

# Non-diabetic Renal Diseases in Patients with Diabetes Mellitus Clinicopathological Correlation

## Abstract

**Background and Aims:** Non-diabetic renal diseases (NDRDs) form an important part of disease manifestations in patients with diabetes. **Methods:** This hospital-based prospective study was conducted to analyze incidence and spectrum of NDRDs in patients with diabetes with or without diabetic nephropathy (DN), effect of early specific interventions on outcome, and renal-retinal relationship in type 1 and type 2 diabetes mellitus with nephropathy. 44 Patients with T2DM with the clinical suspicion of NDRD were subjected to renal biopsy. Renal biopsies were performed by using an automated biopsy gun. Tissue was processed for Light microscopy-LM and Immunofluorescence-IF. Electron Microscopy was done as and when required by reprocessing the tissue embedded in paraffin for LM. Biopsies were reported by one experienced renal pathologist. **Results:** Renal histopathology revealed that of 44 enrolled patients with clinically suspected NDRD, 61.4% had isolated NDRD, 13.6% had NDRD superimposed on DN, and 25% had isolated DN. The most common NDRDs were minimal change disease (19.2%) and DN + chronic pyelonephritis (33.3%) in patients with isolated NDRD, and NDRD superimposed on DN, respectively. In the DN group, no patient had proliferative diabetic retinopathy (PDR) or hypertensive retinopathy, 45.5% had nonproliferative diabetic retinopathy (NPDR) and 54.5% had no microangiopathy in retina. In the NDRD group, 9.1% each had PDR and hypertensive retinopathy, 36.4% had NPDR and 45.4% had no microangiopathy in retina. No patient in the DN group and 72.7% in the NDRD group received specific treatment. In hospital, dialysis support was provided to 27.3% and 21.2% of patients in the DN and NDRD groups, respectively. In the DN group, 72.7% of patients improved with conservative therapy, 18.2% were dependent on dialysis when discharged. One patient died during treatment. In the NDRD group, 78.8% showed recovery in the renal function and clinical improvement, 15.1% were dialysis dependent when discharged. Two patients died during treatment. **Conclusion:** Accurate diagnosis of underlying NDRD by kidney biopsy facilitates initiation of specific therapy, which may lead to clinical improvement in significant number of patients.

**Keywords:** Clinicopathological correlation, Non-diabetic renal diseases, renal biopsy

## Introduction

Diabetic nephropathy (DN) is the leading cause of end stage renal disease worldwide. Despite this, most patients with diabetes mellitus (DM) are not formally evaluated with a renal biopsy. Kidney biopsy can differentiate DN from non-diabetic renal diseases (NDRD), but it is invasive, not suitable for every patient, associated with serious complications (though rare) and other issues like availability and reluctance, especially more in developing countries like India. The diagnosis is mostly made on clinical grounds. Proteinuria or renal failure in diabetic patients is usually interpreted as a clinical manifestation of DN. However,

not all diabetic subjects with proteinuria or renal failure have DN. Non-diabetic renal diseases, though rarer than DN, have been seen to cause proteinuria or renal failure in diabetics.<sup>[1]</sup> The occurrence of NDRD in type 1 diabetes mellitus (T1DM) is rare compared with those with type 2 diabetes mellitus (T2DM). It has been well demonstrated that renal disease in patients suffering from T1DM for over 10 years is usually the result of DN, as proven histologically in >95% of these patients.<sup>[2-4]</sup>

It is usually believed that DN is hard to reverse and further management aims at prevention of progression of disease. But some NDRDs such as minimal change disease, immunoglobulin A (IgA) nephropathy and membranous nephropathy are often treatable and even curable. The

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**Puneet Arora,  
Arpita  
Roychaudhury<sup>1</sup>,  
Rajendra Pandey<sup>1</sup>**

Department of  
Nephrology, Max Super  
Speciality Hospital, Dehradun,  
Uttarakhand, <sup>1</sup>Department of  
Nephrology, Institute of Post  
Graduate Medical Education  
and Research, Kolkata,  
West Bengal, India

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**Address for correspondence:**  
Dr. Puneet Arora,  
Department of Nephrology,  
Max Super Speciality  
Hospital, Dehradun - 248 001,  
Uttarakhand, India.  
E-mail: puneetarora2412@  
gmail.com

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therapy and prognosis of DN and NDRD are quite different and the differential diagnosis is of considerable importance. Hence, it is necessary to suspect, diagnose and treat the concurrent glomerular diseases or the unrelated renal disorders that are superimposed on DN because of the prognostic and therapeutic implications.<sup>[5]</sup>

Non-diabetic renal diseases are an important cause of renal involvement in diabetics but few research works focusing on this entity have been carried out. So, we carried out this study to assess the frequency and spectrum of NDRD in diabetic population and correlate differences in clinical and laboratory parameters between NDRD and DN groups.

## Methods

This hospital-based prospective study was conducted between May 2011 and July 2012 at the Department of Nephrology, Institute of Post Graduate Medical Education and Research (IPGMER), Kolkata, India. Institutional ethics approval was obtained to conduct this study. 44 patients with T2DM were enrolled in this study.

## Objectives

This study was conducted to analyse the following objectives: Prevalence of NDRDs in patients with diabetes mellitus (DM), spectrum of NDRDs in patients with DM, effect of early specific interventions on outcome, and renal-retinal relationship in T1DM and T2DM with nephropathy.

## Inclusion/Exclusion criteria

Patients with T2DM with the clinical suspicion of NDRD were recruited in this study. These patients were subjected to renal biopsy and any of the below mentioned criteria singly or in combination was considered as probable evidence of NDRD: haematuria (RBC >5/hpf, RBC casts); sudden increase in serum creatinine by >2 mg/dL; sudden onset nephrotic syndrome; absence of diabetic retinopathy (DR); duration of DM <5 years; massive proteinuria (nephrotic range) with normal renal functions; significant renal insufficiency (serum creatinine >2 mg/dL) with normal or insignificant proteinuria (<500 mg/dL). Renal biopsy was performed by using an automated biopsy gun. Diabetic nephropathy was diagnosed by the presence of mesangial expansion, with or without the nodular Kimmelsteil-Wilson formation, basement membrane thickening, fibrin caps or capsular drops. Vascular changes of DN included arteriolar hyalinosis, medial hyperplasia of smaller arteries and intimal sclerosis of larger arteries. All patients provided informed consent. Patient were excluded if they met any of the following criteria: had urinary tract infection, calculus renal disease, obstructive uropathy, renal tumours, bleeding diathesis, bilateral contracted kidneys, or single contracted kidney and who refused consent for the study. The outcomes were analysed on

the basis of reduction of proteinuria to less than 50% or more, improvement or stabilization of renal function tests [whether serum creatinine reached their baseline or not] and dialysis independency.

## Statistical analysis

Different values were represented as percentage or mean values wherever required. Statistical analysis was done by statistical software SPSS. For association, the Chi-square and 't' test were performed and 'p' value was calculated to show the significance of observation.

## Results

### Baseline characteristics of patients at the time of renal biopsy

Renal histopathology revealed that of 44 enrolled patients with clinically suspected NDRD, 27 (61.4%) had isolated NDRD, 6 (13.6%) had NDRD superimposed on DN, and 11 (25%) had isolated DN. Patients with NDRD superimposed on DN were clubbed with isolated NDRD and the overall incidence of NDRD was in 33 patients (75%). The mean age ( $\pm$  SD) of patients was comparable in both DN and NDRD groups ( $52 \pm 11.04$  and  $50 \pm 11.15$  years, respectively) with no statistically significant difference ( $p = 0.61$ ). The number of male patients was higher in both groups (9/11 and 19/33, respectively), however, the between-group difference was not statistically significant ( $p = 0.28$ ). Overall, the majority of patients were between 40-60 years of age (65.9%).

The duration of diabetes (mean  $\pm$  SD) was significantly shorter in NDRD group compared to DN group ( $6 \pm 4.6$  years vs.  $10.7 \pm 5.85$  years;  $P = 0.02$ ). The between-group difference in the age of onset of DM was not statistically significant (DN:  $41.3 \pm 8.7$  years; NDRD:  $43.8 \pm 9.2$  years;  $P = 0.43$ ). Prevalence of hypertension was significantly lower in the NDRD group compared with the DN group (63.6% vs. 100%;  $P = 0.02$ ). The incidence of DR was similar in both treatment groups (45.5% in both groups). In the DN group, no patient had PDR or hypertensive retinopathy, 45.5% had NPDR and the rest 54.5% patients had no microangiopathy in retina. In the NDRD group, 9.1% of patients had proliferative diabetic retinopathy, 36.4% patients had NPDR, while 9.1% had hypertensive retinopathy. The rest of the 45.4% patients had no microangiopathy in retina.

The mean percent (SD) haemoglobin A1C (HbA1C) was 7.42% (1.25) in the DN group and 6.88% (0.81) in the NDRD group. The between-group difference was not statistically significant ( $p = 0.1$ ). Likewise, for all other laboratory parameters including 24-hour proteinuria, haemoglobin, serum creatinine, and serum albumin, the between-group difference was not statistically significant [Tables 1 and 2].

**Syndromic diagnosis at presentation**

All the patients who were subjected to renal biopsy were first categorized into 8 syndromes on the basis of their clinical presentation. In the DN group, most of the patients (≥15%) had chronic kidney disease (CKD; 63.6%) and nephrotic-nephritic syndrome (18.2%). In the NDRD group, most of the patients had nephrotic syndrome (21.2%) and nephrotic-nephritic (15.2%) syndrome. The between-group difference in number of patients with any syndrome was not statistically significant except the number of patients with nephrotic-nephritic syndrome ( $P = 0.04$ ; Table 3).

**Criteria to perform biopsy**

Most of the patients met more than one criterion considered atypical for a diabetic patient to have DN. The most common criteria (≥15% in both groups) for which diabetic patients underwent renal biopsy were absence of DR (54.5% in both groups) followed by haematuria (27.3% and 54.5% in the DN and NDRD groups, respectively), sudden rise in serum creatinine >2 mg/dL (27.3% and

42.4%, respectively) and duration of diabetes for less than 5 years (18.2% and 42.4% in both groups; Table 4).

**Isolated NDRD and NDRD superimposed on DN spectrum**

Among patients having isolated NDRD, the most common NDRDs (≥5% of patients) were minimal change disease (19.2%) followed by lupus nephritis (11.5%), post-infectious GN (7.7%), antineutrophil cytoplasmic antibody (+) crescentic glomerulonephritis (7.7%), chronic interstitial nephritis (7.7%), membranoproliferative glomerulonephritis (7.7%), IgA nephropathy (7.7%), and HIV nephropathy (7.7%; Figure 1). Among patients with NDRD superimposed on DN, 33.3% of patients had DN + chronic pyelonephritis and 16.7% of patients each had DN + acute tubular necrosis, DN + kappa light-chain deposition disease, DN + thrombotic microangiopathy and DN + lupus nephritis Class 3 [Figure 2].

**Treatment and outcomes**

Specific treatment (immunosuppression, plasmapheresis etc.) was given to none of the patients in the DN group and 72.7% patients in the NDRD group. Dialysis support was provided to 27.3% in the DN group, and 21.2% in the NDRD group, during their hospital stay. In the DN group, 72.7% of patients improved with conservative therapy, 18.2% patients were dependent on dialysis at the time of discharge from hospital and 1 patient (9.1%) died during treatment, whereas in the NDRD group, 78.8% of patients showed recovery in the renal function and clinical improvement with appropriate specific treatment, 15.1% patients were dialysis dependent at the time of discharge from hospital and 2 patients (6.1%) died during treatment.

**Discussion and Conclusions**

This prospective hospital-based study was designed to highlight the prevalence and spectrum of NDRD in patients with DM with the intention of implementing more insight into the disease. The study also assessed the relationship of various clinical and laboratory parameters with development

**Table 1: Baseline characteristics of patients at renal biopsy**

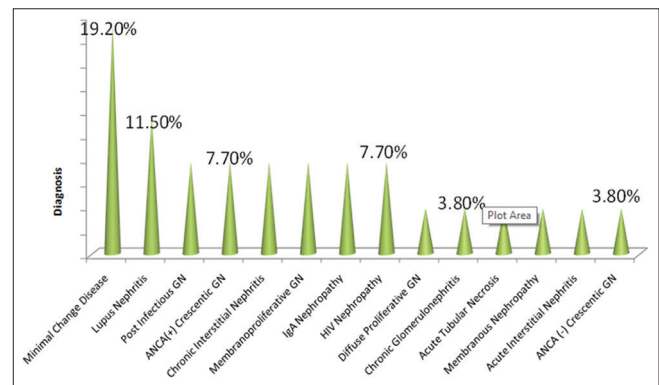
Parameter	DN n=11	NDRD n=33	P
<b>Age and gender</b>			
Age (mean±SD), y	52±11.04	50±11.15	0.61
Male	9	19	0.28
Female	2	14	
Male: Female ratio	4.5:1	1.4:1	
<b>Diabetes mellitus status</b>			
Duration of DM (mean±SD), y	10.7±5.85	6±4.6	0.02
Age of onset of DM (mean±SD), y	41.3±8.7	43.8±9.2	0.43
Hypertension, n (%)	11 (100)	21 (63.6)	0.02
DR, n (%)	5 (45.5)	15 (45.5)	1
<b>Laboratory Parameters</b>			
24 hrs urinary protein, g	4.97±3.2	3.28±2.29	0.12
Haemoglobin, g/dL	8.27±1.42	9.22±2.15	0.18
Serum creatinine, mg/dL	3.79±3.11	3.47±2.92	0.76
Serum albumin, mg/dL	3.53±0.66	3.15±0.65	0.11
HbA1C (%± SD)	7.42±1.25	6.88±0.81	0.1

DM=Diabetes mellitus; DN=Diabetic nephropathy; DR=Diabetic retinopathy HbA1C=Hemoglobin A1c; NDRD=Non-diabetic renal disease; SD=Standard deviation

**Table 2: Age distribution of patients**

Age Group	n (%)		
	DN n=11	NDRD n=33	Total n=44
30-39	4 (9.1)	3 (6.8)	7 (15.9)
40-49	9 (20.5)	5 (11.3)	14 (31.8)
50-59	9 (20.5)	6 (13.6)	15 (34.1)
60-69	3 (6.8)	2 (4.6)	5 (11.4)
70-79	3 (6.8)	0	3 (6.8)

DN=Diabetic nephropathy; NDRD=Non-diabetic renal disease



**Figure 1: Isolated Non-diabetic renal diseases spectrum. ANCA=Antineutrophil cytoplasmic antibodies; GN = Glomerulonephritis; HIV = Human immune deficiency virus; IgA = Immunoglobulin A**

of NDRD. The effect of early specific intervention on outcome of the disease was finally evaluated.

The study aimed to include patients with T1DM and T2DM where there was clinical suspicion of NDRD and both types of patients were screened. But clinical suspicion of NDRD was found only in T2DM patients. This is in accordance with published literature where the occurrence of NDRD has been found to be rarer in patients with T1DM than in patients with T2DM. It has been well demonstrated that renal disease in patients suffering from T1DM for over 10 years is usually the result of DN, as proven histologically in >95% of these patients.<sup>[2-4]</sup> In fact, when biopsied for research purposes only and not for clinical indications, fewer than 1% of T1 DM patients with 10 or

more years of diabetes and fewer than 4% of those with proteinuria and long diabetes duration will have conditions other than or in addition to DN.<sup>[5]</sup>

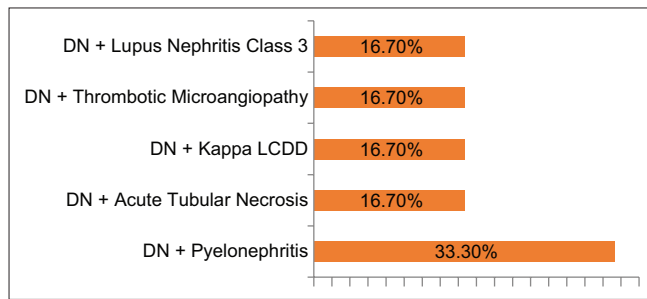
Of all the diabetics observed, clinical diagnosis of NDRD was made in 44 patients who were subsequently biopsied. The incidence of isolated NDRD in selected diabetic patients was 61.4% and when patients with NDRD superimposed on DN (13.6%) were clubbed with isolated NDRD, the overall incidence of NDRD rose to 75% (33 patients). The true incidence of NDRD in T2DM patients cannot be deduced from this study as this would require biopsies in all diabetic patients with nephropathy.

Although the exact incidence of NDRD is not known, the reported frequency of NDRD varies widely in published literature.<sup>[6,7]</sup> Our incidence of isolated NDRD (61.4%) is in accordance with figures reported in various studies from India and other parts of the world (42.5-64%).<sup>[8-10]</sup> In a study, reported incidence of NDRD was very low (12.3%).<sup>[11]</sup> These discrepancies of variable frequencies is probably due to differences in the population being studied, different biopsy policies, geographic and ethnic factors, and lack of uniform criteria for biopsy interpretation.

For other baseline characteristics like age, sex, degree of anaemia, azotaemia, proteinuria, age at onset of DM, serum albumin and HbA1C levels, between-group difference was not statistically significant and were not found to be differential indicators of NDRD in this study.

This study found that duration of diabetes (mean years ± SD) was significantly (p = 0.02) shorter in the NDRD group (6 ± 4.6) than in the DN group (10.7 ± 5.85). Previous studies also concluded that shorter duration of diabetes was associated with NDRD.<sup>[10,12]</sup> Thus, shorter duration of diabetes could be a predictor of underlying NDRD.

Prevalence of hypertension was significantly (p = 0.02) more in the DN group than in the NDRD group in this study. Similar observation was made in other studies.<sup>[9,13]</sup> However, prevalence of hypertension was similar in two groups in some studies.<sup>[10,12]</sup> High prevalence of hypertension in the DN group can be explained by the fact that hypertension itself is responsible for progression of DN.



**Figure 2: Non-diabetic renal diseases superimposed on diabetic retinopathy spectrum. DN = Diabetic retinopathy; LCDD = Light-chain deposition disease**

**Table 3: The proportion of Patients with Syndromic Diagnosis at Presentation**

Syndrome	n (%)		
	DN n=11	NDRD n=33	P
Asymptomatic urinary abnormalities	0	3 (9.1)	0.56
Acute nephritic syndrome	1 (9.1)	4 (12.1)	1
Nephrotic syndrome	1 (9.1)	7 (21.2)	0.65
Nephrotic-nephritic syndrome	2 (18.2)	5 (15.2)	1
Acute kidney injury	0	4 (12.1)	0.55
Rapidly progressive glomerulonephritis	0	4 (12.1)	0.55
CKD	7 (63.6)	5 (15.2)	0.04
End stage renal disease	0	1 (3)	1

CKD=Chronic kidney disease; DN=Diabetic nephropathy; NDRD=Non-diabetic renal disease

**Table 4: The Proportion of Patients who Met Criteria to Perform Renal Biopsy**

Criteria	n (%)		
	DN n=11	NDRD n=33	P
Haematuria (micro/macrosopic)	3 (27.3)	18 (54.5)	0.17
Sudden rise in serum creatinine >2 mg/dL	3 (27.3)	14 (42.4)	0.48
Sudden onset nephrotic syndrome	1 (9.1)	5 (15.2)	1
Absent DR	6 (54.5)	18 (54.5)	1
Duration of diabetes <5 years	2 (18.2)	14 (42.4)	0.28
Massive proteinuria with normal renal function	0	5 (15.2)	0.31
Significant renal insufficiency with normal or insignificant proteinuria	2 (18.2)	0	0.06

DN=Diabetic nephropathy; DR=Diabetic retinopathy; NDRD=Non-diabetic renal disease

Absence of DR is said to be one of the important predictors of NDRD. In this study, DR was absent in equal percentage (54.5%) in patients in both DN and NDRD groups. Controversy exists with regard to absence of DR as an indicator for NDRD. According to a study, absence of DR is a predictor of NDRD,<sup>[14]</sup> However, others considered it as a poor indicator since the chance of DN and NDRD was 50%.<sup>[15]</sup> Therefore, the presence or absence of DR alone does not prove to be significant enough in distinguishing between DN and NDRD in T2DM.

In this study, before renal biopsy, all patients were categorized into eight syndromes based on their clinical presentations. Only the presence of CKD was statistically significantly more in the DN group than in the NDRD group. The reason for biopsying patients with CKD presentation was their atypical clinical features like active urinary sediments, duration of diabetes <5 years etc., The wide and variable spectrums of clinical presentation have been reported in literature.<sup>[9,16,17]</sup> Thus, no clinical presentation is a strong predictor of NDRD other than CKD which is more suggestive of underlying DN.

On the basis of atypical clinical presentations, certain clinical and laboratory criteria were set which merit diabetic patients to undergo renal biopsy to look for NDRD or NDRD superimposed on DN. Between-group difference for any criteria was not statistically significant. Our results favour the results of many reported studies which deny any clinical and laboratory correlation that predict NDRD in diabetic population.<sup>[16,18,19]</sup> But some other studies oppose these results.<sup>[13,18]</sup> Thus, no clinical or laboratory marker strongly predict NDRD in diabetic patients and renal biopsy is the only investigation presently available to make a definitive diagnosis.

Histologically, NDRD comprised a heterogeneous group in the present study. We further classified the spectrum into those with isolated NDRD and those with NDRD superimposed on DN. In the isolated NDRD group, the most common NDRD was minimal change disease (19.2%) which is in accordance with the results of another Indian study.<sup>[9]</sup> In the NDRD superimposed on DN group, DN + chronic pyelonephritis (33.3%) was most common. From a review of the relevant literature, most of which consist of isolated case reports, it appears that a wide spectrum of NDRD could occur in patients with T2DM.<sup>[20,21]</sup> Quite contradicting to the present series, some studies reported IgA nephropathy as the commonest NDRD.<sup>[13,18]</sup> It is to be noted that IgA nephropathy is the most common primary glomerular disease in these countries. Incidence of IgA nephropathy of the total primary glomerular disease in an Indian study<sup>[22]</sup> was only 6%. Hence, its frequency in the NDRD group is also low. These results suggest that prevalence of different categories of biopsy proven renal disease in diabetic patients depends on the usual prevalence of renal disease in general population according

to geographical area and ethnic characteristics and NDRD is merely coincidental in T2DM.

In the DN group, 72.7% of patients improved with conservative therapy, 18.2% patients were dependent on dialysis at the time of discharge from hospital whereas in the NDRD group, 78.8% of patients showed recovery in the renal function and clinical improvement with appropriate specific treatment, 15.1% patients were dialysis dependent at the time of discharge. Similar results were reported in a study in which 43% cases showed recovery with specific treatment.<sup>[11]</sup> In the NDRD group, 2 patients died due to therapy related complications (one crescentic glomerulonephritis patient died due to sepsis after administering cyclophosphamide, while another patient suffering from thrombotic microangiopathy also died due to sepsis after initiating plasmapheresis). Rest of the NDRD patients (4 patients) were dialysis dependent at the time of discharge. In the DN group, one patient died due to myocardial infarction while undergoing haemodialysis.

The precise diagnosis of various NDRDs has obvious therapeutic and prognostic implications as many NDRDs (eg, minimal change disease, membranous nephropathy, IgA nephropathy) are often treatable and even curable with appropriate management. Even when a coexistent NDRD does not have a specific treatment, the information obtained by uncovering the histopathologic lesion by kidney biopsy helps in prognostication.

Thus, as seen in this study, accurate diagnosis by kidney biopsy and appropriate specific treatment depending on the coexistent NDRD leads to clinical improvement in significant number of patients.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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