, microscopic hematuria, nephrotic syndrome, and renal impairment with relatively short duration of diabetes or without retinopathy, although the threshold for biopsy in T2DM patients with renal involvement may vary greatly among practicing nephrologists. In their study, Richard et al.[11] suggested that T2DM patients with renal impairment should have a renal biopsy as part of their investigation. In contrast, Olsen and Mogensen[19] reported that NDRD was rather uncommon in T2DM patients and commented that biopsy should not be routinely performed in T2DM patients with proteinuria.

The value of renal biopsy in selected cases of type 2 diabetes, especially those without diabetic retinopathy and relatively short duration of diabetes, is supported by our study which demonstrated high prevalence of NDRD in the biopsied population (37.3% of all biopsies had either isolated NDRD or mixed lesion, NDRD ± DN). This result was consistent with the findings from other previous studies, with prevalence varying from 27% to 79%.[16–18,20–22] This large variation in the reported prevalence could be explained by the selection criteria, threshold of biopsy, and geographical or ethnic differences. Low threshold for biopsy in carefully selected patients might explain the high prevalence seen in certain studies.

Table 4. The sensitivity and specificity of clinical markers.

Clinical marker	Sensitivity (%)	Specificity (%)	Likelihood ratio
Predicting DN			
Diabetic retinopathy	84	63	2.23
Duration of diabetes mellitus >10 years	63	70	2.11
Predicting NDRD			
Microscopic hematuria	80	57	1.87
Acute renal failure	45	97	13.50

Note: NDRD, non-diabetic renal diseases; DN, diabetic nephropathy.

In this study, diabetic retinopathy was found in 84% (61/73) of patients with DN and 91% (61/67) of T2DM patients with retinopathy had DN. The presence of diabetic retinopathy predicts DN ($p < 0.0001$, sensitivity 84% and specificity 63%). Therefore, the presence of retinopathy increases the threshold for biopsy, whereas normal fundoscopic findings should reduce threshold for a renal biopsy. The strong association between retinopathy and DN was reported in many other studies.[9,17,18,20,21,23] In contrast, several studies report that diabetic patients without retinopathy may have diabetic glomerulopathy or nephropathy at a rate of 44–70%,[15,24–26] indicating that the possibility of DN cannot be excluded confidently by the absence of diabetic retinopathy, although the absence of retinopathy strongly favors NDRD.

Long-standing diabetes of more than 10 years was found to be a significant clinical marker for DN in this study ($p = 0.002$, OR 4.99 for group I vs. group II, sensitivity 63% and specificity 70%). This concurs with studies supporting the observation that duration of diabetes is a significant predictor of DN.[9,15,20,21,23] In contrast, Mak et al.[27] reported that diabetic glomerulosclerosis could not be distinguished from NDRD by age of onset and duration of DM or presence of retinopathy.

Several studies, including a small prospective study by Serra et al., suggest that microscopic hematuria is not an uncommon finding in patients with typical diabetic glomerulopathy (between 35 and 78%) and thus not useful in predicting NDRD.[26,28] However, in our study, microscopic hematuria is significantly associated with NDRD. The importance of microscopic hematuria has also been highlighted in two previous studies,[23,27] which reported that IgA nephropathy was the most common lesion, accounting for 34–57% of all NDRD.

Acute renal failure may be another useful clinical marker for NDRD which in our study was found in 45.0% of patients with NDRD (11/20), as compared with only 2.9% (2/69) of DN patients and 4.8% (1/21) of patients with mixed lesions. This striking difference may be explained by the high prevalence of acute interstitial nephritis in our study population. Our observation that acute interstitial nephritis is the most common cause of NDRD (45.0% of all isolated NDRD and 52.4% of all mixed lesions) is supported by earlier studies[16,21] but is in contrast to reports

from other studies.[15,17,18,20,23,27] The high prevalence of acute interstitial nephritis may be related to the widespread use of traditional medications and over-the-counter drugs like nonsteroidal anti-inflammatory drugs among the patients. A high index of suspicion for renal biopsy is therefore needed, as acute interstitial nephritis is potentially treatable and reversible, with a more favorable prognosis than DN.

Indian patients with DN were found to have shorter duration of diabetes on biopsy compared with Malays and Chinese. This observation suggests that ethnic or genetic factors may play a role in the pathogenesis of DN and similar observations of increased susceptibility in certain ethnic group have been reported previously in the American Black population.[29,30] We observed a higher mean HbA1c at the time of biopsy among Indians, but this is unlikely to explain the apparent ethnic difference in disease susceptibility.

The high prevalence of NDRD in our study supports our decision to biopsy, as the finding of NDRD requires a different therapeutic approach other than or in addition to conventional angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. While the exact prevalence of NDRD will never be known without histological confirmation in diabetic patients with renal disease, a major implication of our study and that of similar studies is that ESRD due to DN cannot be confidently presumed in diabetic patients with ESRD as is currently practiced by renal registries worldwide.

In conclusion, our study, which is one of the largest of its kind, suggest the routine presumption that DN is the cause of ESRD in T2DM patients may not be correct given that a substantial minority has NDRD or mixed lesions. Renal biopsy should always be considered in selected group of T2DM patients with renal involvement since additional disease-specific therapies may potentially be helpful in prolonging renal survival. Our findings, if confirmed and translated into renal registries worldwide, will have a major impact on the epidemiology on causes of ESRD with DN not as common as widely perceived.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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