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Study of Non Diabetic Kidney Disease in Type2 Diabetic Patients with Renal Involvement

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Abstract: *Diabetic nephropathy (DN) is one of the major complications of Diabetes Mellitus. It is estimated that 20-40% of diabetic patients will develop a diabetic renal disease. Diabetic nephropathy is the leading cause of end stage renal disease in India and across the world. But it is not the sole renal disease in diabetic patients. Kidney diseases other than diabetic nephropathy can occur in diabetic patients, and are known as non diabetic renal disease (NDRD), either isolated or superimposed on DN. The prevalence of NDRD is very high in type 2 diabetic patients and it varies widely depending on the populations being studied and the selection criteria. Several predictive factors which can be used as pointers to NDRD have been identified by different studies.*

Objective: *To study the prevalence, clinical spectrum and predictive factors of NDRD in type 2 diabetic patients with renal involvement.*

Methodology: *684 type 2 diabetic patients with renal involvement were screened, of which 646 had overt nephropathy.38 with atypical clinical renal disease were selected for the study, of which 20 had undergone renal biopsy. Patients were grouped into 3,group I-isolated NDRD, group II-isolated DN and groupIII-NDRD superimposed on DN,and their clinical and biochemical parameters were analysed.*

Observations and conclusions: *70% of the patients who underwent renal biopsy had NDRD with or without concurrent DN.Patients with isolated NDRD had shorter duration of diabetes compared to the other groups. Absence of retinopathy and the presence of microscopic hematuria had significant association with NDRD.IgA nephropathy was the commonest etiology of NDRD in our study.*

Keywords: *Diabetic nephropathy, hematuria, non diabetic renal disease, retinopathy.*

I. Introduction

The worldwide incidence and prevalence of diabetes mellitius (DM) are on the rise. As per United Nations Renal Data System (USRDS) reports, diabetes still remains the most common cause for ERSD in the United States and many other countries[1]. 20-40% of the patients with diabetes will develop a diabetic renal disease of which Diabetic Nephropathy (DN) is the most common form. The other forms of diabetic kidney disease collectively known as Non Diabetic Renal Disease (NDRD) occur as either isolated or superimposed on DN[2]. A wide spectrum of NDRD ,including both glomerular and tubulointestitial lesions are reported and the precise diagnosis of which requires histologic examination and immunofluorescence study. In contrast to type1diabetes, the incidence of NDRD is very high in type 2 diabetic patients. Renal biopsy study shows that 25-50% of patients with type 2 diabetes had glomerular lesions unrelated to or in addition to diabetic nephropathy[3,4,5]. Diabetic nephropathy is irreversible, but certain NDRD such as mesangioproliferative glomerulonephritis, IgA nephropathy and membraneous nephropathy are often treatable [6,7]. Hence the distinction of these two entities in diabetic patients is extremely important.

Diabetes specific renal disease (DN) develop in one third of all people with type1 or type 2 diabetes and in other secondary forms of diabetes mellitus. The pathogenesis of diabetic nephropathy is related to chronic hyperglycemia.The mechanism involve

i) The effects of soluble factors - Growth factors, AngiotensinII, Endothelin, Advanced Glycation End products[AGE].

ii) Hemodynamic alterations in the renal microcirculation - Glomerular hyperfiltration or hyperperfusion and increased glomerular capillary pressure.

iii) Structural changes in the glomerulus - Increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis.

Some of these effects may be mediated through Angiotensin II receptors. Smoking accelerates the decline in renal function. Type2 diabetics with marked proteinuria and retinopathy most likely have diabetic nephropathy while those without retinopathy have a high frequency of other renal diseases pathologically unrelated to diabetes [8,9]. Proteinuria and/or hematuria in diabetes mellitus is occassionaly due to a glomerular disease other

than diabetic nephropathy. As examples ,membraneous nephropathy, minimal change disease, IgA nephropathy, focal segmental glomerulosclerosis, Henoch-schonlein purpura(IgA vasculitis), thin basement membrane disease, prolifrative glomerulonephritis and pauci immune crescentic glomerulonephritis have all been described[5,3,10]. Since the renal disease in the setting of diabetes is often ascribed to diabetes ,without further diagnostic efforts, the coincidence of NDRD may be underestimated. Renal biopsy is not routinely done to confirm diabetic nephropathy. The predictors and pointers to the etiology of NDRD were analysed in previous studies. Eighty Type2 diabetic patients underwent renal biopsy in a hospital in South India to rule out NDRD. The positive predictive value of the standard clinical indicators for NDRD in the presence or absence of diabetic retinopathy was 54% and 84% respectively. These values are often higher than that given by the comparable Western studies ,which indicates higher prevalence of NDRD in this part of the world especially that of proliferative glomerulonephrits.

It has been reported that 12-80% of type 2 diabetic patients with renal involvement show non diabetic renal disease[5,11,12,13,14].The large variation reported in these studies may be due to selection bias because of the lack of a standard criteria for performing renal biopsy in atypical diabetic nephropathy. The prevalence of NDRD among Type2 diabetics was 22% in Europe and 26.7% in Asia[15].NDRD in Type 2 diabetic patients has significant impact on prognosis and treatment which are different from diabetic nephropathy[16]. Pham et al analysed the renal biopsy of 233 Type2 DM patients and concluded that 53.2% had NDRD, 27.5% had pure diabetic glomerulosclerosis (DGS) and 19.3% with concurrent NDRD and DGS. The patients with NDRD tended to be younger than those with DGS and had significantly less association with diabetic retinopathy. Of the NDRD, the most common lesion found was focal segmental glomerulosclerosis (FSGS) in 21% followed by minimal change disease (15.3%), IgA nephropathy(15.6%) and membranous glomerulonephritis (13.3%) [7].The reported prevalence of different renal disease among diabetic patients depends upon ethnicity, geographical variation and the institutions' biopsy policy.

Diabetic nephropathy can occur in the absence of retinopathy and the chance of getting diabetic or non diabetic renal lesions are equal in the absence of diabetic retinopathy[16].The presence of retinopathy suggests the concurrence of diabetic nephropathy, but does not exclude non diabetic nephropathy. It is generally agreed that renal biopsy can not be used as a routine diagnostic test in Type 2 diabetic patients with proteinuria. Therefore it is very important to determine the clinical predictive factors for NDRD in Type2 diabetic patients because majority of patients with compatible history and clinical findings do not get any benefit from a renal biopsy. Criteria for renal biopsy in these patients have not been defined. When the criteria for renal biopsy in type I DM (duration of diabetes <5years, micro haematuria, absence of diabetic retinopathy, uncharacteristic changes in renal function or immunological abnormalities) is applied in Type 2 diabetic patients diabetic glomerulosceloris (DGS) is the most commonly found renal lesion. Thus ,these biopsy criteria are not useful in identifying patients with potentially treatable other renal lesions in Type 2 diabetes mellitus. Duration of diabetes and the presence or absence of diabetic retinopathy are not very helpful in distinguishing the type of nephropathy (DN Vs NDRD). However many predictive factors of NDRD have been described in the literature.
The clues for NDRD in type 2 diabetic patients are:
1. Protenuria with normal renal function.
2. Impaired renal function with no protenuria.
3. Absence of retinopathy.
4. Sudden deterioration of renal function.
5. Active urinary sediment.
6. Gross or microscopic hematuria.
7. Short duration of diabetes.

The presence of microhematuria and absence of diabetic retinopathy do not predict the finding of non diabetic renal involvement[16]. Prakash et al reported that 50% of protenuric Type 2 diabetic patients with typical diabetic nephropathy on biopsy did not have diabetic retinopathy[16].The typical histopathological changes noted in diabetic nephropathy include glomerular basement membrane thickening, mesangial expansion, podocyte foot process effacement and afferent and efferent arteriolar hyalinosis. The renal lesions in Type 2 DM are much more complex and differ from Type1 DM and their precise diagnosis require histological examinations. Three patterns are described in these patients
i) Isolated NDRD
ii) Pure diabetic glomerulosclerosis
iii) Concurrent NDRD and DN known as Combined Disease(CD).

A wide spectrum of non diabetic glomerulopathies can occur in patients with Type 2 DM including Membraneous Glomerulonephritis, Focal segmental glomerulosclerosis(FSGS), Minimal change nephropathy(MCN), PRGN, IgA nephropathy and Amyloidosis. The tubulointestitial and vascular changes are likely to be related not only to hyperglycemia, but also to ageing, atherosclerosis and systemic hypertension. In

patients with NDRD the the most common lesion was FSGS(21%), followed by Minimal change disease(15.3%) and in patients with combined disease the most common lesion was IgA nephropathy, Membraneous glomerulonephritis, and arterial /arteriolar nephrosclerois seen in 15.6%, 13.3%, 13.3% of cases respectively [16].

The absence of retinopathy and short duration of diabetes may be useful indicator of NDRD clinically[10]. Rapid decline in renal function in a patient with diabetes suggests the presence of NDRD according to a prospective study by Venkatesh et al[26].

Different studies in the literature have reported different proportion of DN and NDRD among their study cohorts. A summary of the same is given in table 1.

Table 1 DN Vs NDRD literature summary

Authors	No of patients	NDRD	DN	References
Hung F et al	52	20	32	8
Pham TT et al	233	124	109	17
Zhou J et al	110	50	60	12
Parving HH et al	35	08	27	07
Olsen S et al	33	04	29	25
Prakash J et al	260	32	228	18
Prakash J et al	23	10	13	09
ChristensenPK et al	51	07	35	26
Serra A et al	35	06	29	15
Gambara V et al	52	16	19	13
Kveder K et al	76	37	17	19

Since escalating albuminuria may not be reliable as a predictor of GFR decline ,better diabetic nephropathy markers are needed. Neutrophi Gelatinase Associated Lipocalin (NGAL), Kidney Injury Molecule I(KIM I), Liver Type Fatty Acid Binding Protein (LFABP) have emerged as possible markers [20]. Urine Proteomics has recently facilitated Zurbig et al. to create a panel of urinary peptides to predict CKD progression [21].

I.1 Management of NDRD in type2 DM patients

In the light of high prevalence of NDRD, it is appropriate to perform renal biopsy in Type 2 DM patients with clinical suspicion of NDRD. The Kidney biopsy is helpful in following ways

i) It will differentiate diabetic from non diabetic glomerulopathy.

ii) Knowledge of the underlying cause of proteinuria may play an important role in planning the correct treatment of these patients.

iii) Early therapy could prolong the renal survival in these patients.

The nature of treatment will depend on the nature of the underlying NDRD. (corticosteroids for minimal change disease/ FSGS, combination of steroids and cytotoxic drugs for idiopathic membranous nephropathy, intensive immunosuppressive therapy for cresentic GN). The other aspects of the management are similar to that of diabetic nephropathy.

II. Aims of the study

1. To estimate the prevalence of Non Diabetic Renal Disease in Type 2 diabetic patients with renal involvement.
2. To study the spectrum of Non Diabetic Renal Disease in Type 2 diabetic patients.
3. To study the clinical predictive factors of Non Diabetic Renal Disease.

III. Methodology

The study was conducted under the Department of Nephrology, Government T D Medical College , Alappuzha which is a tertiary care hospital in central Kerala, South India. Patients attending the Department of General Medicine and Nephrology who satisfied the inclusion criteria were enrolled in the study during the study period of one year(September 2014 to August 2015). Study was conducted in the cross sectional design. All consecutive Type 2 DM patients with renal involvement in the age group of 13-60 years were included after taking the informed consent.

III.1 Inclusion criteria

All Type2 DM patents

1. Of age group between 30 and 60 years ,of either sex
2. With proteinuria
3. With microscopic or macroscopic hematuria
4.with features of renal failure

III.2 Exclusion criteria

1. Known case of cystic kidney disease.
2. Ischemic Nephropathy
3. Peripheral Occlusive Vascular Disease
4. USG features suggestive of Medical renal Disease of Grade 2 or Grade 3
4. Renal artery stenosis
5. Those who were not willing to give consent

Basic clinical details were collected from all the patients and blood , urine investigation and ultrasonogram of the abdomen was done . Based on these data the need for renal biopsy was assessed. Percutaneous renal biopsy was done under ultrasound guidance . Biopsy samples were analyzed by light microscopy by H&E ,PAS, Acid Fuschin Orange G stains and Immunoflourescence staining .. In necessary cases Methyl violet and Congo red staining were also done. Optic fundae examination were carried out in the Department of Ophthalmology to look for evidence of diabetic retinopathy. Based on biopsy patients were grouped into three

i) Isolated NDRD
ii) NDRD with underlying DN and
iii) Isolated DN

Statistical analysis was done with SPSS vesion16.

IV. Observations and Analysis.

684 patients were included in the study of which 369 were males and 315 were females. 75% of them were above the age of 50 years. 38 patients were chosen for kidney biopsy but it was done only for 20 patients due to various reasons like patient not willing for biopsy, relieved of their symptoms before biopsy etc.9 males and 11 females underwent biopsy. Age distribution of these patients is given in table 2

Table 2 Age distribution

Age groups	Frequency	Percentage
21-30 years	1	5
31-40 years	1	5
41-50 years	10	50
51-60 years	8	40
Total	20	100

Only 10% of the patients who underwent renal biopsy were below 40 years. The duration of diabetes was variable among the subjects which is summarised in Table 3.

Table 3. Duration of diabetes

	Frequency	Percentage
<5 years	11	55
6-10 years	7	35
>11 years	2	10
Total	20	100

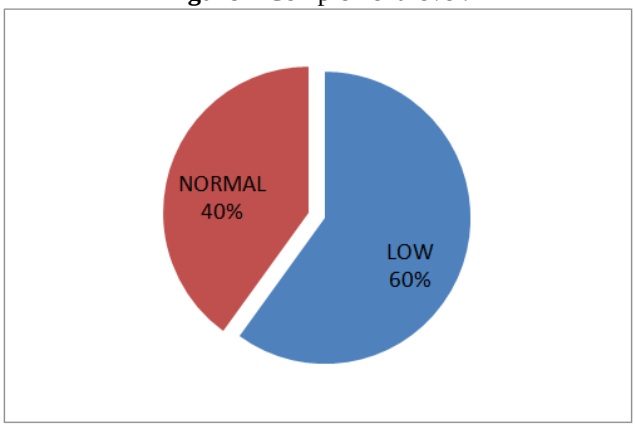
24 hour urine protein estimation was done and one patient had nephrotic range proteinuria. Table4 depicts the degree of proteinuria in the 20 subjects .

Table 4 Proteinuria (mg/24 hours)

	Frequency	Percentage
Absent	1	5
30-300	7	35
300-3500	11	55
>3500	1	5
Total	20	100

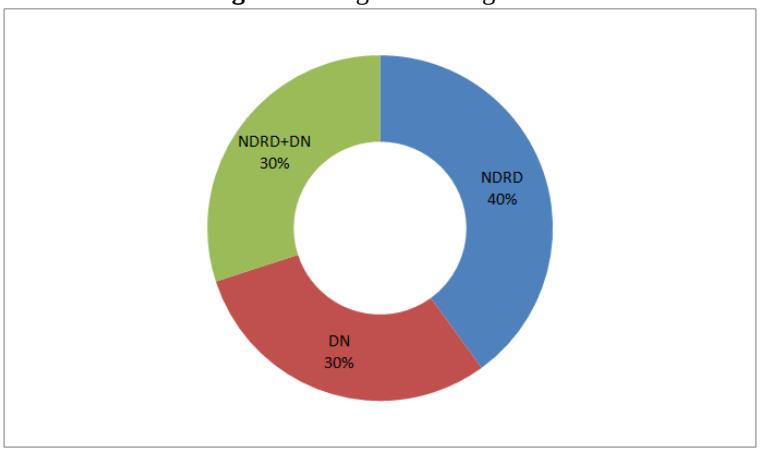
Of the 20 patients 13(65%) had microscopic hematuria and 6 (30%) had macroscopic hematuria . One patient did not have hematuria. Serum C3 complement assay was done and hypocomplimentemia was detected in 12 patients.

Figure 1 Complement level.



Active urine sediment (defined as >5 cells per high power field and /or cellular casts) was seen in 85% of the patients.
Diabetic retinopathy was detected in 70% of the patients.
Based on the renal biopsy report patients were grouped into three diagnostic categories. Fig.2 illustrates the proportion of the three subgroups among the subjects.

Figure 2. Diagnostic categories



The available clinical parameters were analysed in each of the different diagnostic categories . This is shown in the table5

Table 5

Clinical parameters	NDRD	DN+NDRD	DN	TOTAL
Age group 21-30 years	1(100%)	0	0	1
Age group 31-40 years	0	1(100%)	0	1
Age group 41-50 years	3(33.3%)	5(55.6%)	2(11.1%)	10
Age group 51-60 years	3(37.5%)	0	5(62.5%)	8
Sex Males	4(44.4%)	4(44.4%)	1(11.1%)	9
Sex Females	4(33.3%)	2(18.2%)	5(45.4%)	11
Duration of DM </=5 years	6(54.5%)	2(18.2%)	3(27.3%)	11
Duration of DM 6-10 years	2(28.6%)	3(42.9%)	2(28.6%)	7
Duration of DM >/= 10 years	0	1(50%)	1(50%)	2
Hematuria (microscopic)	7(53.8%)	4(30.8%)	2(15.4%)	13

Hematuria (macroscopic)	1(20%)	4(80%)	0	5
Proteinuria Absent	1(100%)	0	0	1
Proteinuria (30-300mg/day)	3(42%)	1(14%)	3(42%)	7
Proteinuria (300-3500mg/day)	4(36%)	4(36%)	3(28%)	11
Proteinuria (>3500mg/day)	0	1(100%)	0	1
Retinopathy absent	8(57%)	5(35%)	1(7%)	14
Retinopthy present	0	1(16%)	5(83%)	6
Urine sediment absent	1(50%)	1(50%)	0	2
Urine sediment Present	7(38.9%)	5(27.8%)	6(33.3%)	18
C3 complement Normal	3(33.3%)	5(55.6%)	1(11.1%)	9
C3 complement Low	5(45.5%)	1(9.1)	5(45.5)	11

Micro hematuria was seen in 13(65%) of which 7 (53.8%) patients had NDRD alone. Overlap of NDRD and DN was reported in 30.8% of cases with micro hematuria. Nephrotic range proteinuria was more common in DN compared to NDRD. NDRD was more common (54.5%) than DN (27.3%) when the duration of diabetes was less than 5 years. Overlap cases constituted 18.3% in this group. No NDRD could be seen in patients with duration of diabetes more than 10 years. Diabetic retinopathy was present 83% of patients with DN whereas no NDRD patients had diabetic retinopathy. In the absence of retinopathy 92.8% had evidence of NDRD (isolated NDRD (57.1%) or combined disease (35.7%). In the absence of retinopathy 7.1% had evidence of DN and 35.7% had evidence of combined disease.

V. Discussions

In our study the average age of the patient who underwent biopsy was 48.55± 7.85 years which is comparable to the results of other studies conducted in South India. In the present study age group with atypical renal symptoms were slightly lower . The sex ratio of patients who were selected for the study was 1.2:1 and that of patients who underwent biopsy was was 1:1.2. Gal et al reported that males had a 2.6 times higher risk of developing incipient or overt nephropathy[22].

Microhematuria was seen in13 patients of which 7 had NDRD and 4 had combined disease. One of the previous study from Japan evaluated patients with hematuria and concluded that patients with hematuria had more severe diabetic nephropathy on renal biopsy, as manifested by advanced diffuse glomerular lesions and by interstitial lesions and by a significantly higher creatinine levels [23]. Our study also shows a similar result with regard to hematuria ($p = 0.02$).

Proteinuria indicates more of diabetic nephropathy than combined disease which was shown by the previous studies like Mak et al in Chinese patients , the same trend is clearly seen in our study too. This study shows that the duration of diabetes in patients with DN is comparatively longer than NDRD.NDRD was seen in 54.5% of patients with duration diabetes < 5 years versus diabetic nephropathy in 27.3% of the cases. None of the patients with NDRD had duration of diabetes greater than 10 years . In the study by Sharma et al , multivariate analysis showed that longer duration of diabetes was associated with a greater likelihood of DN and lower likelihood of NDRD [24].

Diabetic retinopathy is present virtually in every patients with diabetic nephropathy , whereas no NDRD patients had retinopathy. Hence absence of retinopathy should prompt further investigations for non diabetic nephropathies. In our study we observed, in patients without DR, 92.8% had evidence of NDRD and 42.8% had evidence of DN. It means that absence of DR predict NDRD in vast majority of cases., but cannot exclude the lesion of DN. Similarly presence of DR predicts lesions of DN in almost all patients. Thus presence or absence of DR is helpful in predicting the nature of nephropathy in Type2 DM patients.. NDRD was more frequent in patients without DR in comparison to patients with DR and the difference was statistically significant($P<0.05$). However there was no statistically significant difference with respect to DN alone and combined lesions in diabetic patients with or without DR. It was noted that there was no difference with respect to mean age, male gender and dyslipiemia, in diabetic patients with NDRD, DN and mixed lesions. The longer duration of diabetes was positively correlated with development of DN. Different studies from other parts of the world have reported different histologic patterns. IgA nephropathy is the most common NDRD detected in our study(20%)..Post infectious glomerulonephritis in 2 (25%), Granulomatosis with crescent formation in 1 (12.5%), Acute interstitial nephritis in 1 (12.5%) were also reported. The most common NDRD superimposed

on DN was diffuse proliferative glomerulonephritis (n-2) . The other NDRD in this group included chronic tubule interstitial nephritis, amyloidosis and crescentic GN, all consisting of one case each. In summary all type2 DM patients with clinical renal disease do not have classical DN. Non diabetic kidney disease either alone or superimposed on DN were seen in 70% of diabetic patients. Further, diagnosing NDRD is especially important when it leads to a specific change in therapy.

VI. Conclusions

The study demonstrates that the renal complications in Type2 DM may be due to heterogenous non diabetic disease. 40% of our patients with atypical clinical renal disease had NDRD, emphasising the importance of kidney biopsy in this group of population. Renal complication in patients with short duration of Type2 DM should be investigated for NDRD. Longer duration (>10 years) strongly predicts DN. IgA nephropathy was the most common NDRD lesion noted in 50% cases. The most common NDRD superimposed on DN was diffuse proliferative glomerulonephritis. Shorter duration of diabetes, absence of retinopathy, presence of microscopic hematuria, low complement C3 and active urinary sediments are markers associated with NDRD in type 2 diabetes with atypical clinical renal disease and are strong indicators for biopsy. Female gender is more common in Type2 DM with NDRD rather than type2DM with DN.

VII. Suggestions

1. Further studies involving larger sample size or population based studies may be needed to extend the results for population benefits.
2. More clinical criteria should be identified for renal biopsy to determine prevalence of NDRD.

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