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Association of proteinuria with eGFR in CKD- *A Retrospective Study*

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Abstract
Background and objectives: Proteinuria is an integral association of chronic kidney disease (CKD), and heavy proteinuria indicates a rapid decline in renal function. However, the epidemiologic trend of this important biomarker is not well described in the Indian CKD population.
Design, setting, participants & measurements: This cross-sectional study of adults with CKD examined the association of proteinuria with the glomerular filtration rate. The CKD EPI formula used for eGFR and Urinary protein-to-creatinine ratios (Up/c) were used to measure level of proteinuria.
Results: Of the 100 subjects studied, the mean eGFR as measured by CKD EPI equation was 14.43 ml/min per 1.73 m^2. Twenty-four percent of them had normal range (Up/c <0.2), 62% had significant, and 14% had nephrotic-range proteinuria (Up/c >2.0). A decrease in eGFR was associated with an increase in Up/c.
Conclusions: Proteinuria is associated with level of eGFR, cause of CKD, and race. We can actually utilise this proteinuria tool as the severity surrogate index of CKD. Early check over proteinuria can help reduce the progression to CKD and its complications.

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I. Introduction

Proteinuria is an important marker strongly associated with chronic kidney disease (CKD) and is an indicator of glomerular or renal tubular disease. Recently, the National Kidney Foundation has recommended the evaluation of individuals for CKD by either blood parameters to estimate GFR or by urinary screening for the detection of proteinuria. Tests for total urine protein are preferred in adults and children, except for those with diabetes who should be screened for albuminuria (1). Proteinuria is not only a marker of kidney damage, but it is also associated with progressive kidney injury. The increase in urinary protein excretion either by damage to the glomerulus or decrease in tubular re absorption of protein causes injury to renal tubular cells (2). Exposure of tubules to urinary proteins proved to cause interstitial inflammation and subsequent fibrosis, (3) as well as apoptosis in proximal tubular cells (4). Adult and paediatric studies also demonstrate that elevated urine total protein is an independent risk factor for a progressive decline in kidney function (5–9). Although the baseline level of proteinuria is a known risk factor for CKD progression, the determinants of proteinuria and how proteinuria changes with kidney progression are unclear. A better understanding of these phenomena might yield new insights and treatments for kidney disease progression. To that end, an epidemiologic survey of all patients with CKD would be important to assess potential environmental modifiers and differences in groups among patients with CKD (10)The principal aim of the present study is to describe the distribution of proteinuria in a given adult population with mild to moderate CKD and to identify clinical characteristics, including kidney function, associated with elevated levels of proteinuria.

II. Materials and Methods

Study Population

The present study is a record based cross sectional study of patients with CKD admitted to tertiary care centre RIMS, Ranchi from June 2019 to January 2020. Briefly, patient's record taken for this study belonged to age group from 19 to 80 years. Exclusion criteria included: renal, other solid-organ, bone marrow, or stem cell transplantation; dialysis treatment within the past 3 months for causes other than CKD , cancer/leukemia diagnosis or HIV diagnosis/treatment within the past 12 months; current pregnancy or pregnancy within the past 12 months; history of structural heart disease; genetic syndromes involving the central nervous system; and history of severe to profound mental retardation.

As of January 2020,the records of 100 patients were taken and eGFR was calculated using CKD EPI formula. The urine protein/creatinine (Up/c) ratio was determined. In the current study, analysis was restricted

to the 100 patients with measured eGFR and Up/c at baseline as well as known sex, age, CKD diagnosis, and current medication use.

Measurements and Data Collection

The MEDALL laboratory processed all laboratory specimens for testing of blood and urine. Serum creatinine was determined enzymatically (creatinine deiminase reaction) using the Bayer Advia 2400 analyzer. Serum electrolytes, BUN, and glucose were also determined by the Bayer Advia 2400 analyzer. Serum albumin was determined by the bromocresol green binding method.
The GFR measurements were determined by CKD EPI equation.

Sex	Serum creatinine level (μmol/L) (mg/dL)	Equation
Female	≤62 (≤0.7)	$GFR = 144\ (Scr/0.7)^{-0.329} \times (0.993)^{age}$
	>62 (>0.7)	$GFR = 144\ (Scr/0.7)^{-1.209} \times (0.993)^{age}$
Male	≤80 (≤0.9)	$GFR = 141\ (Scr/0.9)^{-0.411} \times (0.993)^{age}$
	>80 (>0.9)	$GFR = 141\ (Scr/0.9)^{-1.209} \times (0.993)^{age}$

Proteinuria was defined by the Up/c level. Participants were identified as having normal ratios (Up/c <0.2), significant proteinuria (0.2 – 2 Up/c), or nephrotic-range proteinuria (Up/c >2).

Urine total protein was measured by binding to pyrogallol red in an acid environment containing molybdate ions. The resulting blue-colored complex absorbs maximally at 600 nm and is proportional to the protein concentration. The method is linear up to 125 mg/L and has an overall coefficient of variation of 3.7 to 4.9%. Urine creatinine was measured using the kinetic reaction of picric acid with creatinine in an alkaline medium (Jaffe). The rate of complex formation is measured at 505 nm and is proportional to the creatinine concentration. The method is linear from 1.5 to 300 mg/dl and the overall coefficient of variation is 1.4 to 2.1%. Both the urine total protein and urine creatinine concentrations were measured by the Bayer Advia 2400 analyzer with the coefficient of variations given by the technical specifications of the manufacturer.

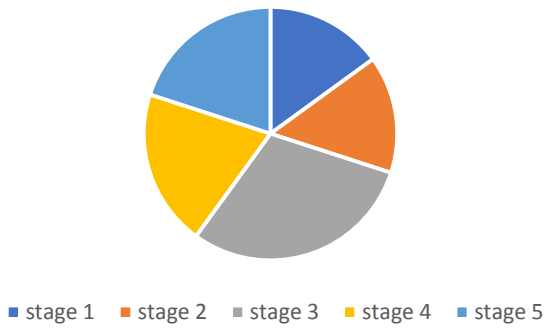
Statistical Analysis

The demographic and clinical characteristics for the overall study population were summarized and analysed by SPSS Software. *P*values were reported to summarize thestrength of the trend. The threshold for statistical significance for these investigations and for other analyses was set to 0.05.

III. Results and observations

In the present study out of 100 patients with clinically, laboratory based and radiologically proven CKD, the the mean eGFR as measured by CKD EPI equation was 14.43 ml/min per 1.73 m^2. The lowest eGFR was 3.9 and highest was 34.2, making most patients to be in stage 3 and stage 4 CKD. The gender wise association showed females to have lower eGFR than men for same age and clinical features matched, by an average of 1.13.

figure 1. CKD-EPI Stage CKD



Twenty-four percent of them had normal range (Up/c <0.2), 62% had significant, and 14% had nephrotic-range proteinuria (Up/c >2.0). The lowest UPCR was 2.1 and highest was 7.78 with average 4.85, making a majority to have nephrotic range proteinuria. Again women had a lead of about 0.003
The relationship between UPCR>2.5 with eGFR was obtained with observation, UPCR<2.5,eGFR<15. N=30, eGFR Mean±SD = 9.03±3.16
UPCR>2.5,eGFR>15. N=11,eGFRMean±SD = 22.03±6.29

It was observed that the low level eGFR was associated with more proteinuria. The A decrease in eGFR was associated with an increase in Up/c.

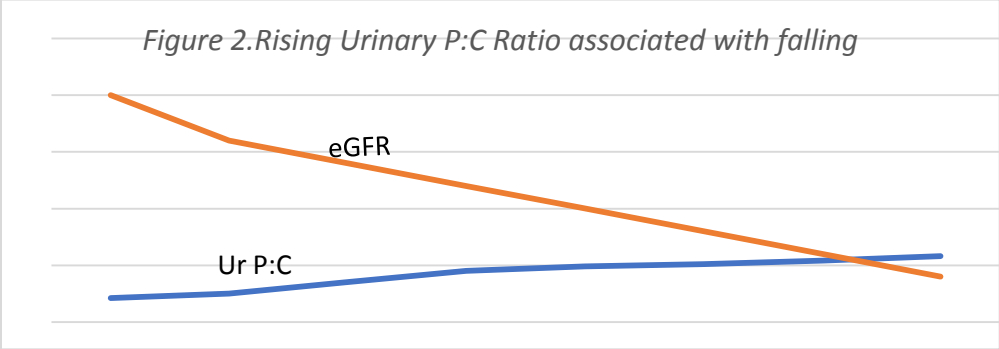


Figure 2.Rising Urinary P:C Ratio associated with falling

IV. Discussion And Conclusion

Proteinuria has strong association with the risk of CKD progression. A mass screening involving 107 192 participants in Okinawa, Japan, proved proteinuria as the most powerful predictor of ESRD risk over 10 years in the general population [11].

The same is valid for diabetic patients. Results from the UK Prospective Diabetes Study 74 revealed that raised urinary albumin concentrations were independently associated with subsequent progression of microalbuminuria (urine albumin excretion between 30 and 300 mg 24 h^{-1}) or renal impairment in type 2 diabetics with but no albuminuria at other hand [11]. Among candidates with diabetic nephropathy, baseline Albumin creatinine ratio was a strong independent determinant of ESRD in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study and in the Irbesartan in Diabetic Nephropathy Trial (IDNT) [12, 13].

Experimental data have given significant insights on the pathophysiology by which CKD progresses. It is now well proven that, independent of the cause, chronic proteinuria in nephropathies have in common a loss of selectivity of the glomerular barrier to protein filtration(14). In the experimental model study of renal mass reduction by five-sixths nephrectomy, the remaining glomeruli undergoes hypertrophy and the tone of the afferent arterioles drops by a greater degree than that of efferent. These changes increase glomerular capillary hydrostatic pressure and leading to more filtrate formed per nephron. These changes, initially helpful to adapt the functional paradigm of nephron loss, but are ultimately detrimental,causing relentless injury of remaining intact nephrons [15]. Enhanced intra- glomerular capillary pressure and perfusion pressure results in stretching of the glomerular capillaries, leading to impaired filter function and loss of larger molecules, such as proteins, in the urine.

The present record based study is a trial to insight of the proteinuria among CKD patients and the association of the same with eGFR. It shows a strong association of degree of proteinuria with falling GFR.

This relation of rising proteinuria with falling GFR can thus be used as a prognostic marker of CKD, and help in early intervention.

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