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# Non-Diabetic Renal Disease in Patients with Type 2 Diabetes Mellitus–Experience from A Tertiary Care Hospital

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## Abstract

**Introduction:** Diabetic nephropathy (DN) is a devastating complication of diabetes mellitus (DM) and leading cause of end stage renal disease (ESRD) globally. Spectrum of nondiabetic renal disease (NDRD) in Type-2 diabetes mellitus (T2DM) varies widely with evolving epidemiology and treatment strategies.

**Aim:** To study the clinical features, laboratory findings, and histological features in the cases of NDRD diagnosed by renal biopsy in patients with type 2 DM.

**Material and Methods:** We conducted a single centre retrospective study including patients with diabetes mellitus type 2 with clinically suspected NDRD who underwent renal biopsy from January 2018 to June 2023. Biopsy findings were categorized into three groups, Group-I (isolated NDRD); Group-II (NDRD superimposed on underlying DN); and Group-III (isolated DN).

**Results:** Out of 96 diabetic patients (65 cases- 67.7% males and 31 cases- 32.3% females), 43 (44.79%) patients were of Group-I (isolated NDRD), 27 (28.13%) of Group-II (NDRD superimposed on underlying DN), and 26 (27.08%) of Group-III (isolated DN). The mean age (in years) was 57.7 ± 10.13, 53.15 ±10.48, and 54.15 ± 9.70 respectively in Group-I, II, and III. The mean duration of diabetes was 5.62 ± 4.99, 6.11 ± 3.72, 7.08 ± 5.20 years in Groups I, II and III, respectively. Diabetic retinopathy (DR) was significantly seen in Group-III DN (57.69%) followed by Group -II (29.62%) and absence of DR in Group-I (p=0.005). HbA1C level was significantly higher in Group-II (7.8 ±2.04 %) and Group-III (7.4% ±1.57 %) in than Group-I (6.8% ±1.58 %) (p=0.003).

Nephrotic syndrome (NS) was the most frequent clinical manifestation in all groups. The most common histological types of NDRD were membranous nephropathy 8 (18.60%) cases followed by focal segmental glomerulosclerosis 5 (11.63%) cases, pauci-immune crescentic glomerulonephritis 5 (11.63%) cases and acute on chronic tubulointerstitial nephritis 5 (11.63%) cases. The most common histological types of coexisting NDRD and diabetic nephropathy were acute on chronic tubulointerstitial nephritis 11 (40.74%) cases followed by post infectious glomerulonephritis 5 (18.52%) cases.

**Conclusion:** NDRD was diagnosed by renal biopsy in 70 (72.92%) patients out of 96 patients with type 2 DM, which confirms renal biopsy is gold standard for diagnosing NDRD in patients with T2D in patients.

**Keyword:** Diabetic nephropathy (DN), non-diabetic renal disease (NDRD), Renal biopsy, Type 2 diabetes mellitus

## Introduction

Diabetic nephropathy (DN) is a devastating complication of diabetes mellitus (DM) and leading cause of end stage renal disease (ESRD) globally.[1] Apart from DN, they can also develop other renal diseases, pathologically unrelated to diabetes and known as non-diabetic renal disease (NDRD). About 45-80% of diabetes patients with renal involvement undergoing renal biopsy are diagnosed to have non-diabetic renal disease (NDRD).[2] Renal injury in patients with type 2 diabetes mellitus can reveal features of either DN or NDRD or a combination of both.[3] The treatment and prognosis of DN and NDRD are quite different and the differential diagnosis is of considerable importance as NDRD are often treatable and even curable.[4] While DN is hard to reverse and further management aims at prevention of progression of disease.[5] There is a wide spectrum of NDRD in type 2 DM due to different clinical features, variable selection criteria for renal biopsy, and epidemiological differences.[4] The clinical distinction between NDRD and DN might be challenging. Renal biopsies being the gold standard to distinguish the two.[6] The indication for renal biopsy in patients of type 2 Diabetes Mellitus included sudden onset of nephrotic syndrome, persistent hematuria, active urinary sediment, rapidly progressive renal failure (RPRF), proteinuria in the absence of diabetic retinopathy (DR), short duration of diabetes, unexplained acute renal failure and immunological abnormalities.[7,8] We carried out this single centre retrospective study to characterise the clinical, laboratory, and histological features of NDRD in type-2 DM patients in our institute.

## Aim

To study the clinical features, laboratory findings, and histological features in the cases of NDRD diagnosed by renal biopsy in patients with type 2 DM.

## Material and Methods

We retrospectively analysed renal biopsies of patients with type-2 DM with clinically suspected NDRD from January 2018 to June 2023. Patients with diabetes mellitus type 2 who underwent renal biopsy presenting with nephrotic syndrome, active urinary sediment, unexplained acute renal failure and rapidly progressive renal failure were included in this study. Incomplete clinical or laboratory data or with inadequate samples in renal biopsy and type 1 diabetes were excluded from the analysis. All biopsies were performed by nephrologists under ultrasonographic guidance using 18-gauge renal biopsy needle. All biopsy samples were processed for light microscopy, immunofluorescence and electron microscopy if indicated. Based on biopsy findings and after confirming inclusion/ exclusion criteria, patients were categorized into three groups; Group-I: isolated

NDRD, Group-II: NDRD superimposed on underlying DN, and Group-III: isolated DN. Clinical details including age, sex, duration of diabetes, presence or absence of hypertension, presence or absence of diabetic retinopathy and indication for biopsy were recorded from our base records. The laboratory parameters included s. creatinine (mg/dL), HbA1C, urinalysis and degree of proteinuria either by 24-h urine collection or by spot urine protein to creatinine ratio. Serological studies included anti- nuclear antibody (ANA), anti-double stranded DNA (dsDNA), C-ANCA, P-ANCA, Anti PLA2R, complement C3 and C4 levels were performed in selected cases. The relation of histological features with clinical and laboratory findings in each group were noted, statistically analysed and comparison with other studies. Statistical analysis was performed using IBM Statistical Package for the Social Sciences for Windows version 21.0 (SPSS Inc., Chicago, IL, USA). Continuous data was expressed as mean ± SD and noncontinuous data in percentage and numerical values. Differences between groups were assessed by using the univariate chi-square test for categorical variables, unpaired t-test or ANOVA for continuous variables; P <0.05 was considered statistically significant.

**Results**

A total of 96 patients with type 2 diabetes who were suspected of having NDRD underwent renal biopsy from January 2018 to June 2023. Out of 96 diabetic patients (65- 67.7% males and 31- 32.3% females), 43 (44.79%) patients were of Group-I (isolated NDRD), 27 (28.13%) of Group-II (NDRD superimposed on underlying DN), and 26 (27.08%) of Group-III (isolated DN).

The mean age of the study population was 55.5 ± 10.12 years. The mean age (in years) was 57.7 ± 10.13, 53.15 ±10.48, and 54.15 ± 9.70 respectively in Group-I, II, and III. (Table1)

Nephrotic syndrome was the most frequent clinical manifestation in all groups. A total of 34 cases (35.41%) had nephrotic syndrome, 28 cases (29.17%) had acute renal failure, 24 cases (25%) had rapidly progressive renal failure (RPRF), 10 cases (10.42%) had active urinary sediment at presentation. (Table 2)

The mean duration of DM was 6.08 ± 4.65 years. The mean duration of diabetes was 5.62 ± 4.99, 6.11 ± 3.72, 7.08 ± 5.20 years in Groups I, II and III, respectively. Duration of DM was less in Group-I compared to Group-II and Group-III but the difference was not statistically significant.

Diabetic retinopathy was absent in Group-I, significantly higher (p=0.005) in Group-III with 15 cases (57.69%) and in Group-II with 8 cases (29.62%).

The mean percent HbA1C level was significantly higher (p=0.003) in Group-II (7.8 ± 2.04 %) and Group-III (7.4 ± 1.57 %) than Group-I (6.8 ± 1.58 %).

The prevalence of hypertension was comparable in all the groups. The presence of microscopic hematuria was similar in all three groups in our study. Microscopic hematuria was observed in 22 (51.16%) cases of Group-I and 14 (51.85%) of cases in Group-II, 11 (42.31%) cases of Group-III. Proteinuria was more in Group-I (4.00 ± 3.92 g) than Group-II (3.68 ± 3.35 g) and Group- III (3.01 ± 3.07 g); the difference was not statistically significant. In this study, patients with Group-I, Group-II and Group- III did not have any difference in serum creatinine levels. The mean ± SD of serum creatinine was observed 4.18 ± 2.69 mg/dL in Group-I, 4.78 ± 2.96 mg/dL in Group-II and 4.24 ± 3.06 mg/dL in Group-III. Low serum C3 and/or serum C4 was observed in 8 (18.60%) cases of Group-I, and 7 (25.93%) cases of Group-II. Positive Serum ANA/dsDNA levels was observed in 4 (9.30%) cases of Group-I, and 1 (3.70%) case of Group-II. Positive Serum C. ANCA was observed

in 2 (4.65%) cases of Group-I, and 1 (3.70%) case of Group-II. Positive Serum P. ANCA was observed in 3 (6.98%) cases of Group-I, and 1 (3.70%) case of Group-II. Positive Serum Ani PLA2R was observed in 3 (6.98%) cases of Group-I, and 1 (3.70%) case of Group-II. (Table 3)

The most common histological types of NDRD (Group-I) were membranous nephropathy 8 (18.60%) cases followed by focal segmental glomerulosclerosis 5 (11.63%) cases, pauci-immune crescentic glomerulonephritis 5 (11.63%) cases and acute on chronic tubulointerstitial nephritis 5 (11.63%) cases. Membranoproliferative glomerulonephritis (MPGN), Minimal change disease, Acute pyelonephritis, IgA Nephropathy, Postinfectious glomerulonephritis, Acute tubulointerstitial nephritis (ATIN), Cast Nephropathy, Acute on chronic thrombotic microangiopathy, Proliferative glomerulonephritis monoclonal deposits (PGNMID), Renal amyloidosis (AA type), Cryoglobulinemic glomerulonephritis were reported in 4 (9.30%), 4 (9.30%), 3 (6.98%), 2 (4.65%), 1 (2.33%), 1 (2.33%), 1 (2.33%), 1 (2.33%),1 (2.33%), 1 (2.33%) and 1 (2.33%) respectively. The most common histological types of coexisting NDRD and diabetic nephropathy (Group-II) were acute on chronic tubulointerstitial nephritis 11 (40.74%) cases followed by postinfectious glomerulonephritis 5 (18.52%) cases. Membranous nephropathy, Focal segmental glomerulosclerosis, Pauci-immune crescentic GN, Membranoproliferative glomerulonephritis, Acute tubulointerstitial nephritis, Cast Nephropathy, Acute on chronic thrombotic microangiopathy, C3 glomerulopathy were reported in 2 (7.41%),2 (7.41%), 2 (7.41%), 1 (3.70%), 1 (3.70%), 1 (3.70%), 1 (3.70%) and 1 (3.70%) respectively. (Table 4)

Table 1: Demographic data

| Characteristics | Total-(n=96) | NDRD (Group-I) (n = 43, 44.79%) | NDRD superimposed on underlying DN (Group-II) (n =27, 28.13%) | DN (Group-III) (n = 26, 27.08%) | P-value |
|---|---|---|---|---|---|
| Age in years (± SD) | 55.5 ± 10.12 | 57.7 ± 10.13 | 53.15 ± 10.48 | 54.15 ± 9.70 | .307 |
| Male | 65 (67.7%) | 26 (60.47%) | 18 (66.67%) | 21 (80.77%) | .219 |
| Female | 31 (32.3%) | 17 (39.53%) | 9 (33.33%) | 5 (19.23%) | |

Table 2: Indications for renal biopsy

| Indications | TOTAL (n=96) n=% | NDRD (Group-I) (n = 43) n=% | NDRD superimposed on underlying DN (Group-II) (n = 27) n=% | DN (Group-III) (n = 26) n=% | P-value |
|---|---|---|---|---|---|
| NS | 34 (35.41%) | 15 (34.88%) | 11 (40.74%) | 8 (30.77%) | 0.31 |
| Acute renal failure | 28 (29.17%) | 12 (27.91%) | 9 (33.33%) | 7(26.92%) | 0.45 |
| RPRF | 24 (25.00%) | 11 (25.58%) | 6 (22.22%) | 7 (26.92%) | 0.94 |
| Active urinary sediment | 10 (10.42%) | 5 (11.63%) | 1 (3.70%) | 4 (15.38%) | 0.124 |

Table 3: Clinical and biochemical parameters in the different groups of patients studied.

| Parameters | Total (n=96) | NDRD (Group-I) (n = 43) | NDRD superimposed on underlying DN (Group-II) (n = 27) | DN(Group-III) (n = 26) | P-value |
|---|---|---|---|---|---|
| Diabetes duration (years) | 6.08 ± 4.65 | 5.62 ± 4.99 | 6.11 ± 3.72 | 7.08 ± 5.20 | 0.64 |
| Diabetic Retinopathy n (%) | 23 (23.96%) | 0 | 8 (29.62%) | 15 (57.69%) | 0.005 |
| HbA1c (%) | 7.3 ± 1.8 | 6.8 ± 1.58 | 7.8 ± 2.04 | 7.4 ± 1.57 | 0.003 |
| Hypertension n (%) | 18 (18.75%) | 9 (20.93%) | 3 (11.11%) | 6 (23.08%) | 0.515 |
| 24-hour urine Protein (g/day) | 3.62 ± 3.54 | 4.00 ± 3.92 | 3.68 ± 3.35 | 3.01 ± 3.07 | 0.578 |
| Hematuria n (%) | 47 (48.96%) | 22 (51.16%) | 14 (51.85%) | 11 (42.31%) | 0.73 |
| S.Creatinine (mg/dL) | 4.36 ± 2.85 | 4.18 ± 2.69 | 4.78 ± 2.96 | 4.24 ± 3.06 | 0.645 |
| Low S. C3 n (%) | 15 (15.63%) | 8 (18.60%) | 7 (25.93%) | 0 | 0.260 |
| Low S. C4 n (%) | 13 (13.54%) | 8 (18.60%) | 1 (3.70%) | 0 | 0.363 |
| S. C-ANCA Positivity n (%) | 3 (3.13%) | 2 (4.65%) | 1 (3.70%) | 0 | 0.948 |
| S. p-ANCA Positivity n (%) | 4 (4.17%) | 3 (6.98%) | 1 (3.70%) | 0 | 0.889 |
| S. ANA Positivity n (%) | 5 (5.21%) | 4 (9.30%) | 1 (3.70%) | 0 | 0.802 |
| S. Anti PLA2R Positivity n (%) | 4 (4.17%) | 3 (6.98%) | 1 (3.70%) | 0 | 0.888 |

Table 4: Histopathological diagnosis in patients in Group-1 and Group-II

| Histopathological diagnosis | Group-I (Isolated NDRD) (n= 43) | Group-II (NDRD superimposed on underlying DN) (n = 27) | Total (n=70) |
|---|---|---|---|
| ACTIN | 5 (11.63%) | 11 (40.74%) | 16 (22.86%) |
| Membranous nephropathy | 8 (18.60%) | 2 (7.41%) | 10 (14.29%) |
| Focal segmental glomerulosclerosis | 5 (11.63%) | 2 (7.41%) | 7 (10%) |
| Pauci-immune Crescentic GN | 5 (11.63%) | 2 (7.41%) | 7 (10%) |
| Postinfectious glomerulonephritis | 1 (2.33%) | 5 (18.52%) | 6 (8.57%) |
| Membranoproliferative glomerulonephritis | 4 (9.30%) | 1 (3.70%) | 5 (7.14%) |
| Acute pyelonephritis | 3 (6.98%) | 0 | 3 (4.29%) |
| Minimal change disease | 4 (9.30%) | 0 | 4 (9.30%) |
| IgA nephropathy | 2 (4.65%) | 0 | 2 (2.86%) |
| ATIN | 1 (2.33%) | 1 (3.70%) | 2 (2.86%) |
| Cast Nephropathy | 1 (2.33%) | 1 (3.70%) | 2 (2.86%) |
| Acute on chronic thrombotic microangiopathy | 1 (2.33%) | 1 (3.70%) | 2 (2.86%) |
| Proliferative glomerulonephritis monoclonal deposits (PGNMID) | 1 (2.33%) | 0 | 1 (1.43%) |

| | | | |
|---|---|---|---|
| Renal amyloidosis (AA type) | 1 (2.33%) | 0 | 1 (1.43%) |
| Cryoglobulinemic glomerulonephritis | 1 (2.33%) | 0 | 1 (1.43%) |
| C3 glomerulopathy | 0 | 1 (3.70%) | 1 (1.43%) |

**Discussion**

In this study, we analysed clinical, laboratory and pathological features in 96 T2DM patients who underwent renal biopsies for various indications from January 2018 to June 2023. Current study is compared with the former study by Kamal Kanodia et al[1] in the same centre with similar demographical environment gives us an idea of the changing trends in NDRD.

In a meta-analysis of 48 studies by Fiorentino et al[9] the prevalence of NDRD in T2DM patients ranges from 3% to 82.9%. The prevalence of total NDRD (isolated and or superimposed on underlying DN) in our study was 72.92% which was comparable to previous study by Kamal Kanodia et al[1] (66%) and in accordance with various studies like Yaqub S et al[10] (69%), Arora P et al [11] (75%), Sun Y et al[12] (59.2%). While Chandragiri S et al [13] reported 30% of the patients had NDRD and Kumar R et al [14] reported 46.8% of the patients had NDRD. These variations of variable frequencies are probably attributed to differences in the population being studied, small study cohort, different selection criteria in indications for biopsy, geographic, ethnic backgrounds.

In our study, the main reasons why diabetic patients underwent biopsies were the presence of proteinuria, microscopic hematuria, active urinary sediment, absence of retinopathy, nephrotic syndrome, signs of acute renal failure, RPRF, immunological abnormality (such as positive S. ANA\ S. dsDNA\S. ANCA) and hypocomplementemia. At the time of renal biopsy, no statistically significant differences were observed between the three groups with regards to age, sex, biopsy indication, diabetes duration, history of hypertension, presence of hematuria, amount of proteinuria, and serum creatine level.

DR was significantly seen in Group-II and III DN and absence of DR in Group-I that suggests absence of DR is said to be one of important predictive factor of NDRD. Same correlation has been reported by previous study by Kamal Kanodia et al [1], by Arora P et al [11], Prasad N et al [15] and Zeng YQ et al [16]

There was no significant difference in the duration of diabetes in all groups. Previous study by Kamal Kanodia et al [1] and several other studies by Kumar R et al [14], Soni SS et al [17] showed shorter duration of diabetes was associated with NDRD. Our study and Erdogmus S et al [18], Bertani T et al[19] which suggests the declining correlation between duration of diabetes and NDRD.

HbA1C (%) level was significantly higher in Group-II and Group-III in than Group-I which is in accordance with various studies like Sobh M et al[20] that suggests HbA1C level is an important predictive factor for DN.

The prevalence of hypertension was similar in all three groups in our study, which is consistent with the findings reported by previous study by Kamal Kanodia et al [1], Soni SS et al [17], Erdogmus S et al [18] and Sobh M et al [20]

We found that patients with isolated DN as well as those with NDRD superimposed on underlying DN tended to have higher levels of proteinuria compared with the group with isolated NDRD; the difference did not statistically significant. which is consistent with the findings reported by previous study by Kamal Kanodia et al [1], Soni SS et al [17] and Matias et al [21] and Yaqub S et al [10].

The presence of microscopic hematuria was similar in all three groups in our study. Same correlation has been

reported by previous study by Kamal Kanodia et al[1], Souza DA et al [8], Yaqub S et al [10] and Sobh M et al [20].

In this study, patients with both isolated NDRD, NDRD superimposed on underlying DN and DN did not have any difference in serum creatinine levels. Similar results were reported in Souza DA et al[8], Pham TT et al [22]. While previous study by Kamal Kanodia et al [1], Sun Y [12] and Soni SS et al [17] concluded that S. Creatinine was significantly high in combined disease than in patients with isolated NDRD and DN.

Low serum complement (C3 and/or C4) levels, positive Serum ANA/dsDNA levels, positive Serum ANCA study positive serum Anti PLA2R were only found in Group I and II and important predictors of NDRD.

The most common histological types of NDRD were membranous nephropathy 8 (18.60%) cases followed by focal segmental glomerulosclerosis 5 (11.63%) cases, pauci-immune crescentic GN 5 (11.63%) cases and acute on chronic tubulointerstitial nephritis 5 (11.63%) cases. The most common histological types of coexisting NDRD and diabetic nephropathy were acute on chronic tubulointerstitial nephritis 11 (40.74%) cases followed by postinfectious glomerulonephritis 5 (18.52%) cases. Previous study by Kamal Kanodia et al [1] reported ATIN, Membranous nephropathy, Membranoproliferative glomerulonephritis and IgA nephropathy as the common histological lesions of isolated NDRD. ATIN, Benign nephrosclerosis and Acute pyelonephritis were common histological lesions in Group II. Types of NDRD reported were different in different studies in the literature.

The pathogenesis of NDRD in patients with diabetes is undetermined. Whether there are common etiologic factors in relation to diabetes or it is just a coincidence is not clear. Several researchers have proposed that the predisposition of DN to superimposed nephritis could be attributed to enhanced exposure of antigenic cellular components, triggering immune responses. [17, 23] Other authors suggested that the co-existence of a different glomerulonephritis in the diabetic renal may be merely coincidental. Renal biopsy is effective diagnostic tool to distinguish the type of renal disease in patients with DM.

**Conclusion**

NDRD was diagnosed by renal biopsy in 70 (72.92%) patients out of 96 patients with type 2 DM, which confirms the significance of the renal biopsy in patients with DM with properly indications.

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