



## Histological Pattern of Renal Disease in Those with Type 2 Diabetes Mellitus (T2DM) (Original Article)

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### ABSTRACT

*The prevalence of nondiabetic renal disease in those with T2DM is very common in multiple series across the world, however, data from India is limited. This study was done by including all subjects of T2DM; who underwent renal biopsies at EMS Memorial Cooperative Hospital, Perinthalmanna, Kerala, India, from September 2009 to August 2016. Seventy-one (Males:47, Females:24, Mean age: 52.93; SD 12.56 years) subjects with T2DM; who underwent renal biopsy; with a suspicion of non-diabetic renal disease were included. The indications for renal biopsy were: acute on chronic renal failure (ACRF) (35.2%), nephrotic syndrome (NS) (31%), acute renal failure (ARF) (14.1%), nephritic syndrome (14.1%), rapidly progressive renal failure (RPRF) (4.2%) and subnephrotic proteinuria (1.4%). The prevalence rates of nondiabetic renal disease (NDRD), diabetic nephropathy (DN) and DN with NDRD were 50.71, 28.16 and 21.13 % respectively. The mean durations of T2DM were 12.45, 12.13 and 5.33 years in patients with DN, DN & NDRD and NDRD, respectively. Wide spectrum of glomerular diseases was observed among those with isolated NDRD; commonest being IgA nephropathy (IgAN) (9.86 %), followed by infection related glomerulonephritis (IRGN) (7.04 %), membranous nephropathy (MN) (5.63%), focal segmental glomerulosclerosis (FSGS) (4.22 %) and miscellaneous (14.1%) lesions. The acute interstitial nephritis (AIN) was the commonest of the tubulointerstitial diseases (TIDs) in those with isolated NDRD. Among the patients with DN with associated NDRD, acute tubular necrosis (ATN) (7.04%) and IRGN (5.63%) were the commonest associated lesions. This study underlines the importance of renal biopsy in patients of T2DM with atypical features.*

**Key Words:** Type 2 Diabetes mellitus, nondiabetic renal disease, diabetic nephropathy.

## INTRODUCTION

Renal diseases in 95% of patients with type 1 diabetes mellitus (T1DM) for over 10 years, in presence of diabetic retinopathy or neuropathy are most likely to be diabetic nephropathy (DN).<sup>[1]</sup> However, in T2DM; 12-82 % of them had renal lesions were due to non-diabetic renal diseases (NDRD) in different series.<sup>[2-11]</sup> The end stage renal disease in T2DM is due to NDRD in 40-60 % of cases, there by stressing the importance of early diagnosis.<sup>[10]</sup> The markers indicating the presence of NDRD include short duration of DM, unexplained worsening of renal disease, absence of neuropathy, absence of retinopathy and presence of active urinary sediments, or features of other systemic diseases.<sup>[9-11]</sup>

## AIMS AND OBJECTIVES

The present study was designed to retrospectively analyze kidney biopsies of patients with DM with the aim to find-out the prevalence of DN, NDRD, and DN plus NDRD.

## MATERIALS AND METHODS

This is a retrospective study which included all consecutive patients of T2DM who underwent renal biopsies at EMS Memorial Cooperative Hospital and Research Centre, Perinthalmanna, Kerala, from September 2009 to August 2016, under guidance of ultrasound using Bard® Max-Core® disposable core biopsy instrument, CR Bard Inc., USA. All the biopsies were analyzed by light microscopy using hematoxylin and eosin (H&E), periodic acid Schiff (PAS), Jones's silver methanamine and Gomori's trichrome stains (MT) and immunofluorescence studies were performed using anti-human IgG, IgA, IgM, C3, C1q, kappa and lambda light chains.

The data was analyzed by SPSS 17 for Windows, by SPSS Inc. IL, USA. Two-sided p value of < 0.05 was considered as statistically significant.

The diagnosis of diabetes mellitus was made according to the criteria stated by the American Diabetes Association. The indications for renal

biopsy were: acute on chronic renal failure, nephrotic syndrome, acute renal failure, nephritic syndrome, rapidly progressive renal failure and subnephrotic proteinuria.

The following data were recorded prior to renal biopsy: age, gender, duration of diabetes, serum creatinine levels, urine microscopy and sediments, total protein amount in 24-hr urine or albumin/creatinine ratio in a spot sample.

Onset of diabetes was defined as the time when T2DM was first diagnosed. Duration of T2DM was defined as the period between the age of onset and renal biopsy.

Diabetic nephropathy was diagnosed by the presence of mesangial expansion, with or without the nodular Kimmelstiel – Wilson (KW) formation, basement membrane thickening, fibrin caps, or capsular drops. NDRDs were diagnosed and categorized as per standard guidelines.<sup>[12]</sup>

## RESULTS

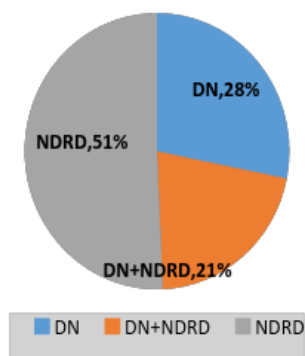
A total 71 patients (Males:47, Females:24, Mean age: 52.93 years) of DM underwent renal biopsy; with a suspicion of non-diabetic renal disease. The demographic data of number of subjects, mean age, gender and duration of T2DM are summarised in table 1.

The prevalence rates of nondiabetic renal disease (NDRD), diabetic nephropathy (DN) and DN with NDRD were 50.71, 28.16 and 21.13 % respectively (Figure 1). The mean age, gender, duration of T2DM and number of subjects with DN, DN+NDRD and NDRD, are summarised in table 2. The mean durations of T2DM were 12.45, 12.13 and 5.33 years in patients with DN, DN+NDRD and NDRD, respectively. The duration of T2DM in subjects with DN or DN+NDRD was higher than those with NDRD; statistically significant (Pearson Chi-square value:29.95 & p:0.038). The gender and age of the subjects did not have any statistically effect on renal pathology (p: >0.05).

**Table 1:** The demographic data of subjects with T2DM

Gender	Number of subjects	Age (years)		Duration of DM (years)	
		Mean	Std. Deviation	Mean	Std. Deviation
Females	24	53.58	14.48	7.78	4.97
Males	47	52.60	11.77	8.92	6.29
Total	71	52.93	12.65	8.53	5.86

**Figure 1:** Histopathologic patten of BPRD in patients of DM underwent biopsy with suspicion of nondiabetic renal dis:



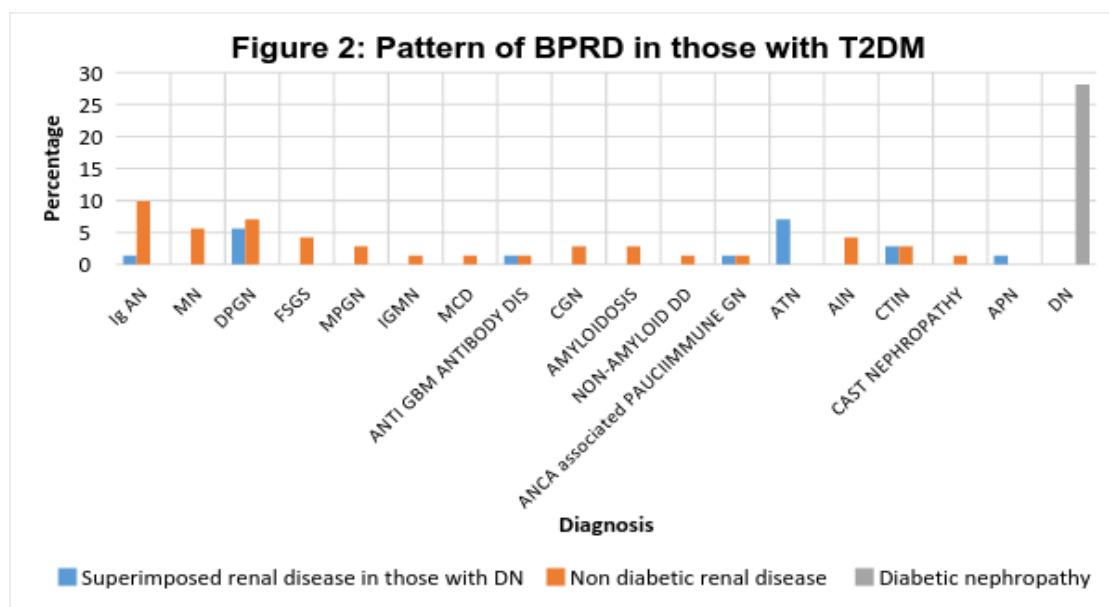
**Non diabetic renal disease (NDRD)**

Fifty-one percent of subjects had NDRD, of them 36.62 % had primary glomerular diseases (PGDs), 5.64 % had secondary glomerular diseases (SGDs) and 8.45 % had tubulointerstitial diseases (TIDs). The Ig AN (9.86 %) was the most common of PGDs followed by IRGN (7.04%), MN (5.63%), FSGS (4.22%), chronic glomerulonephritis (CGN) (2.82%), membranoproliferative glomerulonephritis (MPGN) (2.88%), IgM nephropathy (1.41 %), minimal change disease (MCD) (1.41%) and anti-glomerular basement membrane (GBM) antibody disease (1.41%) (Figure 2).

**Table 2:** Relation of BPRD to duration of T2DM, Age and Gender

Histological diagnosis	Gender		Age (Years)		Duration of T2DM (Years)	
	Males	Females	Mean	Std. Deviation	Mean	Std. Deviation
DN	13	07	52.50	11.10	12.45	6.75
NDRD	21	15	54.47	12.19	5.33	4.07
DN+NDRD	13	02	52.53	13.87	12.13	5.40
All subjects	47	24	52.93	12.65	8.77	6.23

**Figure 2:** Pattern of BPRD in those with T2DM



The primary amyloidosis (2.82%) was commonest among SGDs followed by ANCA related pauci-immune glomerulonephritis (1.41%) and non-amyloid deposition disease (1.41%) (Figure 2).

The acute interstitial nephritis (AIN) (4.22%) was the commonest of TIDs followed by chronic tubulointerstitial nephritis (CTIN) (2.82%) and cast nephropathy (1.41%) (Figure 2).

**Diabetic nephropathy (DN)**

Only 28.16 % of subjects had diabetic nephropathy alone, which was diagnosed by presence of mesangial expansion (PAS and silver positive), with or without the nodular Kimmelstiel – Wilson (KW) formation, basement membrane thickening, fibrin caps, or capsular drops, hyaline vascular changes in the intrarenal vessels (Figure 2).

**Diabetic nephropathy with associated NDRD**

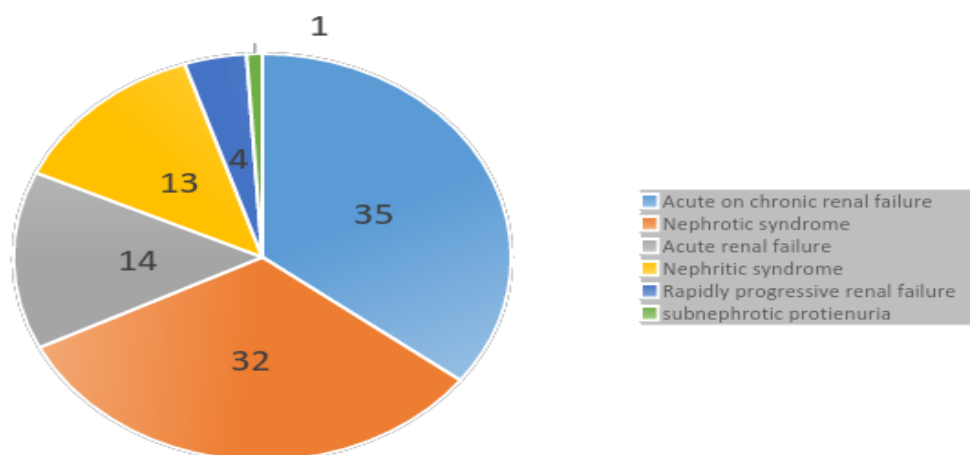
Diabetic nephropathy with associated NDRD was found in 21.13% subjects (glomerular diseases: 9.86 % and TID: 11.27 %). The IRGN (5.63 %), was the most common associated glomerular disease followed by IgAN (1.41 %) anti-GBM antibody disease (1.41%) and ANCA related pauci-immune glomerulonephritis (1.41%) (Figure 2). The acute tubular injury/necrosis (ATIN) (7.04 %) was the most common associated TIDs followed

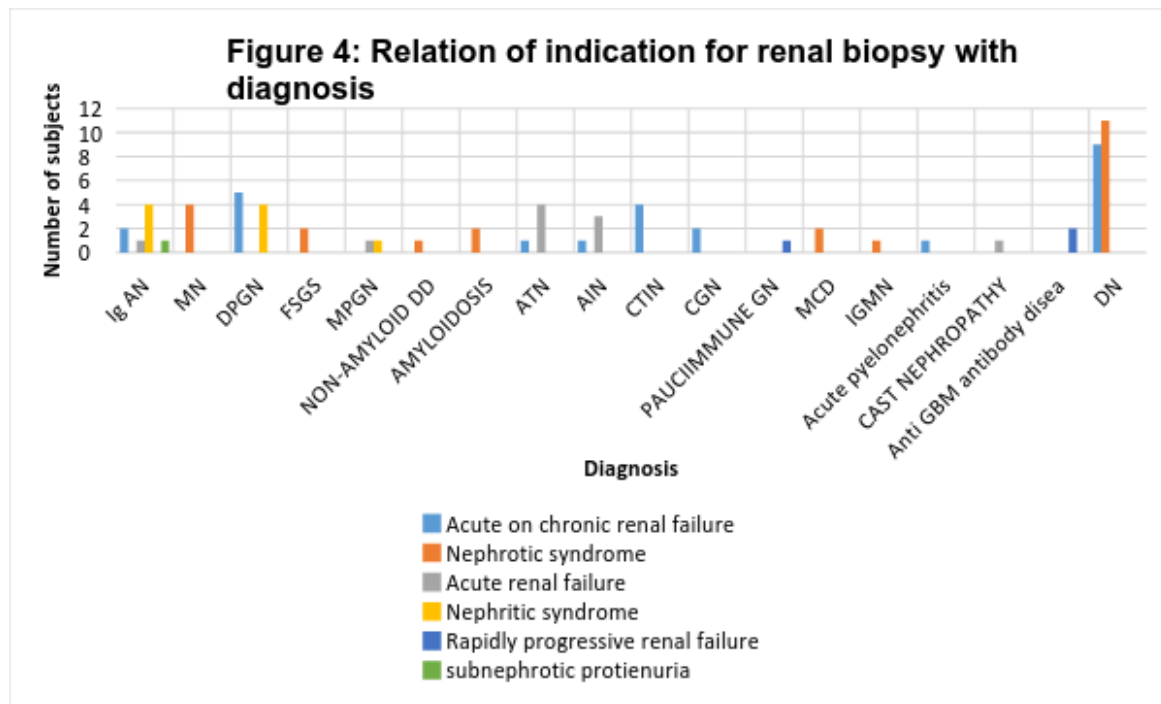
by CTIN (2.82%) and acute pyelonephritis (APN) (1.41%) (Figure 2).

**Relation of indication of renal biopsy with histology**

The commonest indication for biopsy was acute on chronic renal failure (ACRF) (35 %) followed by nephrotic syndrome (NS) (31%), acute renal failure (ARF) (14%), acute nephritic syndrome (ANS) (14%), rapidly progressive glomerulonephritis (RPGN) (4%) and subnephrotic protienuria (1%) (Figure 3). The clinical syndromes and the histological diagnosis are summarised in figure 4. The DPGN was the most common pathology followed by CTIN, IgAN, CGN, AIN, ATN and APN in subjects who underwent renal biopsy for ACRF. The DN was the commonest cause for presentation as NS in T2DM followed by MN, FSGS, amyloidosis, MCD, IgMN, non-amyloid deposition disease. The ATN was commonest cause of ARF followed by AIN, IgAN, MPGN and cast nephropathy. The DPGN and IgAN were the most common causes for ANS followed by MPGN. The ANCA related pauciimmune GN and anti-GBM antibody disease were the causes of RPGN and one subject who underwent biopsy for subnephrotic protienuria had IgAN. The relation of syndromic diagnosis with renal histology was statistically significant (Pearson Chi-square value: 34.27 & p:0.0001).

**Figure 3: Indications for renal biopsy (Percentages)**





## DISCUSSION

The majority of patients whose history and clinical findings are compatible with diabetic kidney disease do not benefit from kidney biopsy, because the diagnosis and treatment is usually not altered.<sup>[1]</sup> However, renal biopsy is helpful in diagnosis and treatment of NDRD in those with T2DM.<sup>[2-11]</sup> The clues for NDRD in T2DM are presence of active urinary sediments, low complement levels, sudden deterioration of renal function, nephrotic proteinuria without retinopathy or neuropathy, impaired renal function with normal and/or low grade of proteinuria, absence of retinopathy and short duration of diabetes.<sup>[9-11]</sup>

In the present study, prevalence rates of NDRD, DN and DN with NDRD were 50.71, 28.16 and 21.13 % respectively. Observations our studies are similar with earlier reports of renal biopsies in patients with T2DM. The prevalence rates of NDRD, DN and NDRD+ND varied from 24.73 to 82.9 %, 6.5 to 66 % and 4 to 44.08% respectively, in earlier studies.<sup>[2-5,7-9]</sup> The variations in percentages is due to heterogeneity of subjects and indications for biopsies. In one study reported from south India, 50 % of the subjects had NDRD and remaining had DN.<sup>[6]</sup>

The commonest NDRDs varied in different studies, due to variations in biopsy policies, geographic and ethnic factors. The TIDs were commonest NDRD in two earlier studies<sup>[7, 9]</sup>, and proliferative GN as the most common in one<sup>[5]</sup> and MN in another study<sup>[6]</sup>.

Primary glomerular diseases (PGD) were commonest cause for NDRD in the present study. A wide spectrum of PGDs were observed with four most common lesions being, The IgAN (9.86 %), IRGN (7.04%), MN (5.63%) and FSGS (4.22%). Almost all types of PGDs have been reported in the literature.<sup>[2-11]</sup> The FSGS, IgAN, MN, post infectious glomerulonephritis and MCD were the commonest PGDs respectively, in earlier studies.<sup>[3,4, 6-8]</sup>

The primary amyloidosis was commonest SGDs followed by ANCA related pauci-immune glomerulonephritis and non-amyloid deposition disease in present study. Whereas, lupus nephritis was the commonest in an earlier study.<sup>[8]</sup>

Diabetic nephropathy with superimposed NDRD was found in 21.13% subjects. (glomerular diseases: 9.86 % and TID: 11.27 %). The acute tubular injury/necrosis (ATIN) was the most common associated TIDs followed by CTIN. The IRGN was the most common associated glomerular disease followed by IgAN. The



prevalence of NDRD superimposed on DN was varied widely (4-41%) in earlier studies. <sup>[3, 7-9]</sup> The IgAN and MN were the most prevalent lesions found in patients with DN in one of the studies. <sup>[3]</sup>

The commonest indication for biopsy in the study was ACRF followed by NS, ARF, ANS, RPGN and subnephrotic proteinuria. The DPGN, DN, ATN, ANCA related pauciimmune GN and IgAN were the most common pathologies in those who underwent renal biopsies for evaluation of ACRF, NS, ARF, RPGN and subnephrotic proteinuria, respectively. The DPGN and IgAN were the most common causes for ANS.

The reported indications for biopsies in earlier reports were similar to the present study; which included NS, ARF, RPRF, absence of retinopathy, hematuria and ACRF. <sup>[2, 4, 7, 8, 9]</sup>

## CONCLUSIONS

The prevalence of NDRD in T2DM is high in our population, especially in subjects who present with atypical features like a ACRF, ARF, RPGN, ANS, thereby making the renal biopsy procedure imperative for its diagnosis and appropriate treatment. The prevalence rates of NDRD, DN and NDRD superimposed on DN were 50.71, 28.16 and 21.13 % respectively. The NDRDs are the cause NS in upto 48 % of cases with remaining due to DN and diagnosis of them needs renal histology. The PGDs were commonest cause for NDRD, followed by TIDs. Among the PGDs the IgAN, IRGN, MN and FSGS were common. The ATN was the commonest TID followed by AIN. The ATN followed by IRGN were the two most NDRD to be associated in those with underlying DN. The mean duration of T2DM was higher in subjects with DN or DN with superimposed NDRD than those with isolated NDRD.

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**Conflicts of Interest:** Nil

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