ORIGINAL RESEARCH

Epidemiological Profile, Clinicopathological Correlation and Treatment response in adult patients with IgA Nephropathy

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ABSTRACT

Aim: Our study aimed at the epidemiological profile, clinicopathological correlation, the response to treatment, predictors of response and risk factors in the progression to chronic kidney disease of IgA nephropathy in adult patients. **Design:** Prospective observational study**. Period:** November 2011-February 2013. **Setting:** Department of nephrology, Madras medical college, Chennai. **Participants:** Eighty seven patients with biopsy proven IgA Nephropathy. **Results:** Out of 87 patients 68(67.8%) was men. The follow period ranges from 6-24 months. The mean age at presentation was 27.3years. Renal syndrome included nephrotic syndrome in 20 (22.9%), the nephritic syndrome in 11 (12.6%), rapidly progressive renal failure in12 (13%), acute kidney injury in 6 (6%) and chronic kidney disease in 5(5.4%).Fifty nine (67.9%) were presented with renal failure at presentation. Mesangial hypercellularity (M1) in 49(83%), tubular atrophy/ interstitial fibrosis score T1 and T2 was noted in 28(46%) and 29(51%) patients respectively were significantly associated with renal failure at presentation Twenty five (28.74%) progressed to chronic kidney disease (GFR<60 ml/min/1.73m^2) on follow up period. Those progressed to CKD ten (40%) had proteinuria >3g/day (nil remission), fourteen (56%) had proteinuria in the range of 0.3-3g/day (partial remission), one (4%) had urinary protein of <0.3g/day. There was statistical significance noted for who had partial /no response to reduction in proteinuria with that progressed to CKD.Crescents noted in7(28%) had no statistical significance. **Conclusion:** Nephrotic syndrome is the most common clinical presentation in IgA nephropathy. Majority presented with renal failure at entry into the study. Severe MEST scoring was significantly associated with renal failure at presentation. Non- responders of proteinuria and those who had severe S in MEST scoring system progressed to CKD. Crescents had no statistical association for progression to CKD. Complete or partial remission of proteinuria had less chance for the progression to CKD.

KEYWORDS: Nephropathy, Glomerulonephritis, Chronic Kidney Disease, End Stage Renal Disease

INTRODUCTION

Of all the primary glomerulonephritis, IgAN is the commonest one.[1] It presents with constellation of clinical syndrome ranging from asymptomatic urine abnormalities to smoldering rapidly progressive glomerulonephritis (RPGN). Incidence in India varies between8.6% to16%.[2-4] With the advance in genetic, more molecular pathways are unraveled, pathogenesis were defined little better than previous, so this commonest glomerulonephritis is revealing its secrets.[5-9] A Better understanding of glycation, galactosylation molecular machineries in depth of enzymes[10] and chaperone[11], better search of happenings of talks of mesangium,podocytes and proximal tubule through cytokines and receptors[12-14], the better knowledge of mucosa marrow axis and TLR clearly will open a better prospectus in treatment.

MATERIALS AND METHODS

Study design: Prospective Observational Study
Study period: November 2011-February 2013

Study centre: Department of nephrology, Madras Medical College, Chennai

Inclusion Criteria: All patients who have biopsy proven IgA nephropathy under the care of the department of nephrology will be included in the study.

Exclusion Criteria: Patients with liver disease, psoriasis malignancy, human immune deficiency virus, systemic lupus erythromatosus, rheumatoid arthritis, reactive arthritis and diabetic nephropathy were excluded

Methods: Patients who got admitted under the care of our department of nephrology were taken of detailed clinical history. Patients were subjected to urinary examination includes urine for protein, deposits like red blood cell, white blood cell. Urine was analyzed for red blood cell cast, white blood cell cast. Urine protein/creatinine ratio was done. Patients underwent hematological investigation like blood hemoglobulin, total count, differential count, peripheral smear study. Blood investigation includes blood urea, serum creatinine, serum electrolyte, lipid profiles were taken.

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Liver function test including serum bilirubin were taken. GFR was estimated by Cockcroft gualt equation (ml/min). Urine and blood was sent for culture and sensitivity. Ultra sonogram of the abdomen was done.

Renal biopsies were done on those presented with unexplained renal failure, nephrotic syndrome, and nephritic syndrome. Renal biopsy tissues sent for histopathological examination. These were done by light microscopy and immunofluorescence study. Glomeruli, tubule, interstitial and vessel were examined with hematoxylin and eosin, periodic acid Schiff and trichrome. MEST scoring was done. Immunofluorescence studies for IgA, IgM, IgG, C3, and C1q were done. Intensity graded from 0 to 4. Those with 2 + and more of dominant or codominant deposit of IgA, diagnosis of IgA nephropathy was made.

After excluding those who met exclusion criteria diagnosis of primary IgA nephropathy were made. Patients were treated according to clinical syndrome Patients with acute kidney injury where there was no renal improvement, then the biopsy was attempted at 5th day to exclude crescents or acute tubular necrosis.

Patients were divided into two cohorts, those had renal failure at presentation (GFR<60ml/min) and those had no renal failure at presentation (>60ml/min). Various factors including clinical and biopsy study were analyzed. Patients were on regular follow up. Those who progressed to chronic kidney disease [CKD (GFR<60 ml/min)], end stage renal disease [ESRD (GFR<15 ml/min)] were analyzed with various clinicopathological factors. These patients were compared with the patients who never reach CKD and ESRD respectively.

Ethical committee approval was obtained from the institution.

RESULTS

A total of 92 patients with biopsy proven IgA Nephropathy were included in the study. Of which five who present with end stage renal disease at presentation were excluded. Eighty seven were finalized into this study. Sixty eight (67.8%) were male. The follow up period ranged from 6-28 months. The mean age at presentation was 27.3years. Thirty nine were presented in 10-19 years age groups (40.2%), followed by twenty five in 20-29 years age groups (28.8%). Five were in 30-39 years age groups (5.7%). Fourteen were in 40-49 age groups (16.1%). Seven were in 50-59 age groups (8%) and one was in 60 years. Patients were stratified according to age groups as given in Table 1.

Clinical presentation of patients were classified as in Table 2. Macrohematuria was noted in 36(40%). Hypertension prevailed in 40 (54%). Edema was present in 66(76%). Oliguria was seen in 59 (67%). Seven were (8%) presented with hypertensive encephalopathy. Nineteen (21.8%) had hypertensive retinopathy.

Table 1	
Total number of patient	87
Male	59(67.8%)
Female	28(27.2%)
Mean age	27.3 years
10-19 years	35(40.2%)
20-29 years	25(28.8%)
30-39 years	5(5.7%)
40-49 years	14 (16.1%)
50-59 years	7 (8%)
60 years	1(1.1%)

Table 1: Stratification as per age group

Clinical presentation	Number of patients	Percentage (%)
Macrohematuria	36	40
Edema	66	76
Oliguria	59	67
Hypertension	40	54
Hypertensive encephalopathy	7	8
Hypertensive retinopathy	19	21.8

Table: 2: Clinical Presentation

Depending upon clinical syndrome patients were categorized as in Table 3. Twenty had nephrotic syndrome (22.9%). Nephritic syndrome was noted in 11 (12.6%). Twelve presented with rapidly progressive renal failure (13%). Six presented with acute kidney injury (6%). Those who presented with end stage renal failure at presentation were excluded from the study.

Syndrome	Number of patients	Percentage (%)
Nephrotic syndrome	20	22.9
Nephritic syndrome	11	12.6
Rapidly progressive glomerulonephritis	12	13
Acute kidney injury	6	6
Chronic kidney disease	5	5.4(excluded)

Table: 3: Clinical syndrome

Renal biopsy findings were tabulated as follows in Table 4 .Scoring was based on Oxford MEST. Mesangial score (M0 & M1) was seen in 28(32.1%) and 59(67.9%) patients respectively. Endocapillary cellularity (E1) was noted in 44(49.4%). Sclerosis score (S0 &S1) observed in 45(51.6%) and 43(51.7%) patients respectively. Tubular atrophy and interstitial fibrosis score of T1 and T2 was noted in 32 (36.7%) and 40 (46%) respectively. Crescents were noted in 16(18.4%). Vessel wall thickening was present in 24 (27.6%).

Biopsy findings	Number (Percentage (%)
M0	28(32.1%)
M1	59(67.9%)
E0	43(49.4%)
E1	44(51.6%)
S0	45(51.7)
S1	42(48.3%)
T0	15(17.2%)
T1	32(36.7%)
T2	40(46%)
Crescents	16(18.4%)
Vascular thickening	24(27.6%)

Table: 4: Biopsy finding

Renal biopsy tissues were also studied with immunoflourescence staining for IgA, IgM, IgG, C3and C1q showed IgA+C3 in 42 (48.2%), IgA+C3+IgM in 30 (34.4%), IgA+C3+ IgM+ IgG in 14 (16.1%),%) and

IgA+C3+IgM+C1q in 7 (8%).Results were given in Table 5.

IF finding	Number & Percentage
IgA + C3	42(48.2%)
IgA+C3+IgM	30(34.4%)
IgA+C3+IgM+IgG	14(16.1%)
IgA+C3+IgM+C1q	7(8%)

Table 5: Immunoflourescence (IF) finding

Clinicopathological variable with renal failure at presentation: Among the 87 patients 59 (67.9%) were presented with renal failure at presentation. Mean age in who presented with renal failure at presentation was 27.9 years. Male dominated as 42 (59%). Male: female 2.4:1. Hypertension was noted in 35 (59%). Macrohematuria occurred in 21 (35.6%).Nephrotic range of proteinuria was present in 27 (47.8%).

Renal biopsy showed mesangial hypercellularity (M1) in 49(83%) ,endothelial proliferation(E1) was seen in 33(56%),segmental score (S1) noted in 49%,tubular atrophy /interstitial fibrosis score T1 and T2 was noted in 28(46%) and 29(51%) respectively. Crescents were noted in 12 (20.2%).Vessel wall thickening was noted in 22. Various factors which were studied between those who presented with renal failure at presentation (GFR <60ml/min) and those without renal failure at presentation were tabulated in Table 6.

Variables	No renal failure at presentation N =28 patients	Renal failure at presentation N =59 patients	P value
Mean age	25.5 years	27.9 years	Not significant
Sex (M% :F %)	61:39	71:29	P=0.33
Hypertension	43%	59%	P=0.1
Macrohematuria	54%	35%	P=0.1727
PCR>3g	39%	46%	P=0.647
M0	36%	17%	P=0.001
M1	64%	83%	
E0	64%	44%	P =0.108
E1	365	56%	
S0	57%	51%	P =0.358
S1	43%	49%	
T0	46.4%	3%	P=0.0019
T1	14.3%	46%	
T2	39.3%	51%	
Crescents	14.2%	20.3%	P=0.568
Vascular thickening	39.2%	22%	P=0.835

Table 6: Variables determining renal failure at presentation

Clinicopathological variable for those progressed to chronic kidney disease: Twenty five (28.74%) were progressed to chronic kidney disease (GFR<60 ml/min) on follow up period. Mean age was 32.6. Sixty four percent were male. Macrohematuria was presented in 7 (28 %).Hypertension persisted in 17(68%). Response to proteinuria was assessed by those achieved complete remission (proteinuria<300mg/day), partial remission (proteinuria 300-3000mg/day) and nil remission (proteinuria>3000mg/day). Ten patients (40%) never attained remission. One attained complete remission. Fourteen (56%) attained partial remission. Mesangial hypercellularity was noted in 18 (72%). Fifteen presented with endothelial hypercellularity (60%). Segmental sclerosis was observed in 17 (68%). Twelve patients (48%) showed tubular atrophy and interstitial fibrosis. Crescents were noted in 7 (28%). Twenty (84%) had GFR <60 ml/min/1.73m^2 since presentation.

Sixty two (71.6%) had normal renal function at the end of follow up period. Mean age was 28. Macrohematuria was present in 29 (47%). Thirty had hypertension (48.3%). Twenty eight patients had complete remission (45%) another twenty four attained partial remission (38.7%).Six never attained remission. Crescents were noted in 9(14.5%). Thirty eight (61.2%) had GFR <60 ml/min at their presentation itself.

Variables analyzed in those who progressed to CKD were tabulated in Table 7.

Variables	Progressed to CKD N =25	Normal renal function at the end of follow up N=62	P Value
Mean age	32.6	28	No significance
Sex (M% :F %)	64;36	60:40	No significance
Hypertension	68%	43%	0.98
Macrohematuria	68%	48.3%	
Response to proteinuria CR	4%	45%	0.0001
Partial response	56%	38.7%	
No response	40%	9.7%	
M1	72%	66%	0.8
E1	60%	46.8%	0.344
S1	68%	40%%	0.001
T0	8%	32.%	0.07
T1	46%	43.2%	
T2	46%	25.8%	
crescents	28%	14.5%	0.2192
GFR<60 ml/min at present	84%	61.2%	0.04
Vessel wall thickening	36%	24%	0.29

Table 7: Variables analyzed in the progression of CKD

Clinicopathological variables in those reach ESRD: Of the total 87 patients 15(17.24%) needed dialytic support due to end stage renal disease. Mean age was 29.4 years. Hematuria was noted in 40%.Hypertension noted in 32%. Those who presented with nephrotic syndrome were 52% and nephritic syndrome was 28%.Crescents was noted in 24%. Variables analyzed in those needed dialytic support are tabulated below in Table 8.

Variables	Patient progressed to ESRD (N=15)
Mean age	29.4
Hematuria (%)	40
Hypertension (%)	32
Nephrotic syndrome (%)	52
Nephritic syndrome (%)	28
Crescents (%)	24

Table 8: Variables analyzed in those needed dialytic support

Treatment response with nephrotic syndrome: Of the 20 patients presented with nephrotic syndrome, all were started with ACEI titrated to reduce the BP target of 125/75 mm Hg, Eighteen were started with steroids. Eleven (55%) had partial remission. Three (20%) had

Response to proteinuria	Progressed to chronic kidney disease	Stable renal function	P=0.5
Complete remission n=3	nil	3	
Partial remission n=11	7	10	
Nil remission n=6			

TABLE 9: Treatment response in nephrotic syndrome

complete remission. Six (30%) never attained remission. Three patients who attained complete remission retained their renal function. Of the seventeen who had partial and nil remission, 7 patients progressed to chronic kidney disease.

Treatment response in RPGN and in AKI: Of the twelve patients presented with rapidly proliferative glomerulonephritis, nine were presented with nephrotic range of proteinuria with nephritic sediment. Steroid was given in 11 and cyclophosphamide with steroid was given in 7 as per vasculitis protocol. Six were progressed to chronic kidney disease. Other six were not.

Acute kidney injury was noted in six patients. Four had acute tubular necrosis. One had crescent and one with no discernible findings.

Survival probability in response to GFR at presentation: Survival probability curve by Kaplan Meyer curve shows that those who had renal failure at presentation had progressed to end stage renal disease than those who had not renal failure (Fig 1).

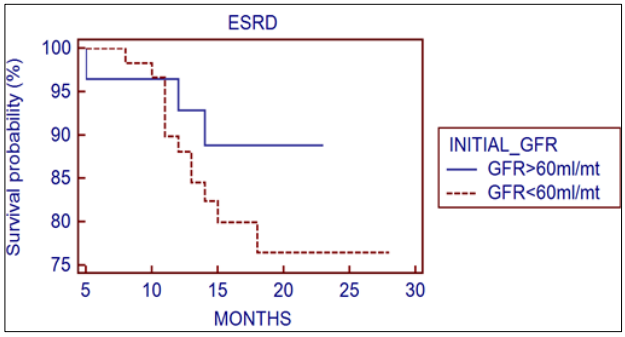

Fig 1: Kaplan Meyer curve showing the survival probability in response to GFR at presentation

Survival probability in response to proteinuria: This Kaplan Mayer curve shows that those who attained no remission went to end stage renal disease more probable than who attained partial or complete response (Fig 2).

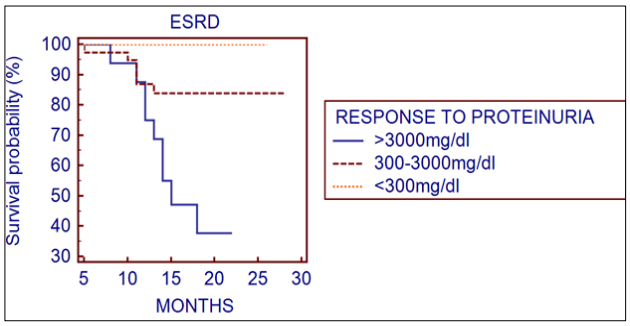

Fig 2: Kaplan Mayer curve showing the survival probability in response to the proteinuria

DISCUSSION

Of the 87 biopsy proven IgA Nephropathy, 68 were male. Male: Female ratio in our study was 2.1:1 which was comparable to Chaco et al,[2] with M: F ratio 1.85:1.

Mean age at presentation in our study was 27.3 years compared to Neha mittal et al. had a mean age of 29.9 years[16], and Muthukumar et al. [17] showed mean age of 25.7 years but a decade younger than that quoted in the western world. The majority were in 10-29 years (70%).

Clinical symptoms: Thirty-six (40%) patients presented with the macrohematuria. Chandrika et al, documented 49.3% had the same.[3] Hypertension was noted in 40 (54%), which was comparable to Chaco et al. (58%). Seven (8%) had hypertensive encephalopathy. Nineteen (12.8%) had hypertensive retinopathy. Muthukumar et al. documented 21.4% had malignant hypertension. Hematuria (macro and micro) observed in 56 (64%) patients. Chako et al. showed 69% had hematuria.

Clinical syndrome: Nephrotic syndrome documented around 3% in western studies. Chako et al. documented 55% had nephrotic syndrome. Chandrika et al. documented 36.7%. Muthukumar et al. documented 25.5% had nephrotic syndrome. Neha mittal et al. study showed 23.1% had nephrotic syndrome[16]. In our study, 22.9% had nephrotic syndrome. Rapidly progressive glomerulonephritis (RPGN) was noted in 13% patients. Muthukumar et al.documented 21% with RPGN.Acute kidney injury was present in 6% patients compared to Muthukumar et al. (4.1%). Mean serum creatinine was 2.03 mg/dl in our study compared to Chako ET al.[2] with 2.3 mg/dl (Table 10).

	Chandrika et al[3]	Chako et al[10]	Neha mittal etal[16]	Muthukumar et al[17]	Prsnt study
Mean age years	30	32	29.9	25.7	27.3
M:F	1.5:1	1.85:1	3:1	2:1	2.1:1
Mean serum creatinine	2.2	2.3	3.1	-	2.03
Hematuria (%)	49.3%	69	78.8	54.9	64%
Hypertension (%)	49	69	81	30	54
Nephrotic syndrome (%)	36.7	55	23.1	25.5	22.9
RPGN (%)	-	-	-	21.4	13
AKI (%)	11	-	-	4.1	6

Table 10: Comparison of clinical presentation and syndrome

Biopsy findings: Renal biopsy results of the 87 patients revealed mesangial hypercellularity (M score>0.5) in 67.9%. Endocapillary proliferation was noted in 51.6%. Sclerosis score (S1) was noted in 49.3%.Tubular atrophy/interstitial fibrosis score (T1&T2) was 36.7% & 46% respectively in our study. Arterial score was 24%.

	Cattran et al [15]	Neha mittal[16]	Hamid Naseri[17]	our study
Endocapillary score (E1)	42%	24.4%	32%	51.6%
Sclerosis score (S1)	76%	48.6%	62%	49.3%
Tubular atrophy/interstitial fibrosis score in (T1&T2)	88%	73.96%	80%	82.7%

Table 11: MEST scoring in various studies

Immunofluorescence study: Immunofluorescence study of renal biopsy tissue in our study showed IgA+C3 present in 42 (48.2%), IgA+C3+IgM in 30 (34.4%), IgA+C3+IgM+IgG in 14 (16.1%),%) and IgA+C3+IgM+C1q in 7 (8%).Chandrika et al showed IgA+C3 present in 105(46.25%), IgA+C3+IgM in 80(35.24%), IgA+C3+IgM+IgG in 20 (8.82%),%)and IgA+C3+IgM+C1q in 5 patients (2.20%). Full house pattern was noted in 4(1.76%), unlike our study.

Clinical presentation of renal failure at presentation (diagnosis): In our study renal failure at presentation (GFR <60 ml/min) was noted in 59 (67.9%).Muthukumar et al.showed 61% had renal failure at diagnosis. The mean age was 27.9 years in who presented with renal failure at diagnosis. Seventy one (81.6%) patients were male, which was comparable to Muthukumar et al. (70%). Hypertension was noted in 35 (59%). Macrohematuria was noted in 21(35.6%), the nephrotic range of proteinuria was present in 27 (46%). hypertension in 28.3% and proteinuria >3g/day in 41.7%,

Biopsy finding in renal failure at presentation: Of the 59 patients who presented with renal failure at presentation, 83% had the mesangial score (M>0.5), 44% had Endocapillary proliferation, 49% had sclerosis score (S1).Tubular atrophy/interstitial fibrosis score (T1&T2) was noted in 47% and 51% respectively. Crescents were noted in 27% of the above cohort. Muthukumar et al.showed interstitial fibrosis in 90% of patients and crescents in 16.7%.

Statistical analysis: The bivariate variables were analyzed by using chi-square fisher's exact test. The multivariable was analyzed by multiple regressions. Male sex, mean age both had no significant correlation in those with renal failure at presentation. Hypertension, Macrohematuria, proteinuria >3g/day were had no significant correlation in this cohort. Mesangial hypercellularity (M score >0.5), tubular atrophy/ interstitial fibrosis score (T1&T2), were significantly associated with renal failure at presentation. Crescents had no significant statistical association. There is no statistical association between vessel wall thickening and those with renal failure at presentation. Muthukumar et al. showed that there were no significant correlation between male, hypertension, macrohematuria, proteinuria >3g/day in those who presented with renal failure at presentation. They showed interstitial fibrosis, vessel wall thickening were associated with renal failure at presentation. By multivariate analysis they showed only interstitial fibrosis was associated with renal failure at presentation, but not vessel wall thickening (Table 12).

Variables	Muthukumar et al	Our study
Mean age(years)	25.7	27.9
Sex (M:F)	2:1	2.1:1
Hypertension (%)	28.3	59
Hematuria (%)	21.7	35
Proteinuria >3g/day	41.7	46
Interstitial fibrosis (%)	90	51
Vessel wall thickening (%)	56	22
Crescents (%)	16.7	27

Table 12: Variables analyzed for those presented with renal failure at diagnosis.

Treatment response in nephrotic syndrome: In our study, 20% presented with nephrotic syndrome all of them are started with ACE inhibitors, and BP was titrated to 120/75 mmHg. Steroid was started in 16 of them, three (15%) attained complete remission, 11(55%) had partial remission, and six (30%) had no remission. Of the 3 who attained complete remission, none progressed to renal failure. Seventeen patients with partial and nil remission, 7 of them progressed to renal failure, 10 were not, but statistically not significant (P=0.54). Reich et al.showed those who had sustained proteinuria >3g/day had 25 fold faster declines in renal function.

Treatment response in RPGN: Twelve (13%) patients presented with RPGN of whom 9 presented with the nephrotic range of proteinuria with nephritic sediment. Steroid was given in 11 patients, and cyclophosphamide with steroid was given in 7 patients as per vasculitis protocol. Half of them progressed to chronic kidney disease, half were not.

Treatment of Acute kidney injury: Acute kidney injury (AKI) was noted in six patients. Four had acute tubular necrosis. One had the crescent and another with no discernible findings. Two need dialytic support, one need immunosuppressive therapy with cyclophosphamide.

Clinical variables in progression of CKD cohort: In our study during follow up period, twenty five patients (28.74%) progressed to chronic kidney disease. Mean age was 32.6years. Twenty eight percentages of them had macrohematuria. Hypertension persisted in 17 (68%). There is no statistical significance noted for hypertension and macrohematuria. Those progressed to CKD 10(40%) had proteinuria >3g/day (nil remission), 14 (56%) had proteinuria in the range of 0.3-3g/day (partial remission), 1(4%) had urinary protein of <0.3g/day. There was statistical significance noted for who had no response to the reduction in proteinuria with that progressed to CKD.

Analysis of biopsy findings in those progresses to CKD: There was no statistical significance noted for the mesangial score (M1) in 72% and Endocapillary proliferation 60% of patients in those who progressed to chronic kidney disease. Segmental score (S1) was noted in 68% who progressed to chronic kidney disease, which was statistically significant. Tubular atrophy/interstitial fibrosis score (T1&T2) was noted in 46% of each who had progressed to chronic kidney disease, which was not statistically significant. Twenty eight percentages had crescents which were not statistically significant. There is no statistical association between vascular wall thickening and chronic kidney disease progression.

Clinicopathological variable in those who reached ESRD: Of the total 87 patients, 15(17.24%) needed dialytic support due to end stage renal disease. Mean age was 29.4 years. Six (40%) associated with hematuria. 8 had sustained hypertension (32%).Those who presented with nephrotic syndrome was (52%), and nephritic syndrome was 28%.Crescents were noted in 24%.By multiple regression analysis there is a significant association between hypertension, segmental

sclerosis(S1), tubular atrophy/interstitial fibrosis score (T1&T2), presence of nephrotic syndrome and response to proteinuria with end stage renal disease warranted dialytic support(P<0.001) of which T score and those respond to proteinuria(as complete remission <300mg/day, partial remission 300-3000mg/day, nil remission >3000 mg/dl) had better significance(P=0.001 and 0.0002 respectively).

CONCLUSION

Nephrotic syndrome is the most common clinical presentation in IgA nephropathy. Majority presented with renal failure at entry into the study. Severe MEST scoring was significantly associated with renal failure at presentation. Non- responders of proteinuria and those who had severe S in MEST scoring system progressed to CKD. Crescents had no statistical association for progression to CKD. Complete or partial remission of proteinuria had less chance for the progression to CKD.

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