

# Prevalence and Clinicopathological Characteristics of Non-Diabetic Renal Disease (NDRD) in Patients with Type 2 Diabetes Mellitus –A Retrospective Study

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## Abstract:

**Introduction:** The prevalence of non-diabetic renal disease (NDRD) in type 2 diabetes mellitus (DM) varies depending on selection criteria and populations studied. Renal biopsies are not routinely performed in diabetic patients, but are indicated when NDRD is suspected. This study evaluated kidney biopsy histopathology and its correlation with clinical and biochemical parameters.

**Materials and methods:** Patients with type 2 DM who underwent renal biopsy for suspected NDRD from January 2015 to May 2023 were included in this study. Baseline characteristics were retrieved. Data analysis included clinical, laboratory, and histopathology findings. Clinical and laboratory data were analyzed in relation to the histopathology findings

**Results:** A total of 41 renal biopsies were performed on type 2 Diabetic patients. Mean age: 48.07±11.9 years, mean diabetes duration: 8.23±7.4 years, mean proteinuria: 11.37±8.0 mg/mmol, and mean creatinine was 2.19±2.05 mg/dl among the studied subjects. A total of 46.3% were hypertensives, 46.34% had diabetic retinopathy and 34.14% had hematuria. Patients were grouped into 3 groups: Group I-pure diabetic nephropathy (DN) group, Group II –NDRD with underlying DN group and Group III-pure NDRD group. Among the studied group, 12 patients (29.26%) had pure DN, 10 patients (24.39%) had NDRD with underlying DN, and 19 patients (46.34%) had pure NDRD. The most common NDRD

findings were membranous nephropathy 5 cases (26.31%) and focal segmental glomerulosclerosis 4 cases (21.05%).

**Conclusion:** This study found a 46.34% incidence of NDRD in diabetic patients. NDRD should be suspected in atypical diabetic presentations, as early diagnosis and treatment may slow kidney disease progression. So, renal biopsy should be performed in diabetics when the clinical scenario is atypical.

**Keywords:** Non-diabetic renal disease (NDRD), renal biopsy, Diabetic nephropathy(DN), Diabetic retinopathy

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## Introduction

Diabetic nephropathy (DN) is characterized by persistent proteinuria, hypertension, and a progressive decline in renal function. About 20-40% of patients suffering from diabetes mellitus eventually develop diabetic renal diseases. It accounts for over 40% of new cases of end-stage renal disease (ESRD) annually, and is considered the leading cause of ESRD in the USA as well as Europe. The characteristic lesion of DN is nodular glomerulosclerosis (Kimmelstiel –Wilson). Renal diseases other than DN can occur in diabetic patients. The absence of retinopathy or neuropathy in patients with evidence of nephropathy may imply that the underlying pathology is unrelated to diabetes. Other clinical predictors of non-diabetic renal disease (NDRD) in diabetic patients include rapid deterioration of renal function (worsening of urea and creatinine), microscopic or macroscopic hematuria. A renal biopsy is not routinely performed in diabetic patients and is indicated however, in patients where NDRD is suspected. Early diagnosis of diseases different from diabetic nephropathy in diabetic patients is fundamental to preserve renal function in patients with renal diseases for which the natural history can be modified by treatment, especially in primary glomerulonephritis, systemic diseases with renal involvement or interstitial nephritis.

## Methodology

### Study design

This is a retrospective study aimed to study the prevalence and clinicopathological characteristics of NDRD in patients with type 2 diabetes mellitus.

### Subjects

All native kidney biopsies performed at Vydehi Institute of Medical Sciences and Research Centre, Bengaluru from January 2015 to May 2023 were retrospectively reviewed. Biopsies performed on patients with type 2 diabetes for clinically suspected NDRD and who fulfilled the inclusion criteria were selected and reviewed. Inclusion Criteria include all diabetic patients with or without hypertension, presence of hematuria (microscopic and macroscopic), sudden onset of macroalbuminuria, rapid decline of renal function, acute renal failure, clinical suspicion of other nephropathies: vasculitis,

glomerulonephritis and other systemic symptoms-rashes, joint pain. Exclusion criteria include non-diabetic patients who were admitted for renal biopsy.

Data was collected in the form of clinical features, past history, family history, medication history(including anti-hypertensives), details regarding comorbidities (duration of diabetes, presence of hypertension defined as SBP>140 mm Hg and or DBP> 80 mm Hg).Also data including age, gender were included. Investigations included complete blood count(CBC), renal function test (serum urea ,serum creatinine), liver function test, urine routine and microscopy, spot urine protein-creatinine ratio(PCR)-to look for proteinuria, USG abdomen-pelvis(to look for kidney morphology, size and corticomedullary differentiation),serum electrolytes,complement levels (C3, C4) and ANA profile (including ds-DNA, anti-Smith antibodies). Glomerular filtration rate was estimated by MDRD (modification of diet in renal disease study) formula.Presence of hematuria was defined as 3 or more red blood cells per high-power field in a centrifuged urine sample prior to biopsy.All patients underwent ultrasound-guided renal biopsy using 18x16G coaxial quick-core biopsy set. Written consent was obtained from each patient prior to the procedure.The histopathology glass slides were reviewed and the pathology reports were retrieved from the department of pathology computerized filing system. Each kidney biopsy was prepared by cutting paraffin blocks at 3 um sections and staining slides with Periodic acid Schiff, hematoxylin and eosin and Jones Methenamine silver.Immunoperoxidase staining was also performed routinely on all slides for IgG, IgA, IgM and C3.

Patients were grouped into 3 groups.Group I-pure diabetic nephropathy (DN) group, Group II –Non diabetic renal disease (NDRD) with underlying diabetic nephropathy group and Group III- pure Non diabetic renal disease(NDRD) group.

## Result

A total of 41 renal biopsies from native kidneys done during the study period.28(54.8%) patients were males. Mean age was 48+11.9years. The mean duration of diabetes was 8.23+7.4years ([Table 1](#)).

Renal biopsy should that among the studied population:12 (29.26%) cases were found to have pure diabetic nephropathy - Group I,10 (24.39%) cases were found to have NDRD with underlying DN - Group II and 19 (46.34%) cases were found to have pure NDRD - Group III.

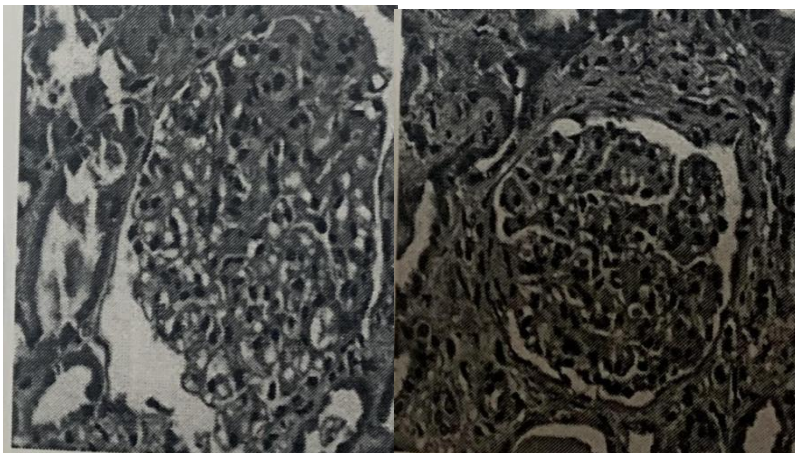
**TABLE 1: CLINICAL AND LABORATORY DATA FOR THE STUDIED DIABETIC PATIENTS (N=41)**

PATIENT CHARACTERISTICS	VALUES
Age in years mean (SD)	48.07±11.9
Male gender (%)	28 (68.29)
Hypertension (%)	19 (46.34)
Retinopathy (%)	19 (46.34)
Duration of diabetes in years mean (SD)	8.23±7.4
Creatinine (mg/dl) mean (SD)	2.19±2.05
Hematuria (%)	14 (34.14)
Urinary proteins (spot PCR)(mg/mmol) mean (SD)	11.37±8.0
GFR ml/min/1.73 m <sup>2</sup> mean (SD)	38.6±36.4

Focal segmental glomerulosclerosis was the most common NDRD among group II-3 (3%) - (Table2). Other histopathological findings include chronic glomerulosclerosis 2(2%), acute tubule-interstitial nephritis, membranous nephropathy, post-infectious glomerulonephritis, hypertensive glomerulosclerosis, and crescentic glomerulonephritis one each (1%).

TABLE 2: HISTOPATHOLOGICAL FINDINGS IN GROUP II (N=10)

HISTOPATHOLOGICAL FINDINGS	NUMBER OF PATIENTS (%)
Focal segmental glomerulosclerosis	3 (3)
Chronic glomerulosclerosis	2 (2)
Acute tubulo-interstitial nephritis	1 (1)
Membranous nephropathy	1 (1)
Post-infectious glomerulonephritis	1 (1)
Hypertensive nephrosclerosis	1 (1)
Crescentic glomerulonephritis	1 (1)



A patient with type 2 diabetes mellitus and hypertension with adult onset nephrotic syndrome – Histology (H and E stain )-shows features suggestive of focal segmental glomerulosclerosis and associated acute tubulo-interstitial nephritis.

Membranous nephropathy was the most common NDRD among group III-5 (26.39%) (Table 3). Other histopathological findings in group III (pure NDRD) include lupus nephritis, minimal change disease, acute tubulo-interstitial nephritis each 2 cases (10.52%), IgA nephropathy, mesangioproliferative glomerulonephritis and membranoproliferative glomerulonephritis one each(5.2%).

TABLE 3: HISTOPATHOLOGICAL FINDINGS IN GROUP III (N=19)

HISTOPATHOLOGICAL FINDINGS	NUMBER OF PATIENTS (%)
Membranous nephropathy	5 (26.31)
Focal segmental glomerulosclerosis	4 (21.05)
Acute tubulo-interstitial nephritis	3 (15.78)
Minimal change disease	2 (10.52)
Lupus Nephritis	2 (10.52)
IgA nephropathy	1 (5.26)
Mesangioproliferative glomerulonephritis	1 (5.26)
Membranoproliferative glomerulonephritis	1 (5.26)



A patient with type 2 diabetes mellitus, suspecting NDRD- histopathology (H and E stain)-showing features suggestive of class 4 lupus nephritis

**Discussion**

Diabetic nephropathy is one of the most frequent and clinically important complications of diabetes, affecting approximately 40% of patients who have had diabetes for more than 20 years and contributing to a substantial number of patients entering into ESRD programs. The first clinical sign suggesting renal involvement due to diabetes is hyper filtration characterized by increased glomerular filtration rate over

120 mL/min/1.73 m<sup>2</sup>, which is followed by the onset of microalbuminuria (albumin excretion >30 mg/g creatinine).

The natural history of the renal involvement in diabetes is better characterized in patients with type I diabetes mellitus (T1DM) since the beginning of diabetes is precisely known. It has been observed that microalbuminuria in patients with T1DM rarely appears within the first five years. Without specific intervention, 80% of type I diabetic patients that develop microalbuminuria will evolve to macroalbuminuria (albumin excretion >300 mg/g creatinine) at an average time of 10–15 years. During this period of time, hypertension will also appear. Once macroalbuminuria is present, the glomerular filtration rate decreases progressively at a variable rate, ranging between 2–20 mL/min/year. Approximately 50% of patients with T1DM and macroalbuminuria will progress to end stage renal disease in a period of 10 years and 75% in a period of 20 years.

The natural history of diabetic nephropathy is less well established in T2DM since, alterations of glucose metabolism are indolent and the diagnosis of diabetes is usually established many years afterwards. A proportion of patients with T2DM already display micro or even macroalbuminuria at the time of diagnosis. Without specific intervention, 20% to 40% of patients with T2DM presenting microalbuminuria are going to progress to macroalbuminuria. However, 20 years after the beginning of macroalbuminuria, only 20% of patients will progress to end stage renal disease.

In a study reviewing 620 biopsies made in patients with diabetes in 2011, Sharma *et al.*, showed that among 2642 native kidney biopsies, 37% of patients showed pure diabetic nephropathy, 36% showed a non-diabetic renal disease and in 27% of patients diabetic nephropathy was associated with a non-diabetic renal disease. In other studies evaluating the renal diagnosis in diabetic patients, similar results have been reported. Among patients with type 2 diabetes the prevalence of NDRD varies widely depending on the selection criteria and the populations being studied. The frequency of NDRD in diabetics has been reported to be 7 - 44%. In the present study, the incidence of NDRD was 46.34% in diabetic patients. This was in accordance with previous studies where the prevalence of NDRD was found to range from 45-57%, but different from other studies where the prevalence of NDRD was around 7-10%. This low prevalence could be explained by the different selection criteria for doing renal biopsy in such patients. Our study confirmed the accepted view that one of the important predictors of NDRD is the absence of retinopathy. However, the presence of retinopathy should not rule out the need for renal biopsy, especially if the clinical scenario is atypical. Our study showed that membranous glomerulonephritis was the commonest NDRD detected in the studied biopsies.

## Conclusion

Non-diabetic renal disease is common in patients with Type 2 diabetes mellitus. Renal biopsy is necessary for precise diagnosis of NDRD and diabetic renal diseases. Renal biopsy in Type 2 DM proteinuric patients using biopsy criteria in Type 1 DM is not useful in identifying patients with potentially treatable NDRD. The clinical clues for NDRD in Type 2 proteinuric patients are (i) Short duration of diabetes, (ii) Rapid loss of renal function, (iii) Heavy proteinuria with normal renal function, (iv) Significant renal dysfunction with minimal/ normoalbuminuria, (v) Active urinary sediment, (vi) Gross hematuria and (vii) Absence of retinopathy. The presence of diabetic retinopathy, suggests the concurrence of DN, but does not exclude non-diabetic nephropathy. Renal biopsy is indicated in

proteinuric Type 2 diabetic patients regardless of presence or absence of diabetic retinopathy for precise diagnosis of DN vs non-diabetic renal disease in such patients.

Early diagnosis of NDRD is crucial as appropriate therapy could prolong renal survival in this patient population. It is important to mention that 40% to 60% of ESRD in diabetic patients is associated with non-diabetic primary renal diseases. Their diagnosis is important because progressive loss of renal function is faster in diabetic renal disease (diabetic nephropathy) in comparison to NDRD. All clinical nephropathies (proteinuria, increased creatinine) in Type 2 DM are not due to diabetic nephropathy. One should be aware of non-diabetic renal diseases in proteinuric Type 2 diabetic patients.

So, conducting a renal biopsy in diabetic patients is important when the clinical scenario is not typical of diabetic nephropathy as many of the pathological lesions found in our group of patients had the potential for treatment with agents other than the standard angiotensin converting enzyme inhibitors or angiotensin receptor blockers commonly used in typical DGS.

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