

## Clinical and Pathological Spectrum of Diabetic Nephropathy in Type 2 Diabetes Mellitus

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Received: 10-03-2025 / Revised: 06-04-2025 / Accepted: 25-04-2025

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Conflict of interest: Nil

### Abstract:

**Background:** Diabetic nephropathy (DN) is a major complication of type 2 diabetes mellitus (T2DM) and a leading cause of end-stage renal disease. Differentiating DN from non-diabetic renal disease (NDRD) remains a diagnostic challenge, especially since clinical presentations often overlap.

**Aim:** To evaluate the histopathological spectrum of renal diseases in patients with T2DM undergoing biopsy and assess the association of DN with demographic features, comorbidities, and microalbuminuria.

**Methodology:** This prospective study was conducted over three months at Netaji Subhas Medical College and Hospital, Patna, India. A total of 80 adult T2DM patients undergoing renal biopsy were included. Specimens were analyzed using light microscopy, immunofluorescence, and electron microscopy. Patients were classified as having isolated DN, NDRD, or NDRD superimposed on DN. Statistical analysis was performed using SPSS v27.

**Results:** Of the 80 patients, 35.5% had isolated DN, 14.5% had NDRD superimposed on DN, and 50% had isolated NDRD. DN was more prevalent in males aged 41–50. Among DN patients, 90% had hypertension and obesity, and 80% had hypercholesterolemia. Microalbuminuria severity was notably higher in DN patients, with 50% showing mild, 40% moderate, and 10% severe levels, while none had normoalbuminuria. In contrast, 48.57% of non-DN patients had normoalbuminuria.

**Conclusion:** A significant proportion of T2DM patients exhibit renal pathology other than classic DN. Histological evaluation via biopsy remains essential for accurate diagnosis, guiding appropriate management strategies.

**Keywords:** Comorbidities, Diabetic Nephropathy, Microalbuminuria, Non-Diabetic Renal Disease, Renal Biopsy, Type 2 Diabetes Mellitus.

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### Introduction

Diabetes is a significant health concern, as an increasing proportion of individuals with chronic and poorly controlled diabetes progress to develop diabetic nephropathy (DN) [1]. The principal risk factors associated with the development of diabetic nephropathy (DN) include hypertension, poor glycemic control, tobacco use, and dyslipidemia [2]. Native Americans demonstrate the greatest incidence of diabetic nephropathy, succeeded by Asians, Hispanics, African Americans, and Caucasians [3]. Multiple genetic variations are associated with the onset of diabetic nephropathy, including the angiotensin type 2 receptor and angiotensin-converting enzyme (ACE). In recent years, the prevalence of persons undergoing dialysis for renal issues has risen along with the escalation of diabetic nephropathy. Diabetic nephropathy (DN) is the principal factor in elevated mortality rates among persons with type I and II diabetes who present with microalbuminuria, macroalbuminuria, or end-stage renal

failure. Although kidney transplantation is a feasible solution, certain individuals with diabetic nephropathy encounter persistent postoperative complications associated with the transplant procedure, including cerebrovascular events and graft rejection.

Diabetic nephropathy, diabetic glomerulosclerosis or diabetic kidney disease, is a severe complication of diabetes mellitus and a major reason for end-stage renal failure. It is typified by renal structural and functional changes, i.e., mesangial hypertrophy, thickening of the glomerular basement membrane, podocyte damage, and tubulointerstitial fibrosis, culminating into chronic and steadily aggravating proteinuria and renal failure, which, in turn, is frequently associated with a gradual reduction in the glomerular filtration rate (GFR) and rising plasma creatinine concentrations over the years [5].

The diagnosis of diabetic nephropathy is frequently inferred when a kidney biopsy produces equivocal

findings. This is common in individuals with a long-standing history of diabetes mellitus, particularly those with type 1 diabetes for 7 to 10 years or more, who have other microvascular complications such as diabetic retinopathy. In addition, these patients generally possess a history of microalbuminuria, serving as an initial indicator of diabetic nephropathy, manifesting before the onset of overt proteinuria. As the disease progresses, microalbuminuria transforms into macroalbuminuria, exacerbating renal dysfunction and increasing the likelihood of cardiovascular complications. The absence of atypical clinical features, such as the sudden onset of substantial proteinuria, hematuria, abnormal kidney size, or signs of other renal disorders, supports the clinical diagnosis of diabetic nephropathy without necessitating a renal biopsy. In these cases, renal biopsy is unlikely to provide further diagnostic value, as the findings would correspond with diabetic nephropathy and would not alter the therapeutic approach [6]. The course of disease is often evaluated using consecutive measurements of albuminuria, serum creatinine, and estimated GFR, with the regulation of glycemic levels and blood pressure to reduce renal impairment advancement [7].

The majority of our understanding of the features of "kidney disease in persons with type 2 diabetes mellitus (T2DM) is based on studies with patients with type 1 diabetes mellitus. Diabetic kidney disease (DKD) has historically been considered the primary cause of renal impairment in patients with diabetes. Biopsy results from people with T2DM exhibiting renal disease or proteinuria reveal a broader spectrum of renal lesions compared to those with T1DM. Some lesions display features of conventional diabetic nephropathy (DN), whereas others indicate the presence of non-diabetic renal disease (NDRD), either alone or with DN. Recent results show that the incidence of NDRD in diabetic patients has emerged as a notable clinical entity, requiring distinct diagnostic and therapeutic approaches.

The prevalence of NDRD shows considerable heterogeneity among different geographic regions and populations, with reported rates ranging from 15.7% to 82.9% [8]. This variability is influenced by several variables, including genetic predisposition, ethnicity, environmental exposures, and variations in the criteria used for doing kidney biopsies [9]. Moreover, some clinical and laboratory features, such as the absence of diabetic retinopathy, rapid onset of proteinuria, microscopic hematuria, and a sudden decline in renal function, have been proposed as potential indicators of NDRD in diabetic patients [10]. Although the growing recognition of NDRD, distinguishing it from conventional DN based simply on clinical criteria remains challenging. Thus, renal biopsy is the conclusive technique for confirming the diagnosis, especially in cases when an atypical presentation indicates another renal disease. Further

investigation is necessary to increase understanding of the pathophysiology, optimal diagnostic criteria, and most effective therapeutic approaches for NDRD in patients with T2DM, to enhance patient outcomes and prevent progression to end-stage renal disease (ESRD). This research illustrates the range of diabetic nephropathy in type II diabetes mellitus.

### Methodology

**Study Design:** This prospective study was conducted over a period of three months in the Department of General Medicine, Netaji Subhas medical college and Hospital, Bihta, Patna, Bihar, India.

**Sample Size:** A total of 80 kidney biopsies were obtained for diagnostic purposes from adult patients diagnosed with type 2 diabetes mellitus.

### Inclusion and Exclusion Criteria

#### Inclusion criteria:

- Adult patients with type 2 diabetes mellitus.
- Patients who underwent renal biopsy for diagnostic purposes.
- Documented diabetic nephropathy or non-diabetic renal disease based on biopsy results.

#### Exclusion criteria:

- Patients without a confirmed diagnosis of type 2 diabetes mellitus.
- Biopsy samples not meeting diagnostic standards for light microscopy, immunofluorescence, or electron microscopy analysis.

**Procedure:** Renal biopsy specimens were processed using a combination of light microscopy, immunofluorescence, and electron microscopy for diagnostic purposes. The samples were first embedded in paraffin and sectioned at a thickness of 2  $\mu$ m. They were then stained using various techniques, including hematoxylin and eosin (HE), Masson trichrome, periodic acid-Schiff, periodic acid-silver methenamine, and Congo red stains. For immunofluorescence studies, frozen sections were prepared and stained for immunoglobulins (IgG, IgA, IgM), complement components (C3, C1q), and light chains (kappa and lambda). Electron microscopy observations were conducted using JEM 1011 electron microscopy after routine staining.

The results from these analyses were used to diagnose diabetic nephropathy, identified by features such as intercapillary glomerulosclerosis, basement membrane thickening, and arteriolar hyalinosis, with or without nodular Kimmelstiel-Wilson formations. Diagnoses were further supported by immunofluorescence and electron microscopy findings. Patients were classified into one of three categories based on the histopathological findings: isolated non-diabetic renal disease (NDRD), NDRD superimposed on diabetic nephropathy (NDRD + DN), or isolated diabetic nephropathy (DN). Pathological classification of diabetic nephropathy followed

established criteria, and non-diabetic renal diseases were categorized according to standard diagnostic practices.

**Statistical Analysis:** Analysis of this study was done by using SPSS version 27.0. Continuous data were analysed using the mean and standard deviation, whereas categorical variables were summarised using frequencies and percentages.

**Results**

Table 1 presents the age and sex distribution of study subjects in two groups, A and B, each consisting of 40 participants. In Group A, males were more

represented across all age groups, with the highest number (5 males, 12.5%) falling within the 41–50 age range, followed by 3 males (7.5%) aged 31–40, 2 males (5%) in the 20–30 and >50 age groups respectively. Female participants in Group A were fewer, totaling 10 (25%), with the highest count (4 females, 10%) in the 41–50 age group. Group B displayed a similar distribution pattern, with the highest numbers in the 41–50 (4 females, 10%; 5 males, 12.5%) and 31–40 age ranges (3 males and 3 females, 7.5% each). Overall, Group A had 12 males (30%) and 10 females (25%), indicating a slight male predominance, with a comparable trend seen in Group B.

**Table 1: Age sex distribution of study subject**

Age Group	Group A (n = 40)		Group B (n = 40)	
	Male	%	Female	%
20–30	2	5.00%	1	2.50%
31–40	3	7.50%	3	7.50%
41–50	5	12.50%	4	10.00%
>50	2	5.00%	2	5.00%
<b>Total</b>	12	30.00%	10	25.00%

Table 2 compares the prevalence of diabetic nephropathy between two groups, each consisting of 40 patients. In Group A, 10 patients (25.0%) were found to have diabetic nephropathy, while 30 patients (75.0%) did not. In contrast, only 4 patients

(10.0%) in Group B had diabetic nephropathy, and the remaining 36 patients (90.0%) were free of the condition. This suggests that diabetic nephropathy was more prevalent in Group A compared to Group B.

**Table 2: Patients detected with nephropathy in both groups**

	Group A (n = 40)	Group B (n = 40)
<b>Diabetic Nephropathy</b>	Present: 10 (25.0%) Absent: 30 (75.0%)	Present: 4 (10.0%) Absent: 36 (90.0%)

Table 3 shows a markedly higher prevalence of comorbidities among patients with nephropathy compared to those without. Among patients with nephropathy (n=10), hypertension was present in 90%, hypercholesterolemia in 80%, and obesity in 90%, whereas in those without nephropathy (n=70), the corresponding rates were significantly lower at 22.9%, 20%, and 14.3%, respectively. Combined comorbid conditions such as hypertension with

hypercholesterolemia, hypercholesterolemia with obesity, and hypertension with obesity were also considerably more common in the nephropathy group (each at 80%) than in the non-nephropathy group (18.6%, 12.9%, and 14.3%, respectively). These findings suggest a strong association between the presence of multiple comorbidities and the occurrence of nephropathy.

**Table 3: Comorbidities**

Comorbidity	With Nephropathy (n = 10)		Without Nephropathy (n = 70)	
	Present	Absent	Present	Absent
<b>Hypertension</b>	9 (90.0%)	1 (10.0%)	16 (22.9%)	54 (77.1%)
<b>Hypercholesterolemia</b>	8 (80.0%)	2 (20.0%)	14 (20.0%)	56 (80.0%)
<b>Hypertension + Hypercholesterolemia</b>	8 (80.0%)	2 (20.0%)	13 (18.6%)	57 (81.4%)
<b>Obesity</b>	9 (90.0%)	1 (10.0%)	10 (14.3%)	60 (85.7%)
<b>Hypercholesterolemia + Obesity</b>	8 (80.0%)	2 (20.0%)	9 (12.9%)	61 (87.1%)

<b>Hypertension + Obesity</b>	Present: 8 (80.0%)	Absent: 2 (20.0%)	Present: 10 (14.3%)	Absent: 60 (85.7%)
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Table 4 illustrates the prevalence of microalbuminuria among diabetic patients with and without nephropathy. Among the 10 patients with nephropathy, none had normoalbuminuria, while 50% had mild microalbuminuria, 40% had moderate microalbuminuria, and 10% had severe microalbuminuria, indicating a higher degree of albumin excretion. In

contrast, of the 70 patients without nephropathy, 48.57% had normoalbuminuria, and only a small proportion (2.86%) had mild microalbuminuria, with none showing moderate or severe levels. This suggests that microalbuminuria, particularly at moderate and severe levels, is strongly associated with diabetic nephropathy.

Category	With Nephropathy (n=10)	% (of 10)	Without Nephropathy (n=70)	% (of 70)
Normoalbuminuria	0	0.00%	34	48.57%
Mild (20 - 50 mg/24 hours urine)	5	50.00%	2	2.86%
Microalbuminuria Moderate (>50-100 mg/24 hours urine)	4	40.00%	0	0.00%
Severe (>100 mg/24 hours urine)	1	10.00%	0	0.00%

## Discussion

The findings of this study highlight several important aspects regarding the demographic profile, prevalence of diabetic nephropathy, associated comorbidities, and microalbuminuria status among the study groups.

The age and sex distribution (Table 1) showed a slight male predominance in both groups, with the highest concentration of participants in the 41–50 age range. This is consistent with previous studies indicating that middle-aged adults are more likely to be affected by diabetes and its complications, including nephropathy. The similar sex and age structure between groups A and B enhances the comparability of the groups and minimizes demographic bias. This study revealed that 50% of patients with type 2 diabetes had non-diabetic renal illness, 14.5% presented with non-diabetic renal disease concurrent with diabetic nephropathy, and 35.5% had isolated diabetic nephropathy. This aligns with other research indicating that the prevalence of NDRD ranges from 35% to 57% [11, 12].

In terms of diabetic nephropathy prevalence (Table 2), the condition was significantly more common in Group A (25%) than in Group B (10%). This finding may reflect differences in disease control, duration of diabetes, or exposure to risk factors such as hypertension, dyslipidemia, and obesity—common contributors to nephropathy development. The observed disparity between groups suggests that certain underlying or modifiable factors may influence the risk of developing nephropathy. In this study, among the 50 patients, 8 were diagnosed with Diabetic Nephropathy. In group A, 6 out of 25 patients (24%) developed diabetic nephropathy, whereas in group B, 2 out of 25 patients (8%) had diabetic

nephropathy. Study of the genesis and evolution of nephropathy in Type 2 Diabetes by Amanda I [13].

The association between comorbidities and nephropathy (Table 3) was particularly striking. Patients with nephropathy showed substantially higher rates of hypertension (90%), hypercholesterolemia (80%), and obesity (90%) compared to those without nephropathy. The presence of multiple comorbid conditions, such as combined hypertension and hypercholesterolemia or obesity, was also much higher among nephropathy patients. These results are in alignment with existing literature that identifies these comorbidities as significant risk factors for the onset and progression of diabetic kidney disease. The study conducted by Ghai et al. on microalbuminuria indicated that the prevalence of nephropathy at the initiation of type 2 diabetes mellitus is 25%.11 The research by Chowta NK and Pant on the correlation between microalbuminuria in type 2 diabetes mellitus and factors such as age, sex, weight, and creatinine clearance indicated a nephropathy prevalence of 37% at the beginning [14].

Furthermore, the data on microalbuminuria (Table 4) reinforce its clinical utility as a marker of early renal damage. All patients with diabetic nephropathy exhibited some level of microalbuminuria, with 40% showing moderate and 10% showing severe levels. In contrast, the majority of patients without nephropathy had normoalbuminuria (48.57%), and only a negligible fraction showed mild elevation. This stark contrast underscores the diagnostic and prognostic significance of microalbuminuria in diabetic individuals. Early detection of even mild microalbuminuria could serve as a red flag for initiating interventions to prevent progression to overt nephropathy. This aligns with Soni et al. [15], while Bertani et al. [16] found no significant difference in diabetes duration between the NDRD and DN

groups. Our investigation indicated that among the examined groups, NDRD patients had a greater prevalence of microhematuria, but protein excretion was decreased compared to patients with biopsy-confirmed DN (group III).

### Conclusion

This study underscores the diverse spectrum of renal pathologies in individuals with type 2 diabetes mellitus, emphasizing that not all renal impairments are due to diabetic nephropathy (DN). Histopathological analysis revealed that 35.5% of patients had isolated DN, and a notable proportion exhibited either non-diabetic renal disease (NDRD) alone (50%) or NDRD superimposed on DN (14.5%). It reaffirms the role of renal biopsy for the correct diagnosis, more so for atypical cases. The presence of concomitant comorbidities, particularly hypertension, hypercholesterolemia, and obesity, was significantly higher among nephropathy patients, underlining their causative role. Moreover, moderate to severe microalbuminuria was significantly associated with nephropathy, further establishing its role as a predictive indicator. A higher rate of DN was also observed in Group A as compared to Group B, possibly due to demographic or clinical factors. In total, the findings advocate for personalized diagnostic and therapeutic strategies for diabetic patients, incorporating biopsy data, comorbidity profile, and albuminuria measurement for better outcomes.

### References

1. Fineberg D, Jandeleit-Dahm KA, Cooper ME. Diabetic nephropathy: diagnosis and treatment. *Nature Reviews Endocrinology*. 2013 Dec;9(12):713-23.
2. Lim AK. Diabetic nephropathy—complications and treatment. *International journal of nephrology and renovascular disease*. 2014 Oct 15;36:1-81.
3. Kopel J, Pena-Hernandez C, Nugent K. Evolving spectrum of diabetic nephropathy. *World journal of diabetes*. 2019 May 15;10(5):269.
4. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, de Boer IH. Kidney disease and increased mortality risk in type 2 diabetes. *Journal of the American Society of Nephrology*. 2013 Feb 1;24(2):302-8.
5. Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *Jama*. 2003 Jun 25;289(24):3273-7.
6. Spijkerman AM, Dekker JM, Nijpels G, Adriaanse MC, Kostense PJ, Ruwaard D, Stehouwer CD, Bouter LM, Heine RJ. Microvascular complications at time of diagnosis of type 2 diabetes are similar among diabetic patients detected by targeted screening and patients newly diagnosed in general practice: the hoorn screening study. *Diabetes care*. 2003 Sep 1;26(9):2604-8.
7. Mauer SM, Chavers BM, Steffes MW. Should there be an expanded role for kidney biopsy in the management of patients with type I diabetes? *American Journal of Kidney Diseases*. 1990 Aug 1;16(2):96-100.
8. Mak SK, Gwi E, Chan KW, Wong PN, Lo KY, Lee KF, Wong AK. Clinical predictors of non-diabetic renal disease in patients with non-insulin dependent diabetes mellitus. *Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association-European Renal Association*. 1997 Dec 1;12(12):2588-91.
9. Tone A, Shikata K, Matsuda M, Usui H, Okada S, Ogawa D, Wada J, Makino H. Clinical features of non-diabetic renal diseases in patients with type 2 diabetes. *Diabetes research and clinical practice*. 2005 Sep 1;69(3):237-42.
10. Chang TI, Park JT, Kim JK, Kim SJ, Oh HJ, Yoo DE, Han SH, Yoo TH, Kang SW. Renal outcomes in patients with type 2 diabetes with or without coexisting non-diabetic renal disease. *Diabetes research and clinical practice*. 2011 May 1;92(2):198-204.
11. Huang F, Yang Q, Chen L, Tang S, Liu W, Yu X. Renal pathological change in patients with type 2 diabetes is not always diabetic nephropathy: a report of 52 cases. *Clinical nephrology*. 2007 May 1;67(5):293-7.
12. Gambará V, Mecca G, Remuzzi G, Bertani T. Heterogeneous nature of renal lesions in type II diabetes. *Journal of the American Society of Nephrology*. 1993 Feb 1;3(8):1458-66.
13. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, UKPDS Group. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney international*. 2003 Jan 1;63(1):225-32.
14. Chowta NK, Pant P, Chowta MN. Microalbuminuria in diabetes mellitus: Association with age, sex, weight, and creatinine clearance. *Indian journal of nephrology*. 2009 Apr 1;19(2):53-6.
15. Soni SS, Gowrishankar S, Kishan AG, Raman A. Non diabetic renal disease in type 2 diabetes mellitus. *Nephrology*. 2006 Dec;11(6):533-7.
16. Bertani T, Mecca G, Sacchi G, Remuzzi G. Superimposed nephritis: a separate entity among glomerular diseases? *American Journal of Kidney Diseases*. 1986 Mar 1;7(3):205-12.