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Incidence, Histopathological Pattern, and Predictors of Non-Diabetic Renal Disease in Type 2 Diabetes Mellitus: A Single-Center Prospective Observational Study

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Abstract

Patients with type 2 diabetes mellitus (T2DM) may have renal involvement because of isolated diabetic nephropathy (DN), isolated non-diabetic renal disease (NDRD), or mixed lesions (DN combined with NDRD). This study was conducted to find out incidence, histopathological pattern, and clinical predictors of NDRD in the Kashmiri population. This is a single-center prospective observational study conducted from August 2015 to July 2017. Patients with T2DM presenting with atypical clinical features of renal involvement underwent kidney biopsy. A total of 33 patients were included. Isolated NDRD was found in 16/33 (48.5%) patients, isolated DN was discovered in 10/33 (30.3%), and mixed lesions in 7/33 (21.2%) patients. NDRD with or without DN was present in 23/33 (69.7%) patients. Overall, the most common renal histopathological lesion in NDRD was immunoglobulin A (IgA) nephropathy present in 7/23 (30.4%) patients. In mixed lesions, FSGS and TMA were the most common renal lesions present in 2/7 (28.57%) patients. The mean duration of diabetes in NDRD and isolated DN groups was 4.4±3.6 and 7.0±2.9 years, respectively (P = 0.04). NDRD was present in 21/23 (91.3%) patients without diabetic retinopathy (P = 0.016). Our data demonstrated that more than half of the patients with T2DM with atypical features had NDRD upon renal biopsy. The absence of diabetic retinopathy and a shorter duration of diabetes were indicators of NDRD. IgA nephropathy was the most prevalent renal pathology. Clinicians must consider kidney biopsy liberally, especially in patients with unclear etiology of a kidney disease. Patients with type 2 diabetes mellitus (T2DM) may have renal involvement because of isolated diabetic nephropathy (DN), isolated non-diabetic renal disease (NDRD), or mixed lesions (DN combined with NDRD). This study was conducted to find out incidence, histopathological pattern, and clinical predictors of NDRD in the Kashmiri population. This is a single-center prospective observational study conducted from August 2015 to July 2017. Patients with T2DM presenting with atypical clinical features of renal involvement underwent kidney biopsy. A total of 33 patients were included. Isolated NDRD was found in 16/33 (48.5%) patients, isolated DN was discovered in 10/33 (30.3%), and mixed lesions in 7/33 (21.2%) patients. NDRD with or without DN was present in 23/33 (69.7%) patients. Overall, the most common renal histopathological lesion in NDRD was immunoglobulin A (IgA) nephropathy present in 7/23 (30.4%) patients. In mixed lesions, FSGS and TMA were the most common renal lesions present in 2/7 (28.57%) patients. The mean duration of diabetes in NDRD and isolated DN groups was 4.4±3.6 and 7.0±2.9 years, respectively (P = 0.04). NDRD was present in 21/23 (91.3%) patients without diabetic retinopathy (P = 0.016). Our data demonstrated that more than half of the patients with T2DM with atypical features had NDRD upon renal biopsy. The absence of diabetic retinopathy and a shorter duration of diabetes were indicators of NDRD. IgA nephropathy was the most prevalent renal pathology. Clinicians must consider kidney biopsy liberally, especially in patients with unclear etiology of a kidney disease.

Keywords: diabetic nephropathy; diabetic retinopathy; focal segmental glomerulosclersosis; IgA nephropathy; non-diabetic renal disease

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Introduction

The incidence of diabetic nephropathy (DN) has dramatically increased in recent years, becoming a significant cause of end-stage renal disease (ESRD) and posing a great burden to the healthcare system (1–4). Patients with type 2 diabetes mellitus (T2DM) may have renal involvement because of isolated diabetic nephropathy (DN), isolated non-diabetic renal disease (NDRD), or DN combined with NDRD (5). This study was conducted to find out incidence, histopathological pattern, and clinical predictors of NDRD in the Kashmiri population.

Material and Methods

This is a prospective observational study conducted in the Department of Nephrology at Sher-i-Kashmir Institute of Medical Science, Srinagar, India, from August 2015 to July 2017. Patients presenting with the following features were included in the study: T2DM in the age group of 18– 80 years presenting with atypical clinical features of renal involvement in the form of proteinuria not corresponding to the usual course of diabetic nephropathy (24 h urine protein > 500 mg, or spot urine > 500 mg/gm within 5 years of onset of diabetes), rapid onset of proteinuria regardless of progression from microalbuminuria to macroalbuminuria, proteinuria without diabetic retinopathy (DR), unexplained abrupt decline in renal function not corresponding to the usual course of diabetic nephropathy (estimated glomerular filtration rate [eGFR] decreases to >50%, or increase in serum creatinine to >200% within 1 month), unexplained hematuria (>3 red blood cells per high power field [RBCs/HPF]), and active urinary sediment (dysmorphic RBCs and RBC casts). All patients underwent renal biopsies. Immunological evaluation in the form of complement levels (C3 and C4), anti-nuclear antibody, anti-myeloperioxide antibody, anti-proteinase-3 antibody, and anti-glomerular basement membrane antibody were conducted as and when indicated clinically.

Statistical Analysis

Continuous variables are presented as mean±SD and categorical variables as frequencies and percentage values. Chi-square test/Fisher's Exact test was employed for comparing categorical variables. Mann–Whitney U test was used for comparing nonparametric numerical data. Statistical analysis was done using the SPSS software version 25. $P < 0.05$ was considered statistically significant.

Results

A total of 33 patients fulfilled the inclusion criteria. Male and female accounted for 72.7% (n = 24) and 27.3% (n = 9), respectively (M–F ratio: 2.6:1). The mean age was 52.1±7.6 years. The mean duration of diabetes mellitus was 5.2±3.6 years (range 6 months–15 years). Duration of diabetes was <5 years in 16/33 (48.5%) and ≥5 years in 17/33 (51.5%) patients. Hypertension (BP ≥ 140/90) was present in 20/33 (60.6%) patients. The mean 24-h urine protein was 4.5±3.9 g/day (range: 0.25–15.0 g/day). Nephrotic range proteinuria was present in 17/33 (51.5%) patients. Proteinuria was absent in one patient. Diabetic retinopathy was absent in 26/33 (78.8%). Microhematuria was present in 18/33 (54.5%) patients. Abrupt decline in kidney function was noted in 21/33 (63.6%) patients. Mean value of hemoglobin A1C (HbA1C) test was 8.1±1.3%. HbA1C was in the range of 7–8% in 25/33 (75.8%) patients.

The most frequent reason for biopsy was proteinuria not corresponding to the usual course of T2DM accounting for 87.8% (29/33), followed by proteinuria without diabetic retinopathy in 75.7% (25/33), and unexplained abrupt decline in renal function not corresponding to the usual course of diabetic nephropathy in 63.6% (21/33) patients. The least common indication of renal biopsy in our patients was active urinary sediment in one patient. Most of the patients had multiple reasons for kidney biopsy. Kidney biopsy results revealed that 16/33 (48.5%) patients had isolated NDRD. Isolated DN was present in 10/33 (30.3%) patients. Mixed lesions (NDRD superimposed on DN) were present in 7/33 (21.2%) patients. Overall NDRD lesions with or without DN were present in 23/33 (69.7%) of T2DM patients. Overall, the most common renal histopathological lesion in NDRD was immunoglobulin A (IgA) nephropathy, present in 7/23 (30.4%) patients, followed by focal segmental glomerulosclerosis (FSGS) present in 6/23 (26.1%) patients. The other less frequent lesions were thrombotic microangiopathy (TMA) present in 04/23 (17.4%) patients, and acute tubular injury (ATI) and membranoproliferative glomerulonephritis (MPGN), each discovered in 2/23 (8.7%) patients in our study.

The spectrum of NDRD in mixed lesions (NDRD superimposed on DN), revealed FSGS and Thrombotic microangiopathy as the most common renal histopathological pattern, superimposed on DN, was present in 2/7 (28.57%) patients. IgA, ATI, and AIN were present in 1/7 (14.25%) patient.

The mean age in the NDRD and isolated DN groups was 51±7.6 and 53±7.9 years, respectively ($P = 0.81$). The mean duration of diabetes in NDRD and isolated DN groups was 4.4±3.6 and 7.0±2.9 years, respectively ($P = 0.04$). The mean 24-h proteinuria in NDRD and isolated DN groups was 4.0±3.5 and 5.8±4.5 g, respectively ($P = 0.16$). The mean HbA1c in NDRD and isolated DN groups was 8.1±1.5 and 8.1±0.3%, respectively ($P = 0.16$).

Non-diabetic renal disease was present in 21/23 (91.3%) patients without diabetic retinopathy ($P = 0.016$).

Nephrotic-range proteinuria was present in 10/23 (43.5%) patients with NDRD (P = 0.26). Male accounted for 15/23 (65.2%) of patients with NDRD (P = 0.22). Microhematuria was present in 12/23 (54.2%) patients with NDRD (P = 0.72). A rapid decline in renal functions was observed in 14/23 (60.9%) patients with NDRD (P = 0.71). Hypertension was present in 13/23 (56.5%) patients with NDRD (P = 0.7). Neuropathy was absent in 17/23 (73.9%) patients with NDRD (P = 0.44). The results are summarized in Tables 1–6.

Discussion

The prevalence of NDRD in T2DM patients with kidney injury as confirmed by kidney biopsy fluctuates between 12.3% and 69% (6, 7), depending on ethnic populations and indications for renal biopsy. The factors predicting NDRD in diabetic patients include the absence of diabetic retinopathy, rapid decline of renal functioning, abrupt onset of nephrotic syndrome, and presence of active urinary sediment (8–10). The most common reason for biopsy in our study was proteinuria not matching to the usual course of T2DM, accounting for 87.8% (29/33), followed by proteinuria without diabetic retinopathy in 75.7% (25/33), and unexplained abrupt decline in renal functioning not matching to the usual course of diabetic nephropathy in 63.6% (21/33) patients. The least common indication of renal biopsy in our patients was active urinary sediment, in 1/33 patients. Most of the patients had more than one reason for the biopsy.

In our study, 16/33 (48.5%) patients had isolated NDRD lesions. Isolated DN was present in 10/33 (30.3%) and mixed lesions (NDRD superimposed on DN) were present in

Table 1: Clinical profile of study patients.

Clinical profile		Frequency	Percentage
Hematuria	Present	18	54.5
	Absent	15	45.5
Proteinuria	<3.5 g/24 h	15	45.5
	≥3.5 g/24 h	17	51.5
	Absent	01	03
Diabetic retinopathy	Present	07	21.2
	Absent	26	78.8
Neuropathy	Present	10	30.3
	Absent	23	69.7
Renal function	Stable	12	36.4
	Abrupt decline	21	63.6
Hypertension	Present	20	60.6
	Absent	13	39.4
HbA1C level	<7%	0	0.0
	7–8%	25	75.8
	>8%	08	24.2

HbA1c: hemoglobin A1C test.

Table 2: Pattern of NDRD with or without associated DN.

NDRD	Frequency	Percentage
FSGS	06	26.1
IgA nephropathy	07	30.4
TMA	04	17.4
ATN	02	8.7
MPGN	02	8.7
Focal necrotizing and crescentic glomerulonephritis (FNCGN)	01	4.3
AIN	01	4.3

NDRD: non-diabetic renal disease; IgA: immunoglobulin A; FSGS: focal segmental glomerulosclerosis; TMA: thrombotic microangiopathy; ATN: acute tubular necrosis; MPGN: membranoproliferative glomerulonephritis; AIN: acute interstitial nephritis.

Table 3: Spectrum of isolated NDRD lesions in T2DM.

Spectrum of NDRD	Frequency	Percentage
IgA nephropathy	6	37.5
FSGS	4	25
TMA	2	12.5
ATN	1	6.3
MPGN	2	12.5
Focal necrotizing and crescentic glomerulonephritis (FNCGN)	1	6.3

NDRD: non-diabetic renal disease; IgA: immunoglobulin A; FSGS: focal segmental glomerulosclerosis; TMA: thrombotic microangiopathy; ATN: acute tubular necrosis; MPGN: membranoproliferative glomerulonephritis.

Table 4: Spectrum of NDRD in mixed lesions.

Spectrum of NDRD	Frequency	Percentage
FSGS	2	28.57
TMA	2	28.57
IgA nephropathy	1	14.28
ATN	1	14.28
AIN	1	14.28

NDRD: non-diabetic renal disease; IgA: immunoglobulin A; FSGS: focal segmental glomerulosclerosis; TMA: thrombotic microangiopathy; ATN: acute tubular necrosis; MPGN: membranoproliferative glomerulonephritis; AIN: acute interstitial nephritis.

7/33 (21.2%) patients. Overall NDRD lesions with or without DN were present in 23/33 (69.7%) of T2DM patients. Prasad et al., in a series of biopsies performed in 583 patients demonstrated that NDRD and mixed lesions were discovered in 49% and 20% of patients, respectively, similar to our results (11). These findings suggested that the index of suspicion for NDRD should be high. Given the widespread use of sodium-glucose cotransporter-2 (SGLT2) inhibitors (gliflozins or flozins), it is potentially high that the incidence of NDRD could rise in the future. The most common NDRD lesion with or without associated DN in our study was IgA nephropathy, present in 7/23 (30.4%) patients, followed by FSGS in 6/23 (26.1%) patients. Zeng et al. reported IgA nephropathy as the most common NDRD in 28.3% patients (12). The other less frequent lesion in our study

Table 5: Relationship of NDRD and Isolated DN across various parameters.

Parameter		NDRD [n = 23]		Isolated DN [n = 10]		P-value
		N	%	N	%	
Gender	Male	15	65.2	09	90	0.22
	Female	08	34.8	01	10	
Hematuria	Present	12	52.2	6	60	0.72
	Absent	11	47.8	4	40	
Proteinuria	< 3.5 g/24 h	12	54.2	3	30	0.26
	≥3.5 g/24 h	10	43.5	7	70	
	Absent	01	4.3	0	0	
HbA1c	≤7%	05	22	0	0	0.29
	>7%	18	78	10	100	
Diabetic retinopathy	Present	02	8.7	5	50	0.016*
	Absent	21	91.3	5	50	
Neuropathy	Present	06	26.1	4	40	0.44
	Absent	17	73.9	6	60	
Renal function	Stable	09	39.1	3	30	0.71
	Abrupt decline	14	60.9	7	70	
Hypertension	Present	13	56.5	7	70	0.70
	Absent	10	43.5	3	30	
Duration	<5 years	14	60.9	02		0.057
	≥ 5 years	09	39.1	08		

NDRD: non-diabetic renal disease; DN: diabetic nephropathy; HbA1c: hemoglobin A1C test.

Table 6: Relationship of NDRD and isolated DN as per gender, duration of diabetes, proteinuria and blood sugar control.

Characteristics	NDRD	Isolated DN	P-value
Age (years)	51.8±7.6	53±7.9	0.81
Duration of diabetes (years)	4.4±3.6	7.0± 2.9	0.04
Proteinuria (g)	4.0±3.5	5.8±34.5	0.16
HbA1c (%)	8.1±1.5	8.1±0.3	0.16

NDRD: non-diabetic renal disease; DN: diabetic nephropathy; HbA1c: hemoglobin A1C test.

was thrombotic microangiopathy (TMA), present in 04/23 (17.4%) patients. The pattern of biopsy-established renal disease in diabetic patients depends on the usual prevalence of renal disease according to the geographical area and ethnic characteristics of the study population.

In our study, the mean duration of diabetes in NDRD and isolated DN groups was 4.4±3.6 and 7.0±2.9 years, respectively (P = 0.04). Similar results were shown by Kritmetapak et al. (13) and Chang et al. (14) suggesting a shorter duration of diabetes as a predictive factor for NDRD. The mean duration of diabetes in our study group was shorter than the previously reported period, probably because of decreased awareness and poor access to healthcare facilities, leading to delay in the diagnosis. The mean 24-h proteinuria was higher in patients with biopsy-established isolated DN versus patients with NDRD. However, the difference was not statistically significant. Similar results were reported by Erdogmus et al. (15). There was no significant difference in the incidence of nephrotic-range proteinuria between NDRD and DN groups. In our study, there was no difference in distribution in NDRD versus DN groups in terms of age, gender, presence or absence of hypertension, and HbA1c. Similar results were reported by Sharma et al. in a single-center study conducted in Eastern India (16). Lack of relationship with glycemic control suggested additional pathophysiological mechanisms for NDRD. Microscopic hematuria was observed in 60% patients with DN, which was similar to other studies (17). The association between diabetic nephropathy and diabetic retinopathy is usually recognized (18–23). In our study, 21/23 (91.3%) patients without diabetic retinopathy had biopsy-established NDRD (P = 0.016). Absence of diabetic retinopathy had a negative predictive value of 91.3% for ruling out DN.

This study had a limitation. It was performed at a single center, so applying its results to the populations of other countries and regions would produce results that need to be interpreted cautiously because of the restrictive patient population of this study.

Conclusions

Our data demonstrated that more than half of patients with type 2 diabetes presenting with atypical features of DN were discovered having NDRD upon renal biopsy. The absence of diabetic retinopathy and a shorter duration of diabetes were indicators of NDRD. IgA nephropathy was the most prevalent renal pathology in patients with type 2 diabetes with isolated NDRD. Clinicians must consider kidney biopsy liberally for diagnosis in such patients, especially in cases where the etiology of kidney disease is unclear.

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Conflict of Interest

The authors declared no conflict of interest.

Author Contributions

Aabid Hussain and Rayees Yousuf Sheikh analyzed and interpreted patient data regarding the indication of kidney biopsies. Manzoor Ahmad Parry, Rayees Yousuf Sheikh, and Aabid Hussain collected biopsy reports and were major contributors in writing the manuscript. Murtaza Rashid Pala helped in analyzing the data and writing the manuscript. All authors read and approved the final manuscript.

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