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RETROSPECTIVE ANALYSIS OF THE EFFICACY OF PROTEINURIA AS A TREATMENT TARGET IN SUBJECTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: Reduction of proteinuria as a targeted strategy in subjects with advanced chronic renal disease is proven to be effective in the current scenario. However, the evidence is lacking owing to lesser available literature data.

Aim: The present study aimed to assess the efficacy of proteinuria as a treatment target in subjects with chronic kidney disease.

Methods: The study assessed 946 subjects having pre-end stage renal disease suggested by baseline GFR <45ml/min/1.73m2 that were assessed for the effect of proteinuria change on renal death (death before dialysis initiation and a composite of dialysis).

Results: For predictors related to annual GFR change in study subjects, the mean of herbal medicine use was -1.51±0.64 with p=0.01, BMI (<-0.4 or >2.4 kg/m2) was 0.64±0.25 with p=0.006, non-diabetes and the non-RAS blockade was 0.73±0.27 with p=0.004, pre-chronic kidney disease was -2.64±0.82 with p=0.002, UPCR was -0.02±0.01 g/g with p<0.001, albumin (< -0.2 or > 0.6 g/dl) was 0.97±0.26 with p<0.001, phosphate was -0.76±0.16 with p<0.001, hemoglobin was 0.62±0.05 with p<0.001, and baseline UPCR was -1.57±0.12 with p<0.001.

Conclusion: The present study helps in the patient-based evidence in supporting the assessment of proteinuria as a therapeutic target in subjects having advanced chronic kidney disease.

Keywords: Chronic kidney disease, end-stage renal disease, glomerular filtration rate, proteinuria

INTRODUCTION

A rapid increase in the prevalence and incidence of CKD (chronic kidney disease) has led to various serious problems in the population globally including India. CKD has posed a large

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burden on the healthcare sector with the increased risks of various comorbidities, bone and mineral diseases, cardiovascular diseases, ESRD (end-stage renal disease), and mortality.[1] The incidence and prevalence of end-stage renal diseases are one of the highest in India in the world. It is estimated that nearly 7% of all expenditure on health is constituted by end-stage renal diseases. Despite of high incidence and prevalence of renal disease, a small proportion of the population is aware of their kidney status or having chronic kidney disease. It is vital to implement a strategy that can prevent the subject from chronic kidney disease to progress to end-stage renal disease to decrease the healthcare burden.[2]

In the past few decades, various guidelines for clinical practice have been dispensed, and formulated various public health policies, clinical practices, and research for the prevention of the progression of chronic kidney disease to end-stage renal disease and for providing multidisciplinary care to the subjects with end-stage kidney disease having the advanced disease.[3] The program seems to help decrease the medical cost, mortality rates, and incidence of end-stage renal disease by providing more effective medical control and more effective diet implication following the national guidelines issued.[4]

Proteinuria has been considered and proved to be an independent risk factor for the continuous decline in kidney function along with a decrease in mortality rates. The medical treatment provided works as a renoprotective management for the decline in the GFR (glomerular filtration rate).[5] Also, the available evidence suggested that a regimen considering various models targeting the reduction in proteinuria can effectively delay the progression of chronic kidney disease. Previous literature data has reported proteinuria as a potential treatment target in subjects with chronic kidney disease. However, owing to the different depictions of the reduction in proteinuria and outcome variables, the literature data has focused on the need for evaluating the individual database at the patient level. Also, some studies assessed subjects with stage 5 chronic kidney disease.[6] The present study aimed to assess the efficacy of proteinuria as a treatment target in subjects with chronic kidney disease.

MATERIALS AND METHODS

The present retrospective clinical study aimed to assess the efficacy of proteinuria as a treatment target in subjects with chronic kidney disease. The study population was recruited from the subjects of the Department of General Medicine of the Institute.

The study included 1178 subjects from both genders. The inclusion criteria for the study were subjects having pre-end stage renal disease, were of age 18 years or more, and subjects from whom the complete data was retrieved from the institutional record. The 232 subjects were excluded from the study. The exclusion criteria were subjects where the age <18 years, eGFR ≥45 ml/min/1.73m2, and subjects where less than two measurements were taken for the level of the serum creatinine leaving the final sample size of 946 subjects.

After final inclusion, the detailed history was recorded for all the subjects followed by the clinical examination and relevant laboratory investigations. All the included 946 subjects had the diagnosis of pre-end stage renal disease suggested by baseline GFR <45ml/min/1.73m2 that were

assessed for effect of proteinuria change till composite of the dialysis or the renal death which was defined as death before dialysis initiation.

The data gathered was analyzed statistically using SPSS software version 21.0 and a t-test. The data is described as frequency and percentage and mean and standard deviation. The level of significance was kept at $p<0.05$.

RESULTS

The present retrospective clinical study aimed to assess the efficacy of proteinuria as a treatment target in subjects with chronic kidney disease. The study assessed 946 subjects where 500 subjects had baseline UPCR (urine protein creatinine ratio) of ≤1.04g/g and 446 subjects had UPCR >1.04 g/g with a respective mean age of 67.2±11 and 63.4±11 years respectively. There were 317 and 221 males. The mean age and gender difference were statistically significant with $p<0.001$. Diabetic nephropathy was significantly higher in subjects with UPCR >1.04 g/g with $p<0.001$. The alcohol status, smoking, employment status, educational level, and marital status were non-significant with p=0.58, 0.06, 0.08, and 0.15 respectively. The GFR, albumin, and hemoglobin were significantly higher in UPCR ≤1.04g/g with $p<0.001$. The calcium was also significantly higher with p=0.02. MAP (mean arterial pressure) was significantly higher in a group with UPCR >1.04 g/g ($p<0.001$). The BMI was comparable in the two groups with p=0.37. CKD stage 3b had a high prevalence in a group with UPCR ≤1.04g/g, whereas stage 5 CKD was higher in UPCR >1.04 g/g ($p<0.001$). The prevalence of cardiovascular disease, PCKD, herbal medication, and RAS blockade use had a non-significant difference in the two groups with p=0.95, 0.07, 0.18, and 0.73 respectively. Hypertension was higher in UPCR ≤1.04g/g, whereas >3 antihypertensive use was higher in UPCR >1.04 g/g ($p<0.001$) as shown in Table 1.

On assessing the changes in various parameters, UPCR, phosphate, and hemoglobin were higher in subjects with UPCR ≤1.04g/g with $p<0.001$. However, changes in albumin, corrected calcium, BMI, and mean arterial pressure was non-significant in the two groups with respective p-values of 1.00, 0.18, 0.33, and 0.05 respectively. The months of assessment for the change were 19.3±8.1 months and 16.7±6.2 months respectively for UPCR ≤1.04g/g and >1.04 g/g respectively with $p<0.001$. The annual GFR change was -0.07±5.84 and -4.01±5.26 for UPCR ≤1.04g/g and >1.04 g/g respectively ($p<0.001$). Composite renal death, dialysis, and mortality were higher in subjects with GFR >1.04 g/g with $p<0.001$ as depicted in Table 1.

Concerning the assessment of the predictors related to annual GFR change in study subjects, the mean of herbal medicine use was -1.51±0.64 with p=0.01, BMI (<-0.4 or >2.4 kg/m2) was 0.64±0.25 with p=0.006, non-diabetes and the non-RAS blockade was 0.73±0.27 with p=0.004, pre-chronic kidney disease was -2.64±0.82 with p=0.002, UPCR was -0.02±0.01 g/g with $p<0.001$, albumin (< -0.2 or > 0.6 g/dl) was 0.97±0.26 with $p<0.001$, phosphate was -0.76±0.16 with $p<0.001$, hemoglobin was 0.62±0.05 with $p<0.001$, and baseline UPCR was -1.57±0.12 with $p<0.001$ as depicted in Table 2.

For the characteristics of the study participants based on the proteinuria status, groups A and B were considered for baseline UPCR ≤0.30 g/g including 630 subjects, and baseline UPCR >0.30

g/g including 316 subjects respectively. Baseline GFR was significantly higher for Group A with p<0.001. Albumin and phosphate levels were significantly higher for Group B with p=0.01 and <0.001 respectively. The calcium levels were comparable in the two groups with p=0.08. Hemoglobin levels were significantly higher in Group A with p<0.001. BMI and MAP had a non-significant difference in the two groups with p=0.65 and 0.44 respectively. CKD stages 3b and 5 had high prevalence in Group A with p<0.001. CKD stage 4 was non-significant in two groups with p=0.31. Hypertension was significantly higher in Group A with p=0.004. RAS blockade use, >3 antihypertensive agents, herbal medications, PCKD, cardiovascular disease, and diabetes had non-significant differences among the two groups with respective p-values of 0.07, 0.08, 0.91, 0.07, 0.35, and 0.06 respectively (Table 3).

The changes in various parameters were assessed over 17.5±7.2 months in Group A and 18.4±8.2 months in Group B. The change in UPCR, albumin, phosphate, and MAP was higher in Group B with p<0.001, 0.01, 0.002, and <0.001 respectively, whereas, hemoglobin change was higher in Group A with p<0.001. The calcium and BMI showed a non-significant change in the two groups with 0.08 and 0.54 respectively. Annual GFR change, composite renal death, and mortality were higher in Group A with p<0.001. Dialysis was comparable in the two groups with p=0.76 (Table 3).

DISCUSSION

The present retrospective clinical study assessed data from 946 subjects where 500 subjects had baseline UPCR (urine protein creatinine ratio) of ≤1.04g/g and 446 subjects had UPCR >1.04 g/g with a respective mean age of 67.2±11 and 63.4±11 years respectively. There were 317 and 221 males. The mean age and gender difference were statistically significant with p<0.001. Diabetic nephropathy was significantly higher in subjects with UPCR >1.04 g/g with p<0.001. The alcohol status, smoking, employment status, educational level, and marital status were non-significant with p=0.58, 0.06, 0.08, and 0.15 respectively. The GFR, albumin, and hemoglobin were significantly higher in UPCR ≤1.04g/g with p<0.001. The calcium was also significantly higher with p=0.02. MAP (mean arterial pressure) was significantly higher in a group with UPCR >1.04 g/g (p<0.001). The BMI was comparable in the two groups with p=0.37. CKD stage 3b had a high prevalence in the group with UPCR ≤1.04g/g, whereas stage 5 CKD was higher in UPCR >1.04 g/g (p<0.001). The prevalence of cardiovascular disease, PCKD, herbal medication, and RAS blockade use had a non-significant difference in the two groups with p=0.95, 0.07, 0.18, and 0.73 respectively. Hypertension was higher in UPCR ≤1.04g/g, whereas >3 antihypertensive use was higher in UPCR >1.04 g/g (p<0.001). These data were compared to the previous studies of Jha V et al[7] in 2012 and Wu I et al[8] in 2009 where authors assessed subjects with demographics comparable to the present study.

The study results showed that for the changes in various parameters, UPCR, phosphate, and hemoglobin were higher in subjects with UPCR ≤1.04g/g with p<0.001. However, changes in albumin, corrected calcium, BMI, and mean arterial pressure was non-significant in the two groups with respective p-values of 1.00, 0.18, 0.33, and 0.05 respectively. The months of assessment for the change were 19.3±8.1 months and 16.7±6.2 months respectively for UPCR

≤1.04g/g and >1.04 g/g respectively with p<0.001. The annual GFR change was -0.07±5.84 and -4.01±5.26 for UPCR ≤1.04g/g and >1.04 g/g respectively (p<0.001). Composite renal death, dialysis, and mortality were higher in subjects with GFR >1.04 g/g with p<0.001. These results were consistent with the previous studies of Ishani A et al[9] in 2006 and Matsushita K et al[10] in 2010 where authors reported similar changes in different renal parameters in pre-CKD subjects of their studies.

For the assessment of the predictors related to annual GFR change in study subjects, the mean of herbal medicine use was -1.51±0.64 with p=0.01, BMI (<-0.4 or >2.4 kg/m2) was 0.64±0.25 with p=0.006, non-diabetes and the non-RAS blockade was 0.73±0.27 with p=0.004, pre-chronic kidney disease was -2.64±0.82 with p=0.002, UPCR was -0.02±0.01 g/g with p<0.001, albumin (< -0.2 or > 0.6 g/dl) was 0.97±0.26 with p<0.001, phosphate was -0.76±0.16 with p<0.001, hemoglobin was 0.62±0.05 with p<0.001, and baseline UPCR was -1.57±0.12 with p<0.001. These results were in agreement with the previous studies of Gaspari F et al[11] in 2013 and Ahmad Ak et al[12] in 2010 where authors reported the similar significance of various kidney disease predictors in their study subjects.

Concerning the characteristics of the study participants based on the proteinuria status, groups A and B were considered for baseline UPCR ≤0.30 g/g including 630 subjects, and baseline UPCR >0.30 g/g including 316 subjects respectively. Baseline GFR was significantly higher for Group A with p<0.001. Albumin and phosphate levels were significantly higher for Group B with p=0.01 and <0.001 respectively. The calcium levels were comparable in the two groups with p=0.08. Hemoglobin levels were significantly higher in Group A with p<0.001. BMI and MAP had a non-significant difference in the two groups with p=0.65 and 0.44 respectively. CKD stages 3b and 5 had high prevalence in Group A with p<0.001. CKD stage 4 was non-significant in two groups with p=0.31. Hypertension was significantly higher in Group A with p=0.004. RAS blockade use, >3 antihypertensive agents, herbal medications, PCKD, cardiovascular disease, and diabetes had non-significant differences among the two groups with respective p-values of 0.07, 0.08, 0.91, 0.07, 0.35, and 0.06 respectively. These results were similar to the studies of Wu HY et al[13] in 2013 and Vejakama P et al[14] in 2012 where authors reported similar associations of various parameters and proteinuria in their respective studies.

On assessing the changes in various parameters over 17.5±7.2 months in Group A and 18.4±8.2 months in Group B. The change in UPCR, albumin, phosphate, and MAP was higher in Group B with p<0.001, 0.01, 0.002, and <0.001 respectively, whereas, hemoglobin change was higher in Group A with p<0.001. The calcium and BMI showed a non-significant change in the two groups with 0.08 and 0.54 respectively. Annual GFR change, composite renal death, and mortality were higher in Group A with p<0.001. Dialysis was comparable in the two groups with p=0.76. These results were in line with the studies of Taal M et al[15] in 2006 and Imai E et al[16] in 2013 where similar changes in various parameters were noted in one year of assessment time.

CONCLUSION

Considering its limitations, the present study helps in the patient-based evidence in supporting the assessment of proteinuria as a therapeutic target in subjects having advanced chronic kidney disease.

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TABLES

Parameter	**Baseline UPCR (urine protein creatinine ratio) ≤1.04g/g (n=500)**	**Baseline UPCR (urine protein creatinine ratio) >1.04g/g (n=446)**	**p-value**
Mean age (years)	67.2±11	63.4±11	**<0.001**
Male gender	317	221	**<0.001**
Diabetic nephropathy	63	233	**<0.001**
Alcohol	46	38	0.58
Smoking	94	95	
Employed	151	153	0.06
Educated	148	134	0.08
Married	383	332	0.15
GFR (mL/min/1.73m2)	27.22±10.07	20.47±9.86	**<0.001**
UPCR (g/g)	0.44±0.27	2.97±2.34	**<0.001**
Albumin (g/dl)	4.5±0.6	4.3±0.3	**<0.001**
Phosphate (mg/dl)	3.6±0.6	4.4±0.6	**<0.001**
Calcium (mg/dl)	9.2±0.4	8.7±0.8	0.**02**
Hemoglobin (g/dL)	11.4±2.2	10.6±2.2	**<0.001**
BMI (kg/m2)	25.3±4.4	25.5±4.8	0.37
MAP (mmHg)	93.6±12.4	98.2±13.7	**<0.001**
CKD stage 3b	209	85	**<0.001**
CKD stage 4	217	202	0.44
CKD stage 5	73	159	**<0.001**
Comorbidities			
RAS blockade use	222	202	**0.**73
>3 antihypertensive	54	74	**<0.001**
Herbal medication	35	39	**0.**18
PCKD	12	6	0.07
Hypertension	372	365	**<0.001**
Cardiovascular disease	87	77	0.95
Diabetes	198	209	**<0.001**
Alterations			
UPCR	0.38±1.13	0.17±2.78	**0.02**
Albumin	-0.1±0.2	-0.1±0.2	1.000
Phosphate	0.0±0.6	0.0±0.5	**<0.001**
Ca (mg/dl)	0.00±0.4	0.0±0.5	0.18
Hemoglobin (g/dl)	0.0±1.2	-0.5±1.4	<**0.001**
BMI (kg/m2)	-0.2±1.4	-0.3±1.6	0.33
MAP (mmHg)	-0.5±14.2	-1.8±15.7	0.05

Interval change (months)	19.3±8.1	16.7±6.2	**<0.001**
GFR change (annually)	-0.07±5.84	-4.01±5.26	**<0.001**
Composite renal death	44	139	**<0.001**
Dialysis	30	123	**<0.001**
Mortality	14	16	0.35

Table 1: Demographic and disease characteristics of study subjects at baseline

Variable	Mean± S. D	p-value
Herbal medicine use	-1.51±0.64	**0.01**
BMI (<-0.4 or >2.4 kg/m2)	0.64±0.25	**0.006**
Non-diabetes and non-RAS blockade	0.73±0.27	**0.004**
PCKD	-2.64±0.82	**0.002**
UPCR (per 10 g/g)	-0.02±0.01	**<0.001**
Albumin (< -0.2 or > 0.6 g/dl)	0.97±0.26	**<0.001**
Phosphate	-0.76±0.16	**<0.001**
Hemoglobin	0.62±0.05	**<0.001**
UPCR (Baseline)	-1.57±0.12	**<0.001**

Table 2: Assessing the predictors related to annual GFR change in study subjects

Parameter	Baseline UPCR ≤0.30 g/g (n=630)	Baseline UPCR >0.30 g/g (n=316)	p-value
Mean age (years)	67.2±11	63.4±11	**<0.001**
Male gender	317	221	**<0.001**
Diabetic nephropathy	63	233	**<0.001**
Alcohol	46	38	0.58
Smoking	94	95	
Employed	151	153	0.06
Educated	148	134	0.08
Married	383	332	0.15
GFR (mL/min/1.73m2)	25.12±10.52	21.94±10.22	**<0.001**
UPCR (g/g)	1.64±2.27	1.55±1.56	0.36
Albumin (g/dl)	4.1±0.6	4.2±0.6	**0.01**
Phosphate (mg/dl)	3.7±0.6	4.3±0.6	**<0.001**
Calcium (mg/dl)	9.2±0.4	9.1±0.4	0.08
Hemoglobin (g/dL)	11.2±2.3	10.6±2.2	**<0.001**
BMI (kg/m2)	25.3±4.4	25.5±4.8	0.65
MAP (mmHg)	96.3±13.3	95.8±12.6	0.44
CKD stage 3b	222	73	**<0.001**
CKD stage 4	274	144	0.31
CKD stage 5	134	98	**<0.001**
Comorbidities			
RAS blockade use	283	161	0.07
>3 antihypertensive	79	49	0.08
Herbal medication	49	25	0.91
PCKD	12	6	0.07
Hypertension	479	254	**0.004**

Cardiovascular disease	113	51	0.35
Diabetes	296	162	0.06
Alterations			
UPCR	-0.55±1.37	1.87±2.25	**<0.001**
Albumin	4.1±0.6	4.4±0.2	**0.01**
Phosphate	0.1±0.7	0.3±1.4	**0.002**
Ca (mg/dl)	0.00±0.4	-0.1±0.5	0.08
Hemoglobin (g/dl)	0.0±1.2	-0.5±1.4	<**0.001**
BMI (kg/m2)	-0.2±1.4	-0.2±1.6	0.54
MAP (mmHg)	-2.4±14.7	1.7±15.2	**<0.001**
Interval change (months)	17.5±7.2	18.4±8.2	0.24
GFR change (annually)	-1.56±5.82	-2.64±6.03	**<0.001**
Composite renal death	96	87	**<0.001**
Dialysis	76	77	0.76
Mortality	19	11	**<0.001**

Table 3: Characteristics of the study participants based on the proteinuria status