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Nondiabetic Renal Disease (NDRD) in Type 2 Diabetes Mellitus (T2DM)

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Abstract

Background: The prevalence of nondiabetic renal disease (NDRD) in those with type 2 diabetes mellitus (T2DM) is common worldwide, however, data from India is limited. *Methods:* This study included subjects of T2DM who underwent renal biopsy with suspicion of NDRD from September 2009 to August 2016. *Results:* Seventy-one subjects (males:47 [66.2%] and females:24 [33.8%]) of T2DM with mean age and standard deviation (SD) of 52.93±12.56 years were included in the study. The indications for renal biopsy included acute on chronic renal failure (ACRF) in 35.2% (25), nephrotic syndrome (NS) in 31% (22), acute renal failure (ARF) in 14.1% (10), nephritic syndrome in 14.1% (10) and others in 5.6% (4) of subjects. The prevalence rates of NDRD, diabetic nephropathy (DN) and DN with NDRD were 50.71 (36), 28.16 (20) and 21.13% (15) respectively. Among the subjects with NDRD, 69.44% (25) had primary glomerular diseases (PGDs), 16.67% (6) had tubulointerstitial diseases (TIDs) and 13.89% (5) had secondary glomerular diseases (SGDs). The IgA nephropathy (IgAN) was the commonest of the PGDs affecting 28% (7) followed by post-infective glomerulonephritis (PIGN) in 20% (5), membranous nephropathy (MN) in 16% (4), focal segmental glomerulosclerosis (FSGS) in 12% (3) and miscellaneous lesions in 24% (10). The acute interstitial nephritis (AIN) and primary amyloidosis were the commonest of TIDs and SGDs respectively. Among the patients with combination of DN with NDRD, 53.33% (8) were TIDs and 46.67% (7) had glomerular diseases. The acute tubular injury/necrosis (ATN) and PIGN were the commonest of TIDs and glomerular disease respectively. The figures in brackets representing number of patients. *Conclusions:* Majority of the subjects with T2DM had NDRD either alone or in combination with DN in the study, underlining the utility of renal biopsy for their diagnoses in those with appropriate indication. Wide spectrum of PGDs, TIDs and SGDs were found in the study.

Keywords: Type 2 Diabetes Mellitus; Non-Diabetic 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) [1]. However, in T2DM 12-82% of them had renal lesions were due to non-diabetic renal diseases (NDRD) in different series [2-11]. The end stage renal disease in T2DM is due to

NDRD in 40-60% of cases there by stressing the importance of early diagnosis [10]. 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 [9-11].

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.

Meterials and Methods

This is a retrospective study which included all consecutive patients of T2DM who underwent renal biopsies 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), Jone's silver methaneamine and Gomori's trichrome stains (MT) and immunofluorescence (IF) studies were performed using anti-human IgG, IgA, IgM, C3, C1q, kappa and lambda light chains. The IF analysis was done using anti-mouse IgG (whole molecule)-FITC (fluorescein isothiocyanate) antibody sourced from goat on frozen sections.

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

The indications for renal biopsy were: acute on chronic renal failure (ACRF), nephrotic syndrome, acute renal failure, nephritic syndrome, rapidly progressive renal failure and subnephrotic protienuria.

The ACRF was diagnosed if, there was a rapid decline of renal function characterized by progressive decline in glomerular filtration rate manifested by increasing serum creatinine or oliguria or need for dialysis in stable case of chronic kidney disease. Patients underwent renal biopsy after exclusion of pre-renal, obvious intra-renal lesions like acute pyelonephrits, accelerated hypertension and post-renal causes for acute worsening of renal function.

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 and presence of pseudolinear pattern on IF. The NDRDs were diagnosed and categorized as per standard guidelines [12].

The protocol was submitted to the institutional ethical committee and was approved as it was retrospective study without any added cost to the patients or the institution.

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 observations were analyzed and presented as mean, standard deviation, percentage, and patient number as per relevance. Statistical tests used were Pearson's Chi square test and Fishers Exact test as applicable in analysis. The $p < 0.05$ (2-sided) was considered as statistically significant.

Results

A total 71 patients (Males: 47 [66.2%] and Females: 24 [33.8%], 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 summarized in Table 1. The prevalence of different histologies are presented as percentages followed by figures in brackets representing number of patients diagnosed with the type of lesion.

The prevalence rates of NDRD, DN and DN with NDRD were 50.71 (36), 28.16 (20) and 21.13% (15) respectively (Figure 1). The mean age, gender, duration of T2DM and number of subjects with DN, DN+NDRD and NDRD, are summarized in Table 2. The mean duration of T2DM were 12.45, 12.13 and 5.33 years in subjects 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 ($p > 0.05$).

Non-Diabetic Renal Disease (NDRD)

The NDRD was found in 50.71% (36 of 71) of subjects. Among the subjects with NDRD, 69.44% (25) had primary glomerular diseases (PGDs), 16.67% (6) had tubulointerstitial diseases (TIDs) and 13.89% (5) had secondary glomerular diseases

(SGDs). The IgAN was the most common among PGDs affecting 28% (7) of subjects followed by PIGN in 20% (5), MN in 16% (4), FSGS in 12% (3), chronic glomerulonephritis (CGN) in 8% (2), membranoproliferative glomerulonephritis (MPGN) in 8% (2), IgM nephropathy in 4% (1), and minimal change disease (MCD) in 4% (1) (Figure 2). All the cases of PIGN in the study were characterized by low C3 and normal C4 and were secondary to infections.

The acute interstitial nephritis (AIN) was the commonest among TIDs found in 50% (3) subjects followed by chronic tubulointerstitial nephritis (CTIN) in 33.33% (2) and cast nephropathy in 16.67% (1).

The primary amyloidosis was commonest among SGDs affecting 40% (2), followed by non-amyloid deposition disease 20% (1), ANCA related pauci-immune glomerulonephritis in 20 % (1) and anti-glomerular basement membrane (GBM) disease in 20 % (1).

Diabetic Nephropathy (DN)

The isolated diabetic nephropathy was found in 28.16 % (20 of 71) of subjects and was diagnosed by presence characteristics as described in methods.

Diabetic Nephropathy with Associated NDRD

Diabetic nephropathy with associated NDRD was found in 21.13% (15 of 71) subjects of which 53.33% (8) were TIDs and 46.67% (7) had glomerular diseases. The acute tubular injury/necrosis (ATN) was the commonest TIDs affecting 62.5% (5) followed by CTIN in 25% (2) and acute pyelonephritis (APN) 12.5% (1) of subjects (Figure 2). The PIGN was the commonest glomerular disease affecting 57.14% (4) of subjects, followed by IgAN in 14.28% (1) anti-GBM disease in 14.28% (1) and ANCA related pauci-immune glomerulonephritis in 14.28% (1).

Relation of Indication of Renal Biopsy with Histology

The commonest indication for biopsy was acute on chronic renal failure (ACRF) in 35.2% (25) followed by nephrotic syndrome (NS) in 31% (22), acute renal failure (ARF) in 14.1% (10), acute nephritic syndrome (ANS) 14.1% (10), rapidly progressive glomerulonephritis (RPGN) 4.2% (3) and subnephrotic protienuria in 1.4% (1) (Figure 2). The clinical syndromes and histological diagnosis are summarized in Figure 3.

The PIGN 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 PIGN and IgAN were the most common causes for ANS followed by MPGN. The ANCA related pauciimmune GN and anti-GBM 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 & $p < 0.01$).

Table 1: The demographic data of subjects with Type 2 diabetes mellitus

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

Table 2: Relation of renal histology to duration of type 2 diabetes mellitus, age and gender

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

NDRD: non-diabetic renal disease
DN: diabetic nephropathy
DN+NDRD: diabetic nephropathy with non-diabetic renal disease

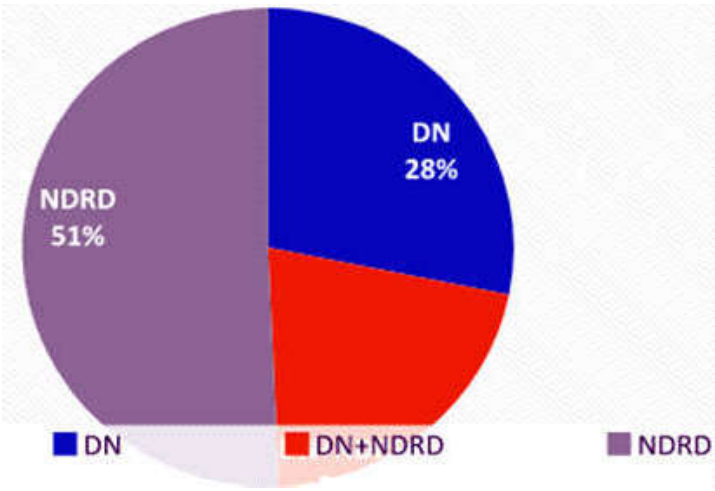

Fig. 1: Broad categorization according to renal histology in subjects with type 2 diabetes mellitus

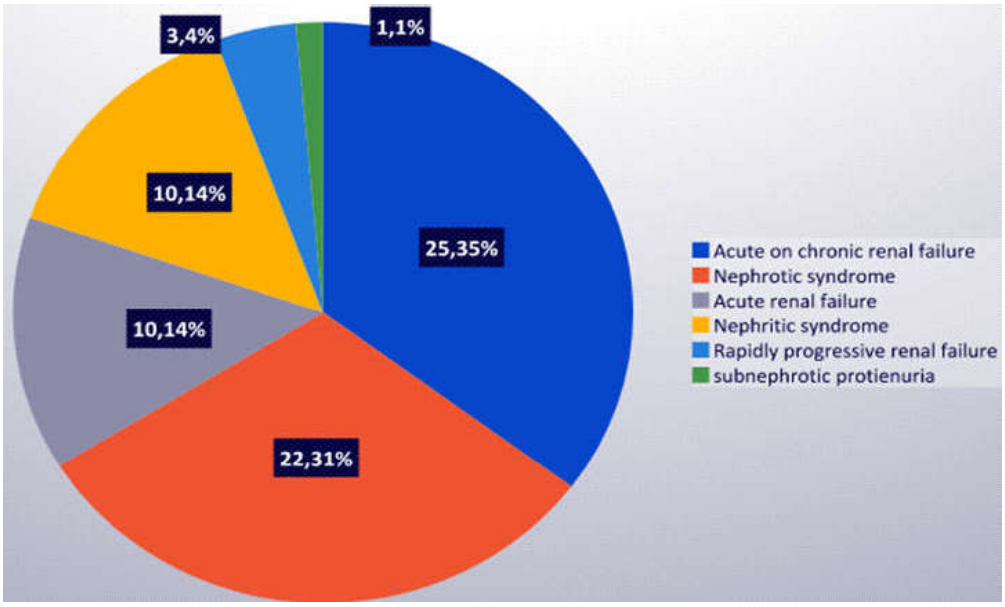

Fig. 2: Indication for renal biopsy (Number of subjects and percentage)

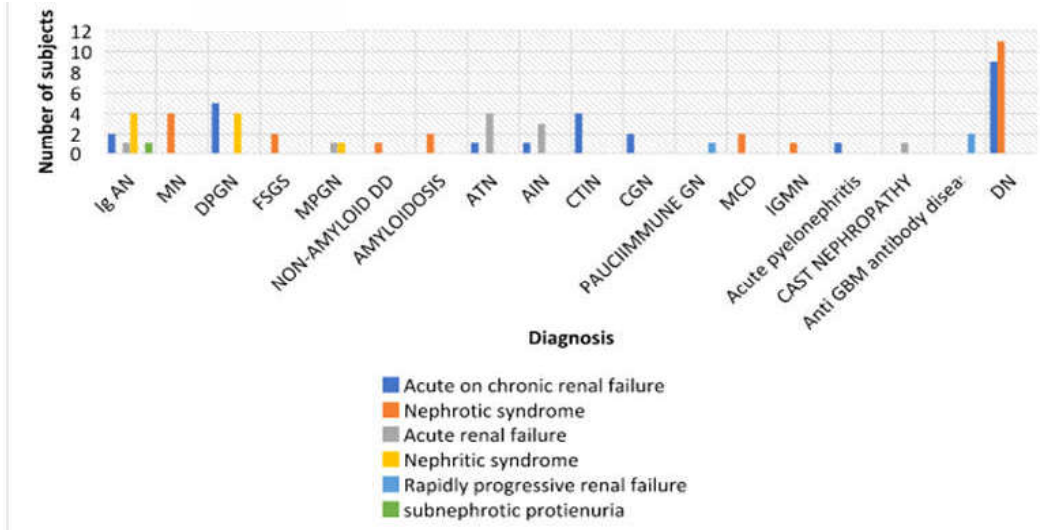

Fig. 3: Relation of indication for renal biopsy with diagnosis

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 [1]. However, renal biopsy is helpful in diagnosis and treatment of NDRD in those with T2DM [2-11]. 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 [9-11].

In the present study, prevalence rates of NDRD, DN and DN with NDRD were 50.71, 28.16 and 21.13 % respectively. Observations our study 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 [2-5,7-9]. 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 [6].

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 [7, 9] and proliferative GN as the most common in one [5] and MN in another study [6].

Primary glomerular diseases (PGDs) were commonest cause for NDRD in the present study, with four most common being, The IgAN, PIGN, MN and FSGS. Almost all types of PGDs have been reported in the literature [2-11]. The FSGS, IgAN, MN, post infectious glomerulonephritis and MCD were the commonest PGDs respectively, in earlier studies [3,4, 6-8].

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 [8].

Diabetic nephropathy with superimposed NDRD was found in 21.13% subjects, with ATIN and PIGN being the two common associated lesions in the present study. The prevalence of NDRD superimposed on DN was varied widely (4-41%) in earlier studies [3, 7-9]. The IgAN and MN were the most prevalent lesions found in patients with DN in one of the studies [3].

The commonest indication for biopsy in the study was ACRF followed by NS, ARF, ANS, RPGN and subnephrotic protienuria. The reported indications for biopsies in earlier reports were similar to the present study; which included NS, ARF, RPRF, absence of retinopathy, haematuria and ACRF [2, 4,7,8,9].

Limitations

The smaller sample size and absence of electron microscopic evaluation are two major limitations of the study.

Conclusions

The prevalence of NDRD in T2DM is high in our population, especially in subjects who underwent renal biopsy due to presence with atypical features. 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 up-to 48% of cases. The PGDs were commonest cause for NDRD, followed by TIDs. Among the PGDs the IgAN, PIGN, MN and FSGS were common. The ATN was the commonest TID followed by AIN. The ATN followed by PIGN 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.

Source(s) of Support: Nil

Conflicts of Interest: Nil

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