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A study of non-diabetic kidney diseases in type 2 diabetes mellitus patients presenting to tertiary care hospital in south India

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Abstract

Background: Due to various lifestyle modifications and other causes, metabolic disorders are on the rise in developing countries such as India. Patients with Type 2 DM often experience diabetic nephropathy, they can also develop other renal diseases, pathologically unrelated to diabetes and known as non-diabetic kidney disease (NDKD) which may present as isolated lesion or superimposed with diabetic nephropathy. The spectrum of NDKD type-2 diabetics is primary glomerular disease, secondary glomerular diseases and tubulointerstitial disease. Hence, the need was felt to carry out this study to evaluate the renal biopsies performed on type-2 diabetic patients with suspicion of NDKD and to associate the histopathological findings with clinical presentations and laboratory parameters.

Methods: A prospective study was conducted at SDM Medical College and Hospital, Dharwad among 50 patients with type 2 DM. Data was collected using a predesigned, pre-tested, semi- structured questionnaire and analysed using SPSS software version 16.

Results: Out of 50 study subjects, 32% had Non- diabetic renal disease (NDRD), 28% had NDRD superimposed on underlying DN and 40% had Diabetic nephropathy (DN). Histopathological diagnosis among the total 30 patients with NDRD and NDRD+DN showed ATIN in 23.3%, Benign nephrosclerosis in 10%, Membranous nephropathy in 10%, Membranoproliferative glomerulonephritis in 10%, IgA nephropathy in 10%, Postinfectious glomerulonephritis in 10%, Lupus nephritis in 10%, Acute pyelonephritis in 6.7%, Mesangioproliferative glomerulonephritis in 3.3%, Focal segmental glomerulosclerosis in 3.3% and Crescentic glomerulonephritis in 3.3% of the patients.

Conclusion: The incidence of NDRD among DM patients was very high. Shorter duration of DM with haematuria, proteinuria, absence of retinopathy, with low serum complement levels strongly predict NDRD. Renal biopsy should be considered in NDRD patients to determine the underlying cause of proteinuria.

Keywords: non diabetic kidney disease; diabetes mellitus; nephropathy; renal biopsy; metabolic disorders

Introduction

Diabetes mellitus (DM), one of the non-communicable diseases (NCDs) that have emerged as a leading global health problem. DM refers to a group of common metabolic disorder that shares phenotype of hyperglycemia. It is a long-standing illness that needs continuing medical care and support to prevent acute complications and to reduce the risk of long-term complications [1]. Globally, around 450 million people are suffering from diabetes mellitus. The age-standardized global prevalence of diabetes mellitus among adult population has nearly doubled since year 1980, rising from 4.7 to 8.5% [2]. The greatest increase in the prevalence of diabetes mellitus is reported from low and middle-income countries. Asia, being the epicentre for the epidemics of diabetes, is responsible for more than 60% of the global burden of diabetes mellitus [3, 4]. India, with 69.2 million people with T2DM, is the country with 2nd highest number of people living with diabetes mellitus worldwide next to China [5].

Diabetes specific renal disease (diabetic nephropathy) which is a devastating complication of diabetes, develops in about one-third of all people with Type 1 or Type 2 diabetes and it contributes to about 30% of end-stage renal disease (ESRD) in various countries which is leading among maintenance haemodialysis patients. The survival is less in them compared to other ESRD patients [6].

Although, patients with Type 2 DM often experience diabetic nephropathy, they can also develop other renal diseases, pathologically unrelated to diabetes and known as non-diabetic kidney disease (NDKD) which may present as isolated lesion or superimposed with diabetic nephropathy. It has been reported that 12-80% of Type 2 diabetic patients with renal involvement show non-diabetic kidney disease [7]. The spectrum of NDKD type-2 diabetics is primary glomerular disease, secondary glomerular diseases and tubulointerstitial disease. Among primary glomerular disease, FSGS is commonest lesion followed by minimal change disease and membranous nephropathy. Some studies had showed that tubulointerstitial nephritis as commonest NDKD [8].

Diabetic nephropathy is very difficult to reverse whereas NDKD is treatable and remittable so the differential diagnosis of these two entities is of considerable importance. There are few clinical and diagnostic clues which will suggest NDKD. Kidney biopsy is necessary to diagnose these diseases, but it cannot be used as routine diagnostic test in type-2 diabetics with proteinuria. Hence, this study was undertaken in order to evaluate the renal

biopsies performed on type-2 diabetic patients with suspicion of NDKD and to associate the histopathological findings with clinical presentations and laboratory parameters.

Methodology

Study design and Area

The present prospective study was conducted on total of 50 patients with diabetes mellitus admitted to medical /nephrology ward for kidney biopsy from SDM Medical College and Hospital, Dharwad.

Inclusion Criteria

Patients with type-2 DM admitted with

1. Active urinary sediment (fragmented RBCS/RBC casts/microhaematuria)
2. Sudden deterioration of renal function (decrease in glomerular filtration rate (GFR) more than 1 ml/min/1.73m^2 /month)
3. Heavy proteinuria with normal renal function
4. Impaired renal function with normal and/or low grade of proteinuria
5. Low complement levels
6. Absence of retinopathy/neuropathy
7. Short duration of diabetes

Exclusion Criteria

Type-2 DM pts admitted with

1. Presence of moderate to severe NPDR/PDR with /without treatment
2. Presence of peripheral neuropathy
3. Long duration of DM with slow decline GFR
4. B/L small kidneys

Methods

Before conducting the study, Ethical clearance was obtained from the Institutional Ethical Committee of SDM Medical College. Written informed consent was obtained from all the patients who were recruited in the study. Data was collected in the case proforma which included clinical examination. Relevant investigations were carried out and recorded. It included:

- Complete hemogram
- Blood Urea.
- Total protein and albumin
- Urine Routine/Microscopy, urine albumin /pus cells RBC, urine 24hour urinary protein
- Serum creatinine
- T cholesterol/ LDL/HDL/TG as routine investigations.

Renal biopsies were performed by automated biopsy gun. Tissue was processed for light microscopy (using Hematoxylin and eosin, periodic acid Schiff, Masson's trichrome, and Jones silver methenamine staining), immunofluorescence. The biopsies were reported by Nephropathologist of our institute.

Data Analysis

Data was compiled using MS Excel (2010) and statistical analysis was done using SPSS software version 16. The patient characteristics are presented as frequencies for the categorical variables and as the means and standard deviations. Chi-square test, Fischer's exact test were applied to find out association and t-test (unpaired) was applied to compare mean values. Fisher's exact test was used when more than 20% cells had expected value < 5 and any one of the cells had expected value < 1. All statistical analysis was carried out at 5% level of significance and p value <0.05 was considered as significant.

Variables: Diagnosis of DKD (Diabetic Kidney diseases) was based on the renal findings including glomerular basement membrane (GBM) thickening, mesangial expansion, nodular glomerulosclerosis, hyaline insudation in glomeruli in the form of fibrin cap, capsular drop or hyaline thrombi, arteriolar hyalinosis and arteriosclerosis. Immunofluorescence studies helped in differentiating diabetic glomerular lesions from NDKD. Diffuse linear staining of GBM and tubular basement membranes for IgG due to nonimmunological trapping of proteins in thickened abnormal basement membranes, and nonspecific entrapment of IgM, C3 and light chains were compatible with DKD. NDKD (Nondiabetic Kidney disease) and/or superimposed kidney disease comprising of membranous nephropathy (MN), Ig a nephropathy, focal segmental glomerulosclerosis (FSGS), and tubulointerstitial nephritis (TIN) were differentiated by the histopathologic evaluation.

Observations

Out of 50 study subjects, 19 (38%) were females and 31 (62%) were males. The mean age of the 50 study participants was 54.16 ± 6.49 years. 16 (32%) had Non-diabetic renal disease (NDRD), 14 (28%) had NDRD superimposed on underlying DN and 20 (40%) had Diabetic nephropathy (DN). The mean age of patients with NDRD was 55.38 ± 7.03years, NDRD+DN was 52.64 ± 6.60 and DN was 54.25 ± 6.06years. However, this difference was statistically not significant (p value<0.05). NDRD was more common in males. Whereas NDRD+DN and DN was more common among females. This association was statistically significant (p value = 0.008). The mean Duration of DM among patients with NDRD was 6.06 ± 2.72years, NDRD+DN was 7.36 ± 1.59years and DN was 7.60 ± 1.87years. However, this difference was statistically not significant (p value<0.05). Retinopathy was not seen in patients with NDRD, but seen 1 (7.1%) of patients with NDRD+DN and 5 (25%) of patients with DN. The mean Proteinuria among patients with NDRD was 4.20 ± 2.91g/day, NDRD+DN was 3.48 ± 1.66g/day and DN was 7.91 ± 1.71g/day. This difference was statistically highly significant (p value <0.001). The mean Serum Creatinine among patients with NDRD was 2.31 ± 0.92 mg/dL, NDRD+DN was 6.44 ± 1.73 mg/dL and DN was 3.68 ± 0.65 mg/dL and this difference was also statistically highly significant (p value <0.001). Haematuria was seen in 8 (50%) of patients with NDRD, 9 (64.3%) of patients with NDRD+DN and 9 (45%) of patients with DN. But this association was not statistically significant (p value >0.05). Low serum C3and/ or C4 was seen in 2 (12.5%) of patients with NDRD, 2 (14.3%) of patients with NDRD+DN and 5 (25%) of patients with DN. High serum ANA/dsDNA was seen in 1 (6.2%) of patients with NDRD, 2 (14.3%) of patients with NDRD+DN and 3 (15%) of patients with DN. Both of this association were not statistically significant (p value >0.05). Histopathological diagnosis among the total 30 patients with NDRD and NDRD+DN were ATIN in 7 (23.3%), Benign nephrosclerosis in 3(10%), Membranous nephropathy in 3(10%), Membrano proliferative glomerul one phritis in 3(10%), IgA nephropathy in 3(10%), Post-

infectious glomerulonephritis in 3 (10%), Lupus nephritis in 3 (10%), Acute pyelonephritis in 2 (6.7%), Mesangio pro-life rative glomerulonephritis in 1 (3.3%), Focal segmental glomerulosclerosis in 1 (3.3%) and Crescentic glomerulonephritis in 1 (3.3%).

Table 1: Gender wise distribution of study participants.

Gender	Frequency	Percentage
Female	19	38%
Male	31	62%
Total	50	100%

Table 2: Type of Renal disease in study participants.

Type of Renal disease	Frequency	Percentage
Non- diabetic renal disease (NDRD)	16	32%
NDRD superimposed on underlying DN (NDRD+DN)	14	28%
Diabetic nephropathy (DN)	20	40%
Total	50	100%

Table 3: Histopathological diagnosis in study participants.

Histopathological diagnosis	NDRD (n=16)	NDRD+DN (n=14)	DN (n=20)
ATIN	3 (18.8%)	4 (28.6%)	7 (23.3%)
Benign nephrosclerosis	1 (6.3%)	2 (14.3%)	3 (10.0%)
Membranous nephropathy	2 (12.5%)	1 (7.1%)	3 (10.0%)
Membranoproliferative glomerulonephritis	2 (12.5%)	1 (7.1%)	3 (10.0%)
IgA nephropathy	2 (12.5%)	1 (7.1%)	3 (10.0%)
Mesangioproliferative glomerulonephritis	1 (6.3%)	0	1 (3.3%)
Focal segmental glomerulosclerosis	1 (6.3%)	0	1 (3.3%)
Postinfectious glomerulonephritis	1 (6.3%)	2 (14.3%)	3 (10.0%)
Lupus nephritis	2 (12.5%)	1 (7.1%)	3 (10.0%)
Crescentic glomerulonephritis	1 (6.3%)	0	1 (3.3%)
Acute pyelonephritis	0	2 (14.3%)	2 (6.7%)

Table 4: Baseline characteristics & clinical evaluation of study participants.

Variables	NDRD (n=16)	NDRD+DN (n=14)	DN (n=20)	P value
Age (years)	55.38 ± 7.03	52.64 ± 6.60	54.25 ± 6.06	0.524
Proteinuria (g/day)	4.20 ± 2.91	3.48 ± 1.66	7.91 ± 1.71	<0.001
Serum Creatinine (mg/dL)	2.31 ± 0.92	6.44 ± 1.73	3.68 ± 0.65	<0.001
Systolic Blood pressure (mm Hg)	132.88 ± 8.70	134.86 ± 10.63	137.20 ± 15.23	0.573
Diastolic Blood pressure (mm Hg)	85.31 ± 2.70	87.64 ± 1.44	87.45 ± 3.72	0.051
Duration of DM (in years)	6.06 ± 2.72	7.36 ± 1.59	7.60 ± 1.87	0.088
Gender				
Female	3 (18.8%)	10 (71.4%)	6 (30.0%)	0.61
Male	13 (81.2%)	4 (28.6%)	14 (70.0%)	
Retinopathy				
Yes	0	1(7.1%)	5 (25.0%)	0.58
No	16 (100%)	13 (92.9%)	15 (75.0%)	
Haematuria				
Yes	8 (50.0%)	9 (64.3%)	9 (45.0%)	0.531
No	8 (50.0%)	5 (35.7%)	11 (55.0%)	
Low serum C3and/ or C4				
Yes	2 (12.5%)	2 (14.3%)	5 (25.0%)	0.570
No	14 (87.5%)	12 (85.7%)	15 (75.0%)	
High serum ANA/dsDNA				
Yes	1 (6.25%)	2 (14.3%)	3 (15.0%)	0.691
No	15 (93.8%)	12 (85.7%)	17 (85.0%)	
Indications for renal biopsy				
NS	5 (31.2%)	5 (35.7%)	12 (60.0%)	0.172
AKI	3 (18.8%)	2 (14.3%)	6 (30.0%)	0.514
CRF	1 (6.25%)	2 (14.3%)	3 (15.0%)	0.691
RPRF	1 (6.25%)	2 (14.3%)	2 (10.0%)	0.765
HTN	1 (6.25%)	1 (7.1%)	5 (25.0%)	0.187

Discussion

A prospective study was conducted among the diabetic patients admitted in SDM Medical College for renal biopsy. The study was conducted to evaluate the non-diabetic kidney disease among the diabetic patients. 50 patients were included in the study for the period of 12 months.

Age

In the present study mean age of the study participants was 54.16 ± 6.49 years and 62% of them were males. Out of 50 study subjects, 32% had Non- diabetic renal disease (NDRD), 28% had NDRD superimposed on underlying DN and 40% had Diabetic nephropathy (DN). The mean age of patients with NDRD was 55.38 ± 7.03 years, NDRD+DN was 52.64 ± 6.60 and DN was 54.25 ± 6.06 years. These results are similar to a study conducted by Mami I *et al*, where the mean age of patients with NDRD was 55.2 ± 10.6 years, NDRD + DN was 54.1 ± 11.8 and DN was 47.4 ± 7.6 years [9]. In another study done Kanodia KV *et al* also, the mean age of patients with NDRD was 55.08 ± 10.71 years, NDRD + DN was 55.65 ± 8.71 and DN was 54.45 ± 9.01 years [10]. In a similar study conducted by Erdogmus S *et al*, the mean age of patients was little higher with NDRD was 60 years, NDRD + DN was 60 years and DN was 61 years [11].

Gender

According to our study, NDRD was more common in males, whereas NDRD+DN and DN were more common among females. However, these results are in contrast to a similar

study done by Erdogmus S *et al*, where, NDRD was more common in females, whereas NDRD+DN and DN was common in males [11]. A similar study done by Mami I *et al*, also showed male predominance with male: female ratio of 1.06 in NDRD, 3.8 in NDRD + DN and 1.25 in isolated DN [9]. In another study done Kanodia KV *et al*, also there was male predominance where among 152 diabetic patients, 111 were males and 41 were females. Among males 20 patients had NDRD, 29 had NDRD + DN and 60 patients had isolated DN [10].

Duration of DM

The mean duration of DM in our study in patients with NDRD was 6.06 ± 2.72 years, NDRD+DN was 7.36 ± 1.59 years and DN was 7.60 ± 1.87 years. In a similar study conducted by Erdogmus S *et al*, the duration of DM in patients with NDRD was 6 years, NDRD+DN was 12 years and DN was 10 years.[11] In another study done Kanodia KV *et al*, the duration of DM in patients with NDRD was 5.59 ± 4.96years, NDRD + DN was 7.13 ± 3.95 years and DN was 10.45 ± 6.62 years [10].

Retinopathy

According to our study retinopathy was not seen in patients with NDRD, but was seen among 7.1% patients with NDRD + DN and 5.25% patients with DN. These results are similar to study conducted by Kanodia KV *et al*, where there was no case of retinopathy in patients with NDRD group, but was seen with 11.42% patients with NDRD + DN and 12.19% patients with DN [10]. A similar study done by Mami I *et al* also, retinopathy was less in patients with NDRD with 12% cases, compared to NDRD+DN with 45% patients and 50% of patients with DN with significant results association.[9] In another study conducted by Erdogmus S *et al* also, Retinopathy was less in patients with NDRD (8.3%), but seen most commonly with NDRD + DN (25%) and DN (75%) [11].

Blood Pressure

In the present study the mean systolic blood pressure among patients with NDRD was 132.88 ± 8.70 mmHg, NDRD + DN was 134.86 ± 10.63 mmHg and DN was 137.20 ± 15.23 mmHg. The mean diastolic blood pressure among patients with NDRD was 85.31 ± 2.70 mmHg, NDRD + DN was 87.64 ± 1.44 mmHg and DN was 87.45 ± 3.72 mmHg. These results are similar to the findings in another study done by Kanodia KV *et al*, the mean systolic blood pressure among patients with NDRD was 132.57 ± 9.54mmHg, NDRD+DN was 139.27 ± 15.36mmHg and DN was 132.49 ± 30.03 mmHg and the mean diastolic blood pressure among patients with NDRD was 84.34 ± 5.23 mmHg, NDRD + DN was 86.36 ± 8.47mmHg and DN was 85.63 ± 8.35 mmHg.[10] A similar study done by Mami I *et al*, the mean systolic blood pressure among patients with NDRD was 132.57 ± 9.54 mmHg, NDRD+DN was 139.27±15.36 mmHg and DN was 132.49±30.03mmHg and the mean diastolic blood pressure among patients with NDRD was 84.34 ± 5.23mmHg, NDRD+DN was 86.36 ± 8.47 mmHg and DN was 85.63 ± 8.35 mmHg [9].

Proteinuria

In our study, the mean proteinuria among patients with NDRD was 4.20 ± 2.91g/day, NDRD + DN was 3.48 ± 1.66 g/day and DN was 7.91 ± 1.71 g/day. A similar study done by Mami I *et al*, the mean proteinuria in patients with NDRD was 3.3 ± 4.0 g/day, NDRD+DN was 3.8 ± 3.3 g/day and DN was 2.9 ± 2.5 g/day.[9] In one more study conducted by Kanodia KV *et al*, the mean Proteinuria among patients with NDRD was 2.56 ± 2.91g/day, NDRD + DN was 2.5 ± 1.01g/day and DN was 6.92 ± 30.9 g/day [10].

Serum Creatinine

In the present study the mean serum creatinine among patients with NDRD was 2.31 ± 0.92 mg/dL, NDRD+DN was 6.44 ± 1.73 mg/dL and DN was 3.68 ± 0.65 mg/dL with statistically highly significant. In a similar study conducted by Erdogmus S *et al*, the serum creatinine levels were little lower as compared to our results. In their study, the mean Serum Creatinine levels with NDRD in was 1.46mg/dL, NDRD+DN was 1.74 mg/dL and DN was 1.32mg/dL.[11] A similar study done by Mami I *et al*, the mean Serum Creatinine levels with NDRD was 351 ± 391 µmol/L, NDRD + DN was 268 ± 280 µmol/L and DN was 383 ± 348 µmol/L [9].

Haematuria

Haematuria was seen in 50% patients with NDRD, 64.3% patients with NDRD + DN and 9.45% patients of DN. In another study done by Kanodia KV *et al* also, 34.28% patients with NDRD, 34.28% patients with NDRD + DN and 25.60% patients with DN had haematuria.[10] A similar study done by Mami I *et al*, 36% patients with NDRD, 25% patients with NDRD + DN and 5% of patients with DN had haematuria [9].

Complement levels

Serum C3 and/or C4 was low in DN (25%), followed by NDRD+DN (14.3%) and NDRD (12.5%). High serum ANA/dsDNA was seen in 6.2% patients with NDRD, 14.3% of patients with NDRD+DN and 15% patients with DN. Contrastingly, serum C3 and/or C4 was also low in 14.29% patients of NDRD and NDRD+DN and 2.43% patients with DN in a study done Kanodia KV *et al*. High serum ANA/dsDNA was seen in 5.7% of patients with NDRD, 2.86% of patients with NDRD+DN and 2.43% of patients with DN [10].

In our study, among NDRD, 31.2% had NS, 18.8% had AKI, 6.2% had CRF, 6.2% had RPRF and 6.2% had HTN. Among those with NDRD+DN, 35.7% had NS, 14.3% had AKI, 14.3% had CRF, 14.3% had RPRF and 7.1% had HTN. Among those patients with DN, 60% had NS, 30% had AKI, 15% had CRF, 10% had RPRF and 25% had HTN are the indication for renal biopsy.

In another study done Kanodia KV *et al*, the most common histological lesion in NDRD was ATIN (38.57%) followed by benign nephrosclerosis (15.72%), MN (10%), IgAN (7.14%), MPGN (7.14%), and MePGN (4.2%). But in NDRD+DM, ATIN was commonly seen in 57.14% followed by benign nephrosclerosis in 25.71%.[10] In a similar study conducted by Erdogmus S *et al*, the DRD+NDRD 50% patients had TIN, 25% patient had MN and 25% patient had FSGS.9 A similar study done by Mami I *et al*, the most common NDRD was FSGS in 21%, followed by membranous nephropathy in 19% patients, and Ig A nephropathy in 12% patients [11].

Conclusion

- The incidence of NDRD among DM patients was very

high.

- Shorter duration of DM with haematuria, proteinuria, absence of retinopathy, with low serum complement levels strongly predict NDRD.
- Renal biopsy should be considered in NDRD patients to determine the underlying cause of proteinuria.

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