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Spectrum of Biopsy Proven Renal Diseases (BPRD): A Single Center Experience

(Original article)

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ABSTRACT

Kidney biopsy is one of the most important tools in the assessment of kidney disease as histopathological diagnosis promotes evidence based practice in Nephrology. This is a study was done by including all consecutive percutaneous kidney biopsies (273; Males:147, Females: 126) performed at EMS Memorial Cooperative Hospital, Perinthalmanna, Kerala, India, from September 2009 to February 2016. Among the biopsy proven renal diseases (BPRD); primary glomerular diseases (PGD) were the commonest (78.39%) followed by secondary glomerular diseases (SGD) (12.45%) and tubulointerstitial diseases (TID) (9.16%). The IgA Nephropathy (IgAN) was the commonest PGD and majority had mesangial hypercellularity (M1) (93.54%), tubular atrophy (T1 or T2 67.74%) and the most common pattern was M1, E0, S0, T1, suggesting that patients of Indian subcontinent have aggressive disease type; unlike western literature. The focal segmental glomerulosclerosis (FSGS) was the second commonest PGD and majority were of not otherwise specified (NOS) type. FSGS, membranous nephropathy (MN) and minimal change disease (MCD) were the 3 most common causes for PGD causing nephrotic syndrome. Diabetic nephropathy and lupus nephritis (LN) were the two most common biopsy proven SGD. Among the patients of diabetes mellitus (DM) who underwent renal biopsy with suspicion of non-diabetic renal disease (NDRD); 58.33% had NDRD, 16.67% had DN+ NDRD and 25% had DN alone. This study the changing pattern BPRD in comparison to earlier studies. This study also, confirms the aggressive nature of IgAN in Indian patients and underlines the importance of renal biopsy in patients of DM.

Key Words: *Renal biopsy, primary glomerular diseases, secondary glomerular diseases, Oxford-MEST classification,*

INTRODUCTION

Kidney biopsy is one of the most important tools in the assessment of kidney disease as histopathological diagnosis promotes evidence based practice in Nephrology. Kidney biopsy is safe procedure which helps to reach the correct diagnosis andto use of treatment based on histopathologic diagnosis and predict the clinical course and outcome. [1-8] The pattern of biopsy proven renal disease (BPRD) varies based geographic area and also changes with time. [2-8] There is limited data regarding BPRD,as there is no renal biopsy registry India.This study was conducted to analyze the histopathologic pattern of renal of renal biopsies from a tertiary care centre in south India.

AIMS AND OBJECTIVES

- To classify the BPRD based on histopathology in different age groups
- To analyze the difference in pattern of BPRD based on gender and age groups.

MATERIALS AND METHODS

This is a retrospective study of all consecutive percutaneous kidney biopsies performed at EMS Memorial Cooperative Hospital and Research Centre, Perinthalmanna, Kerala, from September 2009 to February 2016. All the biopsies were performed under ultrasound guidance usingBard® Max-Core® disposable core biopsy instrument, CR Bard Inc., USA.All the biopsies were analyzed by light microscopy using hematoxylin and eosin, periodic acid Schiff, Jone's silver methaneamine and Gomori's trichrome stains and immunofluorescence studies were performed using anti-human IgG, IgA, IgM, C3, C1q, kappa and lambda light chains. Electron microscopy was done in few cases.

The indications of renal biopsies in the study were;steroid dependant or resistant nephrotic syndrome (SDNS or SRNS), adult onset nephrotic syndrome, unexplained renal failure, rapidly progressive renal failure (RPRF), acute nephritic syndrome (ANS) with features suggesting diagnosis other than PIGN (post infective glomerulonephritis), renal involvement in systemic disease, familial renal disease, asymptomatic urinary abnormality (proteinuria >1g/day and or haematuria) and diabetes mellitus with features suggestive of nondiabetic renal disease.

Statistical analysis was done using SPSS 17 for Windows, by SPSS Inc. IL, USA. The quantitative variables (age) have been described as mean ± SD and range. The prevalence of biopsy proven renal disorders was summarized as counts and percentages. A Chi-square test was used to assess the trends in the prevalence of BPRD, among gender categories.

RESULTS

A total of 273 (Males:146, Females: 127) subjects, aged from 7-80 years (Mean:40.89, SD: 15.75) who underwent renal biopsies, were included in the study (Table 1), 1 patient was excluded because of inadequate sample. Both males and females were of similar age (Table 1); the difference was statistically insignificant (p:0.076). Among the BPRD; primary glomerular diseases (Table 1: 78.39%) were the commonest followed by secondary glomerular diseases (Table 4: 12.45 %) and tubulointerstitial diseases (Table 5: 9.16%).

Primary glomerular diseases (PGD)

Ig A nephropathy(IgAN)(22.71%) was the most common of the biopsy proven PGD, followed by FSGS (13.55%), DPGN (10.99%), MN (7.69%), MCD (7.69%), CGN (4.03%),Pauci-immune crescentic GN (ANCA positive) (2.93%), MesPGN (2.56%), IgMN (1.46%), non-amyloid deposition disease (1.10%), MPGN (type 1) (1.10%), Anti GBM antibody disease (1.1%), Amyloidosis (primary) (0.70%)FPGN (0.40%), and C3 Glomerulopathy (0.40%) (Table 2).

Ig A Nephropathy

The IgAN was the most common (22.71%, 62 out of 273) of PGD, in our study (Table 1). The mean age of the patients was 38.08 years and male: female ratio was 1.48:1. The IgAN was classified

according to the Oxford-MEST classification [mesangial hypercellularity score (M; M0 ≤ 0.5, M1 >0.5), the presence of endocapillary proliferation (E; E0: absent, E1: present) and segmental glomerulosclerosis/adhesion (S; S0: absent, S1: present), and the severity of tubular atrophy/interstitial fibrosis (T; T0 ≤ 25%, T1: 26–50%, T2 >50%]. Majority of the patients had mesangial hypercellularity (93.54%, 58 patients) and tubular atrophy (67.74%, 40; T1-43.55% or 26, T2-24.19% or 14 patients) (Table 3, Figure 1). Only few patients had endocapillary proliferation (18.33%, 11), and segmental sclerosis (45%, 25) (Table 5, Figure 2). Glomerular crescents (involving 5-20% of glomeruli) were found in 10% (6 patients, 5 fibrocellular, 1 cellular) of patients with IgAN. The most common type of IgAN as per Oxford-MEST classification in the study was M1, E0, S0, T1 (20.97%, 13 out of 62) and the least common type was M0, E0, S0, T0 (4.84%, 3 out of 62). 3 patients with IgAN had purpuric skin lesions and were diagnosed as Henoch Schonlein purpura.

Focal segmental glomerulosclerosis (FSGS)

The FSGS was the second (13.55%, 37 out of 273) commonest of PGD in the study. The mean age of the patients was 36.72 years and male: female ratio of 1.64:1. In majority of the patients with FSGS;it was NOS (not-otherwise specified) type (94.59%, 35), followed by tip (2.7%, 1) and perhilar variants (2.7%, 1 patient). None of the patients in our study had collapsing or cellular variant FSGS.

Diffuse proliferating glomerulonephritis (DPGN)

The DPGN was the third (10.99%, 30 out of 273) commonestof PGD in the study. The mean age of the patients was 43.63 years and male: female ratio of 1:1. All the patients had low C3 and 4 patients low C4, morphologically it was suggestive of post-infective glomerulonephritis.

Membranous nephropathy (MN)

The MN was the fourth (7.69%, 21 out of 273) commonestof PGD in the study. The mean age of the patients was 50.90 years and male: female ratio of 1.1:1. In all the patients it was morphologically suggestive of primary MN, however, anti PLA2R antibody antibodies were not estimated.

Minimal change disease (MCD)

The MCD was the fourth (7.69%, 21 out of 273) commonest of PGD along with MN in the study. The mean age of the patients was 30.14 years and male: female ratio of 0.9:1. Six out 21 patients were aged 12-15 years (Mean:13.33) and were biopsied for SDNS, and others were aged from 23-65 years (Mean:36.87) and biopsied for adult onset nephrotic syndrome.

Secondary glomerular diseases (SGD)

Diabetic nephropathy (5.49%) was the most common, biopsy proven SGD, followed by LN (5.13%), postpartum HUS, Alport's disease, MPGN (Cryoglobulinemia),LCDD and Membranous nephropathy (Hepatitis B infection) (Table 4).

Diabetic nephropathy (DN)

The DN was the commonest SGD 9.16 % (25 out of 273); 5.49% (15/273), having DN alone and 3.67% (10/273) having DN in association with non-diabetic renal disease (NDRD).The mean age in patients with DN alone was 52.2 yearsand male: female ratio was 2:1. The commonest NDRD to be associated with DN was acute tubular necrosis (ATN) (6.67%, 4) followed by DPGN (1.67%, 1), IgAN (1.67%, 1), anti GBM antibody disease (1.67%, 1), pauci-immune crescentic GN (1.67%, 1),CGN (1.67%, 1) andCTIN (1.67%, 1). The number in brackets representing percentages and the number of patients among 60 with DM who underwent renal biopsy.The patients with NDRD were included in respective categories of based on histological diagnosis.

Lupus nephritis (LN)

The LN was second commonest (5.13%, 14 out of 273) SGD. The mean age in patients with LN was 26.14 years (Range: 11-39) and all were females. The LN was classified as per ISN/RPS (International Society of Nephrology and Renal Pathology Society) 2004 classification. The class

IV G-A was most common type (42.85%, 6 out of 14) followed by class III A (21.43%, 3), class IV A/C (14.28%, 2), class IV+V (14.28%, 2) and class III A/C (7.14%, 1 patient).

Miscellaneous secondary glomerular diseases

The rarer secondary glomerular diseases included postpartum HUS, Alport's disease, MPGN (Cryoglobulinemia) LCDD (Multiple Myeloma) and Membranous nephropathy (HBV infection). The patient with Alport's disease was confirmed by electron microscopy.

Tubulointerstitial diseases (TID)

ATN (3.66%) was themost common, biopsy proven TID followed by, CTIN (2.56%) Cast nephropathy (1.5%), AIN (1.1%), ACN (0.4%) (Table 5).

BPRD in patients with Diabetes mellitus (DM)

A total 60 patients (Males:39, Females:21, Mean age: 52.53 years) of DM underwent renal biopsy; with a suspicion of non-diabetic renal disease. The indications for renal biopsy were: nephrotic range proteinuria without progression through microalbuminuria, macroscopic haematuria, red cell casts, sterile pyuria, acute on chronic renal failure, absence of diabetic retinopathy, nephrotic range protienuria with duration of DM<5 years. The nondiabetic renal disease (NDRD) was found in 58.33% of those with diabetic mellitus, diabetic nephropathy with superimposed nondiabetic renal diseasein 16.67% and 25.00% had diabetic nephropathy (DN) alone in renal biopsy (Table 6, Figure 2). The mean duration of diabetes mellitus was 10, 9,33 and 6.83 years in patients with DN, DN+NDRD and NDRD, respectively.

The most common nondiabetic renal disease was Ig A nephropathy (11.67%, 7) followed by DPGN (8.33%, 5), MN (6.67%, 4), FSGS (5%, 3), CGN (3.33%, 2), MPGN (3.33%, 2), primary amyloidosis (3.33%, 2), CTIN (3.33%, 2), AIN (3.33%, 2), MCD (1.67%, 1), IgM nephropathy (1.67%, 1), pauci-immune crescentic GN (1.67%, 1),anti GBM antibody disease (1.67%, 1), non-amyloid deposition disease (1.67%, 1) and cast nephropathy (1.67%, 1 patient) (Figure 3). The number in brackets representing percentages and the number of patients; among 60 with DM who underwent renal biopsy.

Table 1: The demographic data of subjects undergoing renal biopsy

Gender	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Females	127	39.08	16.582	1.471	36.17	41.99	7	80
Males	146	42.47	14.867	1.230	40.04	44.90	8	76
Total	273	40.89	15.751	0.953	39.02	42.77	7	80

Table 2: Primary glomerular diseases (PGD)								
Renal disease	**Patients (n & %)**	**HTN (n & %)**	**Nephrotic syndrome (n & %)**	**Renal failure (n & %)**	**Males (n)**	**Females (n)**	**Age in years (Mean& Range)**	**p-value (M & F)**
Ig A Nephropathy (IgAN)	62 (22.71)	29 (46.77)	4 (6.45)	38 (61.29)	37	25	38.08 (12-75)	0.42
Focal Segmental Glomerulosclerosis (FSGS)	37 (13.55)	22 (59.46)	29 (78.38)	14 (37.84)	23	14	36.73 (17-69)	0.36
Diffuse proliferative Glomerulonephritis (DPGN)	30 (10.99)	13 (43.33)	6 (20)	25 (83.33)	15	15	43.63 (8-70)	0.51
Membranous nephropathy (MN)	21 (7.69)	9 (42.86)	15 (71.43)	4 (19.05)	11	10	50.90 (23-80)	0.78
Minimal change disease (MCD)	21 (7.69)	2 (9.5)	18 (85.71)	0	10	11	30.14 (12-65)	0.46
Chronic Glomerulonephritis (CGN)	11 (4.03)	8 (72.73)	1 (9.09)	11 (100)	8	3	46.36 (30-61)	0.22
Pauci-immune crescentic GN	8 (2.93)	1 (12.5)	0	8 (100)	3	5	43.87 (23-65)	0.31
Mesangioproliferative GN (MesPGN)	7 (2.56)	5 (71.42)	2 (28.57)	2 (28.57)	1	6	36.14 (23-46)	**0.02**
IgM Nephropathy (IGMN)	4 (1.46)	1 (25)	3 (75)	0	1	3	22.24 (14-29)	0.22
Non-amyloid deposition disease (NADD)	3 (1.10)	0	1 (50)	0	2	1	47.33 (36-58)	0.68
Membranoproliferative GN (MPGN)	3 (1.10)	2 (66.67)	2 (66.67)	1 (33.33)	2	1	51.33 (44-65)	0.68
Anti GBM antibody disease	3 (1.10)	0	0	3 (100)	3	0	53.33 (49-60)	0.11
Primary Amyloidosis	2 (0.7)	0	1 (50)	1 (50)	2	0	64.5 (54-75)	0.19
Focal proliferative GN (FPGN)	1 (0.4)	1 (100)	0	1 (100)	0	1	67	0.26
C3 Glomerulopathy (C3G)	1 (0.4)	0	0	0	0	1	26	0.26
Total	214(78.39)	93	82	108	118	96	40.28 (12-80)	
HTN: BP≥140/90, Renal failure: e GFR <60ml/min/1.73m2 (MDRD equation, 4 variable)								

Table 3: Histopathologic classification of IgA nephropathy as per Oxford classification				
Grade	Mesangial hypercellularity	Endocapillary proliferation	Segmental sclerosis	Tubular atrophy
0	04	50	34	20
1	58	12	28	27
2	NA	NA	NA	15

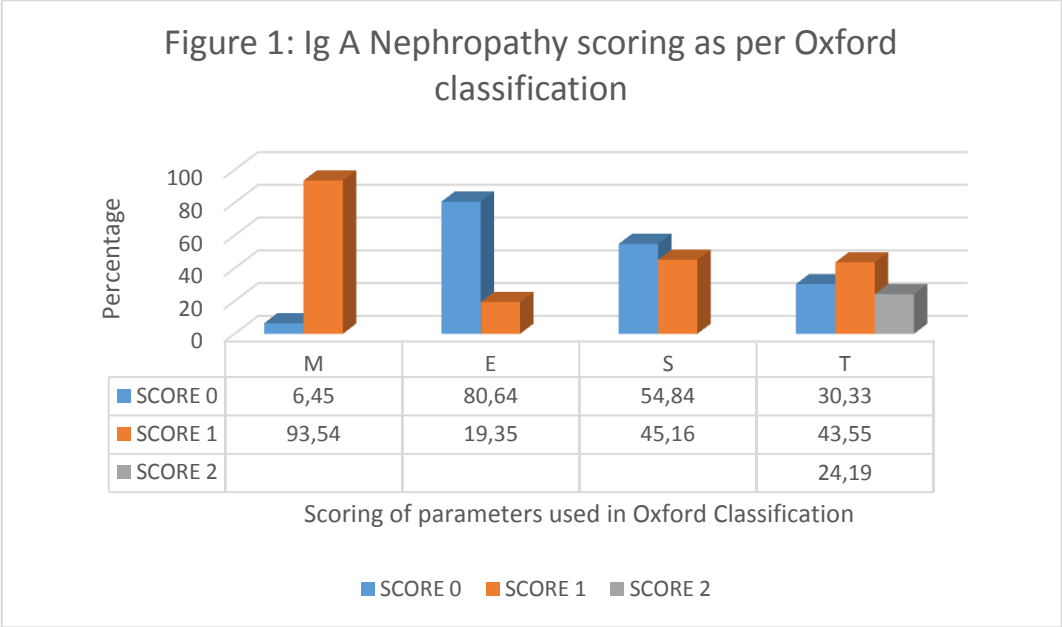


Table 4: Secondary glomerular diseases (SGD)

Renal disease	Patients (n & %)	HTN (n & %)	Renal failure (n & %)	Nephrotic syndrome (n & %)	Males (n)	Females (n)	Age in years (mean & range)	p-value (M & F)
Diabetic nephropathy (DN)	15 (5.49)	7 (46.67)	6 (40)	8 (53.33)	10	5	52.2 (30-65)	**0.001**
Lupus nephritis (LN)	14 (5.13)	0	2 (14.28)	6 (42.86)	0	14	26.14 (11-39)	**0.007**
Hemolytic uremic syndrome (HUS D-, postpartum)	1 (0.4)	1 (100)	1 (100)	0	0	1	36	0.48
Alport's syndrome (AS)	1 (0.4)	1 (100)	0	0	0	1	16	0.48
Membranoproliferative (MPGN)	1 (0.4)	0	0	1 (100)	0	1	72	0.48
Membranous nephropathy (MN)	1 (0.4)	0	0	1 (100)	0	1	7	0.48
Light chain deposition disease (LCDD)	1 (0.4)	0	0	0	1	0	49	0.14
Total	34 (12.45)	9	9	16	11	23	36.90 (11-72)	

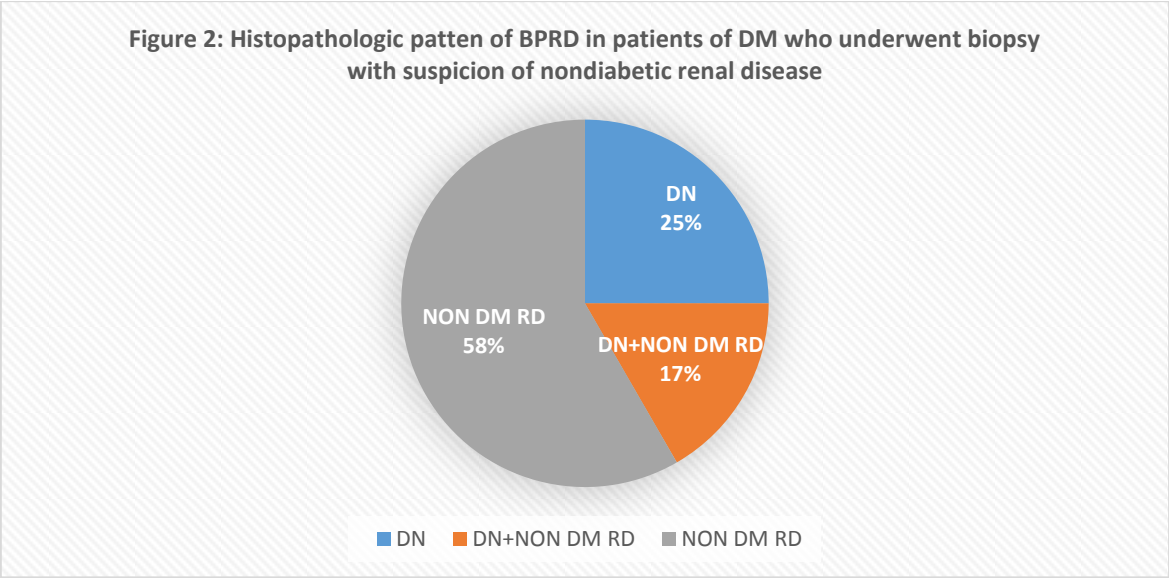
HTN: BP≥140/90, Renal failure: e GFR <60ml/min/1.73m2 (MDRD equation, 4 variable)

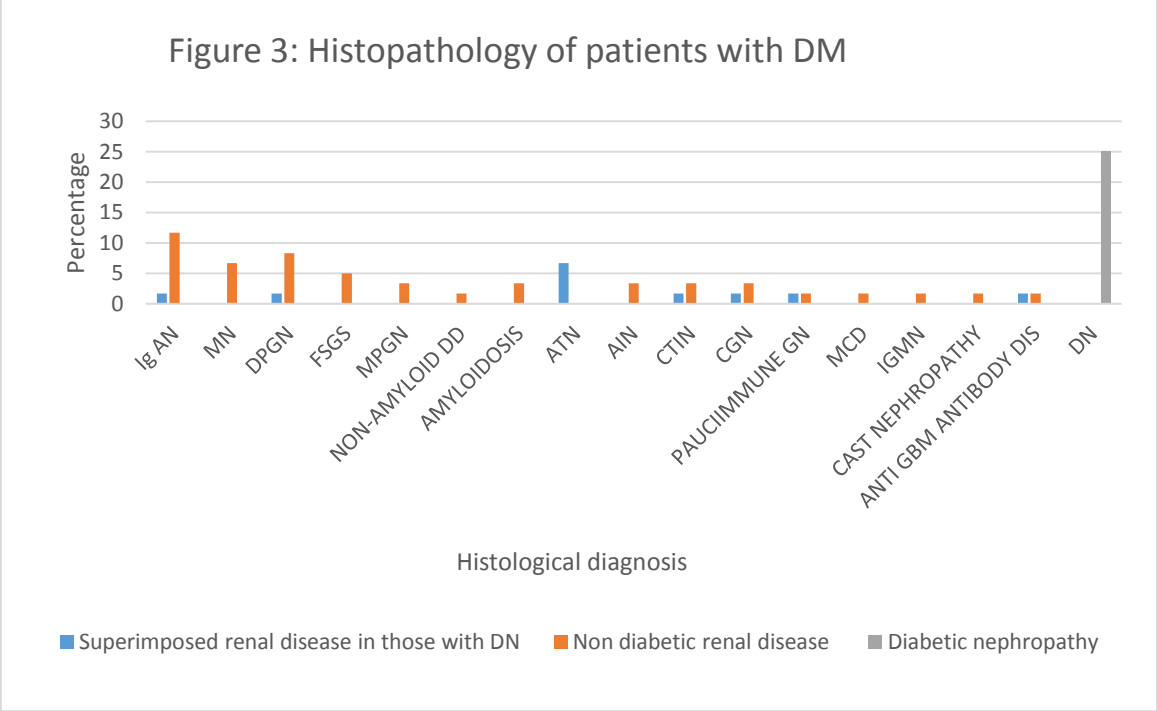
Table 5: Tubulointerstitial diseases (TID)

Renal disease	Patients (n & %)	HTN (n &%)	Renal failure (n & %)	Nephrotic syndrome (n & %)	Males (n)	Females (n)	Age in years (mean & range)	p-value (M & F)
Acute tubular necrosis (ATN)	10 (3.66)	1 (10)	8 (80)	0	7	3	44.1 (17-63)	0.6
Chronic Tubulointerstitial nephritis (CTIN)	7 (2.56)	4 (57.14)	7 (100)	0	4	3	48 (40-60)	0.65
Cast nephropathy (CN)	4 (1.5)	1 (25)	4 (100)	0	3	1	54 (47-61)	0.25
Acute interstitial nephritis (AIN)	3 (1.1)	0	3 (100)	0	1	2	64.67 (48-76)	0.24
Acute cortical necrosis (ACN)	1 (0.4)	0	1 (100)	0	1	0	40	0.44
Total	25 (9.16)	6	25	0	16	9	50.15 (17-76)	

HTN: BP≥140/90, Renal failure: e GFR <60ml/min/1.73m2 (MDRD equation, 4 variable)

Table 6: Pattern of BPRD in patients DM; who underwent renal biopsy with suspicion of non-diabetic renal disease					
Renal disease	**Patients: number and percentage**	**Males**	**Females**	**Age (range, mean)**	**Duration of DM in years (range, mean)**
Diabetic nephropathy	15 (25.00)	10	5	30-65, 52.2	10 (3-16)
Diabetic nephropathy with superimposed non-diabetic renal disease	10 (16.67)	9	1	27-65, 51	9.33 (2-15)
Non-diabetic renal disease	35 (58.33)	20	15	23-80, 53.62	6.83 (1-15)
Total	60	39	21	23-80, 52.2	7.94 (1-16)





DISCUSSION

This retrospective study of 273 consecutive renal biopsies, illustrates the distribution of BPRD among patients at single centre. The PGD were the commonest (78.39%) of BPRD; followed by SGD (12.45%) and TID (9.16%) similar to earlier reports from India. [2-8]

Primary glomerular diseases (PGD)

The Ig A nephropathywas the commonest PGD in present study is consistent with our previous report from AIMS, Kochi, Kerala. [2] The MCD, Mesangioproliferative GN (non-IgAN), and MN were the commonest PGD in earlier reports. [3-8] Variations in prevalence of PGD may be related to the demographic profile and period of study. [2-8]

The biopsies of patients with IgAN was classified according to the Oxford-MEST classification. Majority of the patients had mesangial hypercellularity (M1) (93.54%), tubular atrophy (67.74%; T1-43.55, T2-24.19). The segmental sclerosis (S1) was present in 45% and only few patients had endocapillary proliferation (E1) (18.33%) and glomerular crescents (10%). The most common type of IgAN as per Oxford-MEST classification in the study was M1, E0, S0, T1 (20.97%) and the least common type was M0, E0, S0, T0 (4.84%).

The observations of present study in IgAN (Oxford-MEST classification) are consistent earlier reports from India, which showed that patients of Indian subcontinent have aggressive disease type; unlike western literature. [9-11] The mesangial hypercellularity (M1) was noted in 68.18%, endocapillary proliferation (E1) was noted in 24.24%, and segmental sclerosis (S1) in 48.48% and tubular atrophy in 74.23 % (T1=1 30.30% and T=2 in 43.93%). [9] In an Iranian study;the morphologic variables of MEST classification were; M1: 90.2 %, E1: 32 %, S1: 67 %, T in grades 1 and 2 were in 30% and 19% respectively, similar to present study. [10] In a study from Brazil, segmental sclerosis (S1), mesangial hypercellularity (M1) and endocapillary proliferation (E1), tubular atrophy (T1 & T2) were observed, in 47.6, 42.2, 13.7 and 22.2% of the patients respectively. [11] The reports using Hass classification for IgAN from India, also showed that the Indian patients suffer from an advanced disease. [9, 12]

FSGS was the second commonest (13.55%) PGD in present study consistent with earlier reports. [2-4,8] In majority of the patients with FSGS; it was NOS type (94.59%) followed by tip (2.7%) and perhilar variants (2.7%).

FSGS, MN and MCD were the 3 most common causes for PGD causing nephrotic syndrome in our study, similar to earlier reports. [3,5,6,8,13-15]

Secondary glomerular diseases (SGD)

Diabetic nephropathy and LN were the two most common biopsy proven SGD, in our study, consistent with earlier reports. [2,4,6,8] The amyloidosis, HUS/TTP, were the second commonest SGD, in other reports, unlike our study. [2,3,7] Among the patients of DM who underwent renal biopsy with suspicion of NDRD; 25% DN;16.67% had DN+NDRD and 58.33% had NDRD. Observations our study are consistent with earlier reports of BDRD in patients with DM. The prevalence rates of DN, NDRD+ND and NDRD were 6.5, 10.7 and 82.9% respectively in one study and 21.18, 40 and 38.82 % of patients, respectively in another study. [16, 17] Two studies from India also showed that the NDRD were 25-64% of patients of DM, similar to present study. [18, 19] The mean duration of diabetes mellitus was lower in patients with NDRD than DN or DN+NDRD. The four most common NDRD were Ig AN followed by DPGN, MN, FSGS, TID in present study. The commonest NDRD were IgAN, MN and TID in one study and TID and glomerulopathies in another study. [16,17] The common NDRD in Indian studies were MCD, TID and Lupus nephritis. [19]

Tubulointerstitial diseases (TID)

TID were the least frequent of the BPRD, in our study, consistent with earlier reports. [2,4-8]ATN was themost common, biopsy proven TID followed by, CTIN, Cast nephropathy, AIN and ACN.

CONCLUSIONS

The prevalence rates of PGD, SGD and TID in this study were78.39, 12.45 and 9.16 % respectively. The Ig A nephropathywas the commonest PGD in present study is consistent with our previous report from AIMS, Kochi, Kerala. Variations in prevalence of PGD may be related to the demographic profile and period of study.Majority of the patients of IgAN had mesangial hypercellularity (M1) tubular atrophy (T1 or T2) with most common pattern being M1, E0, S0, T1, suggesting that patients of Indian subcontinent have aggressive disease type; unlike western literature. FSGS was the second commonest PGD in present study consistent with majority being it was NOS type. FSGS, MN and MCD were the 3 most common causes for PGD causing nephrotic syndrome.

Diabetic nephropathy and LN were the two most common biopsy proven SGD. Among the patients of DM who underwent renal biopsy with suspicion of NDRD; 25% DN; 16.67% had DN+NDRD and 58.33% had NDRD. The mean duration of diabetes mellitus was lower in patients with NDRD than DN or DN+NDRD. The four most common NDRD in patients with DM were Ig AN followed by DPGN, MN, FSGS, TID.

ATN was themost common, biopsy proven TID followed by, CTIN, Cast nephropathy, AIN and ACN.

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