Chronic Kidney Disease (CKD) Stages and Proteinuria Range Relationship

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Abstract

Aim: Clinical trials consistently showed kidney protective effects of proteinuria reduction. The endeavour in this study was to see whether the degree of proteinuria was related to the progressive stages of chronic kidney disease.

Methods: This Observational study was carried out on a total of 100 patients above 18 years of either sex with chronic kidney disease in the Department of Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. Data were collected through semi-structured questionnaire. Students t- Test and Chi-square (χ^2) tests were done, and p value <0.05 was considered significant.

Results: The mean eGFR for the study population was 16.74 ± 12.92 ml/min/1.73 m^2. The mean eGFR was 40.44 ± 7.88 ml/min/1.73 m^2, 21.22 ± 3.27 ml/min/1.73 m^2 and 6.69 ± 2.73 ml/min/1.73 m^2 in stage 3, stage 4 and stage 5 respectively. The overall range of proteinuria was from 1+ to 2+ in stage 3, from 2+ to 4+ in stage 4 and from 3+ to 4+ in stage 5. For 1+ proteinuria mean eGFR was 43.9 ± 12.08 ml/min/1.73 m^2 (stage 3), for 2+ proteinuria mean GFR was 21.2 ± 8.52 ml/min/1.73 m^2 (stage 4) and for 3+ proteinuria mean GFR was 9.4 ± 7.03 ml/min/1.73 m^2 (stage 5). eGFR in subjects with 3+≤ proteinuria was significantly lower than that in subjects with 2+ ≤ proteinuria.

Conclusion: The range of proteinuria increased with the progressive stages of CKD.

Keywords: Chronic Kidney Disease (CKD) • Proteinuria • Glomerular Filtration Rate (eGFR)

Introduction

Chronic kidney disease is a concern for both developing and developed countries. The burden associated with CKD includes the impact on the health of an individual and the impact on the society and health sector as a whole. The global death of CKD was 1.2 million in 2017 [1].The dialysis costs estimated is 40,000 to 80,000 euro/year/patient based on country [2]. Treatment as well as dialysis cost is a huge burden in the developing country (e.g., Bangladesh) as chronic kidney disease is treacherous and undiagnosed until its latest stages. Furthermore, CKD cannot be detected only with serum creatinine in most of the cases (90%) [3]. Therefore, early diagnosis and screening is essential that can save the financial burden. Urine testing for protein can be a great independent tool for diagnosis of CKD. Normal urinary protein excretion is considered to be <150 mg/24 hours. Total urinary proteins measured are comprised of immunoglobulins, assorted globulins, and Tamm-Horsfallmucoprotein. Persistent proteinuria is defined as two or more positive quantitative tests of protein excretion, separated by at least 2 weeks. Persistently elevated total urinary protein signifies: a) leakage of protein due to glomerular basement membrane defect; b) impaired tubular uptake of protein or c) increased filtration of low molecular weight protein (example- multiple myeloma, myoglobinuria).

Common benign causes of proteinuria are orthostatic proteinuria, dehydration, vigorous activity or exercise, and fever. Among others, the pathological causes of proteinuria include glomerular dysfunction and multiple myeloma. Though ACR (albumin: creatinine ratio) measures the proteinuria more accurately, dipstick measurement is widely used at the urban and rural health centers in Bangladesh. A result of 1+ equivalent to 30 mg of protein / dL and is positive; 2+ equivalent to 100 mg /dL,3+ to 300 mg/ dL, and 4+ to ≥ 2,000 mg /dL. False-positive proteinuria results occur in alkaline urine, when urine is highly concentrated; with gross hematuria; in the presence of some antibiotics; and urine contamination with semen or vaginal secretions [4]. False-negative proteinuria occur with dilute urine or nonalbumin or low molecular weight urinary proteins.

The postulated pathological mechanism shows that excessive filtration of proteins across the glomerular basement membrane bring enormous protein in contact with the mesangium and the tubular cells that can mediate inflammation through activation of complement and production of cytokines and mediators by tubular cells and thus may stimulate interstitial inflammation and scarring [5]. Therefore, proteinuria is the potential main target to address for diagnosis and staging of CKD.

The updated KDIGO (Kidney Disease Improving Global Outcome) classification of CKD is based on cause, GFR category and albuminuria category (CGA) [6]. The stages of Chronic Kidney Disease are based on GFR - Stage 1: GFR >90 (normal function): Stage 2: GFR 60-89 (mild CKD); Stage 3A: GFR 45-59 (Mild to Moderate CKD); Stage 3B: GFR 30-42 (Moderate to Severe CKD); Stage 4: GFR 15-29 (Severe CKD); and Stage 5: GFR <15 or dialysis (Kidney Failure). But the limitations of GFR is i). It is only an estimate, less reliable at extremes of body composition, ii). Confidence intervals are wide, iii). Creatinine level must be stable over days; GFR is not valid in assessing acute kidney injury, iv). In the elderly here is controversy about categorizing people as having chronic kidney disease on the basis of GFR alone, v). GFR is not valid in under-18 s or during pregnancy, and vi). Ethnicity is not taken into account as eGFR should be multiplied by 1.21 for black people [7].

On the contrary, Urine testing for protein is a cost effective and easy tool for its acceptable sensitivity and high specificity. Numerous clinical studies and the updated CGA staging of CKD demonstrated a correlation between the degree of proteinuria and the rate of progression of renal failure and prognosis. This lead to our hypothesis that proteinuria could be

an independent marker of staging of CKD, not simply a marker of prognosis. The rationale that proteinuria could be a biomarker for CKD staging [8] are i). Proteinuria is a marker of kidney damage, ii). Clue to the diagnosis of CKD, iii). Risk factor for progression of kidney disease, iv). Hypothesized marker of vascular permeability, v). Hypothesized surrogate outcome for kidney disease progression. Here proteinuria is considered to be a biomarker for CKD diagnosis and staging that will lead the diagnosis and staging of CKD easier; delaying the progression of CKD to end stage renal disease, subsequently resulting in better prognosis.

The classification of CKD is changing over years. There is pros and cons on GFR to consider and so on the current staging system. There is also great support for revising the CKD definition and classification system [9]. This study attempted to find the relation of magnitude of proteinuria with successive stages of CKD.

Materials and Methods

Sample size

The present The sample size was determined by following formula :

$$n = \frac{z^2 \times pq}{d^2} where$$

n=The desired sample size

z=The standard normal deviate, set at 1.96 at 5% level which corresponded to 95% confidence level, the assumed target population was P to have a particular characteristics and q=1-p

Here P=0.11, D was the degree of accuracy level considered as 5%, which assume, was 0.05.

Putting the values in the above equation the sample size n is estimated as

$$n = \frac{(1.96)^2 \times 0.11 \times 0.89}{(.011)^2} = 384$$

So, finally 384 subjects were selected. But due to time constrain and availability of the study subjects ultimately 100 subjects was enrolled.

Inclusion criteria–

• Both males and females of 18 years and above.

• Patients with Chronic kidney disease of stage 3 onwards.

Exclusion criteria-

• Patients having gross hematuria.

• Patients with pregnancy.

• Factors other than kidney disease known to affect urinary albumin excretion like Patients with UTI, CCF and acute febrile illness.

• Patients on dialysis.

• Chronic kidney disease stage 1 and 2.

eGFR Calculation:

eGFR: (MDRD) study equation: eGFR=175×(creatinine in µmol/L/88.4)-1.154×(age in years)-0.203×(0.742 if female) × (1.21 if black)

Randomization Methods

Purposive sampling

Procedures: The study subjects were then enrolled in this study. The objective of the study was discussed in details with the patients or their attendants. Demographic information was prospectively recorded and substantiated by means of inspection of medical record. Information included was the subject's age, gender, medical history, clinical examination, followed by evaluation of renal function. CKD was diagnosed on basis of clinical findings and subsequent S. creatinine, Urine routine and microscopic examination and renal USG or renal biopsy.

Blood sampling and assays

Overnight fasting serum levels of Creatinine was sent. eGFR was calculated using the following equation: 175×(Creatinine in µmol/L/88.4)$^{-1.154}$×(age in years)$^{-0.203}$×(0.742 if female) × (1.21 if black). Reduced eGFR was defined as eGFR <60 ml/min/1.73 m^2.

Urine samples were collected from the patients and sent for routine and microscopic examination within 1 hour of collection. The sample was graded as: –, negative; ± , trace positive; +, positive (30 mg/dl); 2+, positive (100 mg/dl); 3+, positive (300 mg/dl); or 4+, positive (>2000 mg/dl) according to the report.

Data processing and statistical analysis

Data was edited after filling the questionnaire. Data obtained were coded and entered in MS (Microsoft)-Excel sheet. Data were summarized as mean with statistical significance level defined as p <0.05. P values were calculated by Fisher's exact test. Demographic and baseline characteristics were compared with the use of the Chi-square test or Fisher's exact test. SPSS (Statistical Package for the Social Sciences) software of 11.5 versions is a computer program was used for data analysis.

Results and Discussion

The olfactory This cross sectional and observational study was carried to evaluate the range of proteinuria of CKD patients hospitalized in a tertiary care hospital on 100 subjects above 18 years of age in the Department of Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.

In the study male was predominant than female, 63% were male and rest 37% were female (Table 1). The reason could be explained that the females are neglected regarding treatment and their delayed presentation to the clinician [10]. Maya Rao conducted a study which revealed that females with CKD were underdiagnosed than males. This study also depicted male predominance.

Table 1. Gender distribution of the study subjects (n=100).

Gender	Number	Percentage
Male	63	63
Female	37	37

Among 100 patients, mean age was 43.26 ± 13.07. Majority (27+28=57%) of the respondents was found in the age group of 28-37 and 38-47. The mean age for stage 3 was 36.31 ± 14.0 years, for stage 4 was 39.06 ± 11.6 years and for stage 5 was 47.98 ± 2.97 years (Table 2). From the youngest to the oldest age group, eGFR decreased significantly with age which was statistically significant. Coresh et al. [11] found that the prevalence of CKD increased with age with stages 1 and 2 increasing from 2% to 3% at age 20 to 39 years to 9% to 10% after the age of 70 years. Douville P et al. [12] showed that the GFR reduction is progressive after the age of 30 and continue to decline steadily after the age of 60 which was in general agreement of this study finding.

Table 2. Age distribution of the study subjects (n=100).

Age Group (yrs)	Number	Mean age	Mean S. Creatinine
18-27	9	23.2 ± 3.49	2.94 ± 1.41
28-37	27	31.70 ± 2.93	5.66 ± 3.65
38-47	28	42.14 ± 2.41	5.41 ± 4.09
48-57	15	52.13 ± 2.70	6.84 ± 2.08
58-67	21	62.33 ± 2.20	7.19 ± 4.21

The majority (91%) of the subjects presented with swelling of face, feet and ankle (31%), Nausea, vomiting and loss of appetite (23%), Breathlessness (11%), Urinary complain (hematuria, polyuria, nocturia, oliguria) (19%), and generalized weakness (7%) (Figure 1).

The etiology for CKD were diabetes (30%), hypertension (19%), glomerular disease (primary or secondary (16%), Systemic Inflammatory disease (15%), previous H/O Kidney disease (11%), tubulointerstitialdisease (6%), and others (8%) (Figure 2). Bangladesh Renal Registry Report [13] (1986-1996) noted the etiologies of the chronic kidney diseases were glomerulonephritis (47.0%), diabetic nephropathy (24.3%) and hypertension

(30.0%) which was in general agreement with these finding and reflects the higher prevalence of glomerulonephritis in the country. The major causes of kidney disease and subsequent kidney failure in the US are diabetes (accounting for 44.4%) and hypertension (accounting for 26.8%), both of which are increasingly common. Conditions accounting for the remaining 29% include primary glomerulopathies like focal glomerulosclerosis and IgA nephropathy, inherited conditions like polycystic kidney disease, and autoimmune conditions like lupus [14]. The similar result was found in the present study.

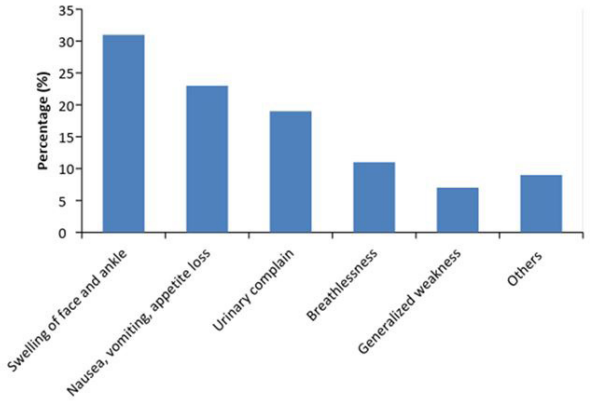

Figure 1. Clinical presentations of the study subjects (n=100). Multiple responses were elicited. It was revealed that majority (91%) of the subjects presented with swelling of face, feet and ankle (31%), Nausea, vomiting and loss of appetite (23%), Breathlessness (11%), Urinary complain (hematuria, polyuria, nocturia, oliguria) (19%), and generalized weakness (7%).

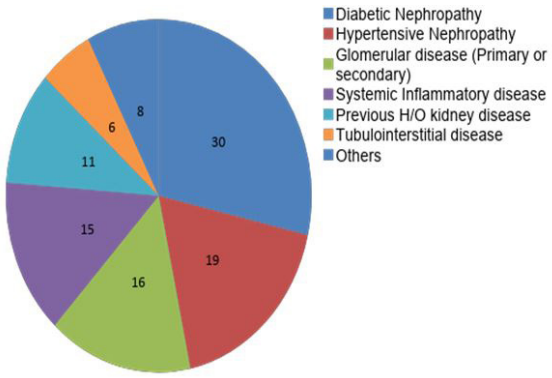

Figure 2. Etiology for CKD of the study subjects (n=100). *Multiple responses were elicited. The etiology for CKD were diabetes (30%), hypertension (19%), glomerular disease (primary or secondary) (16%), systemic inflammatory disease (15%), previous H/O Kidney disease (11%), tubulointerstitial disease (6%), and others (8%). **Note:** (■) Diabetic Nephropathy, (■) Hypersensitive Nephropathy, (■) Glomerular disease (Primary or secondary), (■) Systemic Inflammatory disease, (■) Pervious H/O kidney disease, (■) Tubulointerstitial disease, (■) Others.

The maximum number of frequency of 4+ proteinuria, 3+ proteinuria was in stage 5; whereas the maximum number of frequency of 2+ proteinuria, 1+ proteinuria was in stage 4 and stage 3, respectively. However, the overall range of proteinuria was from 1+ to 2+ in stage 3, from 2+ to 4+ in stage 4 and from 3+ to 4+ in stage 5 (Table 3). The t-test was significant.

Table 3. Frequency of estimated proteinuria in different stages of CKD (n=100).

Stage	Trace	1+	2+	3+	4+
Stage 3	1	8	6	1	0
Stage 4	0	0	17	8	7
Stage 5	0	1	8	20	23

The mean eGFR for the study (100) population was 16.74± 12.92 ml/min/1.73 m^2. The number of patients with eGFR 30-59 ml/min/1.73 m^2 (stage 3) was 16% and with eGFR 15-29 ml/min/1.73 m^2 (stage 4) was 32% and with eGFR less than 15 ml/min/1.73 m^2 (stage 5) was 52% (Table 4). The mean eGFR was 40.44±7.88 ml/min/1.73 m^2, 21.22±3.27 ml/min/1.73 m^2 and 6.69±2.73 ml/min/1.73 m^2 in stage 3, stage 4, and stage 5, respectively. The mean serum creatinine of the study population was 5.84 ± 3.70 mg/dl. The mean serum creatinine was 1.87 ± 0.30 mg/dl, 3.19 ± 0.38 mg/dl and 8.69 ± 2.97 mg/dl in stage 3, stage 4, and stage 5, respectively (Figure 3). The distribution of serum creatinine and eGFR in the study population showed inverse reciprocal relationship.

Table 4. Distribution of study subjects by stages of CKD (n=100).

Stage	eGFR	Frequency	Percentage
Stage 3	30-59	16	16
Stage 4	15-29	32	32
Stage 5	<15	52	52

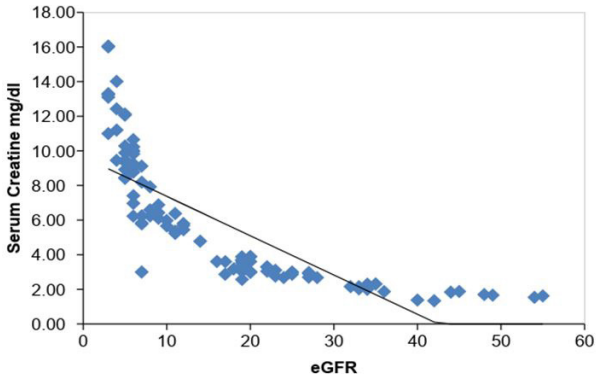

Figure 3. Distribution of mean S. creatinine and eGFR of the study population.

Nubuyoki [15] reported that they identified a strong, graded relationship between end-stage renal disease and positive dipstick urinalysis for proteinuria (adjusted odds ratio 2.71) (Figure 4). This observational study was supported by these studies.

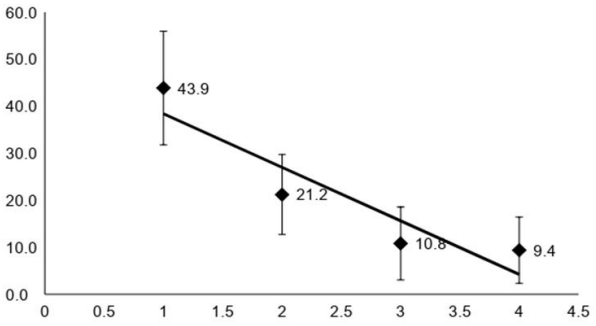

Figure 4. Relationship between eGFR and Proteinuria of the study population showed inverse relationship. r2=0.9993 which was statistically significant.

Conclusion

In our study, for 1+ proteinuria mean eGFR was 43.9 ± 12.08 ml/min/1.73 m^2 (stage 3), for 2+ proteinuria mean GFR was 21.2 ± 8.52 ml/min/1.73 m^2 (stage 4) and for 3+ proteinuria mean GFR was 9.4 ± 7.03ml/min/1.73 m^2 (stage 5). Decline in eGFR was accompanied with the rise of proteinuria. p value was <0.05 which was statistically significant. So, rise of proteinuria was closely linked to the progressive stages of CKD. This relationship is suggested to be considered in future update of CKD staging. However, we recommend the following two points. Further study is needed using ACR or PCR for quantification of proteinuria as they estimate proteinuria more accurately. In our country, ACR or PCR is not widely used yet.A multicentric prospective case control study with large sample size and longer duration is recommended to generalize the findings.

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Conflict of Interest

The authors declare that they have no competing interest.

Ethics approval

Approved by the Medicine Department of Bangabandhu Sheikh Mujib Medical University (BSMMU) and BCPS (Bangladesh College of Physicians and Surgeons).

Consent to participate

Informed written consent was taken from the patients before examination, investigation and data collection.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contribution

MY contributed to study proposal, design of the research, data collection, analysis and interpretation and writing the manuscript. MJC contributed to the correction and critical approval of the manuscript. NKB and AA contributed to the revision. All authors have gone through and approved the final manuscript.

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