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Original Article

# Title of the article: Study of Serum Uric Acid and C - reactive protein Levels in Patients with Chronic Renal Disease

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ABSTRACT

Background: Chronic kidney disease (CKD) is a worldwide health problem rising at alarming rate. Patients with CKD are at high risk for cardiovascular disease (CVD) and are more likely to die of CVD than to develop end-stage renal failure. Either inflammation or hyperuricemia has been related with increased cardiovascular risk and mortality. A hypothetical relationship between serum uric acid levels and CRP has been tested recently in chronic renal disease patients. Aims: Present study was planned to evaluate the serum C-reactive protein and uric acid levels and correlate them with Glomerular filtration rate (GFR) in patients of chronic kidney disease. Methods: 45 cases of diagnosed CKD on conservative treatment or dialysis were selected. They were categorized into stage 4 and 5 depending on GFR. Serum C- reactive protein and uric acid levels were estimated in them. Results: In our study group serum CRP and uric acid levels were raised significantly in all patients. Also it is found that the increase in serum uric acid level from mean7.7 mg/dL in stage 4 CKD to mean 8.5 mg/dL in stage 5 CKD is statistically significant ($p < 0.01$). Mean CRP in studied patients was found to be elevated (mean 7.7+/-1.8 mg/L). Serum CRP value was found to be elevated in 80 % of patients in stage 4 and in 88 % of patients of stage 5 CKD. Furthermore increase in mean serum CRP from mean 7.1 mg/L in stage 4 CKD to mean 8.2 mg/L in stage 5 CKD is also statistically significant ($p < 0.05$) Conclusion: CRP estimation in CKD is helpful in predicting an increased risk of cardiovascular death. Either inflammation or hyperuricemia has been related with increased cardiovascular risk and mortality.



## 1. Introduction

Chronic kidney disease (CKD) is a worldwide health problem rising at alarming rate. According to World Health organization Global Burden of Disease project, diseases of the kidney and urinary tract contribute to global burden with approximately 850,000 deaths every year and 115,010,107 disability adjusted life years. CKD is 12th leading cause of death and 17th cause of disability. [1] In Indian scenario, changes in lifestyle and urbanization resulted in obesity, hypertension and diabetes, which are associated with increased risk of CKD. The exact prevalence of CKD in India is not clear in the absence of regular national registry data and quality of data provided by small observational studies or personal experiences is quiet-uneven. [2,3,4]

The Kidney Disease Outcome Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) defined chronic kidney disease as: 'Kidney damage for three or more months, as defined by structural or functional abnormalities of the kidney, with or without decreased Glomerular Filtration Rate (GFR), manifested

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by pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities in imaging tests and GFR < 60 ml per minute per 1.73 $m^2$ for three months or more, with or without kidney damage. [5]

Patients with CKD are at high risk for cardiovascular disease (CVD) and are more likely to die of CVD than to develop end-stage renal failure. Moreover, patients with CVD often develop CKD during the course of their disease, which may go unrecognized. Therefore, an unknown proportion of people whose death and disability-attributed-to-CVD-have-kidney-disease-as-well. [6]

Recently C-reactive protein (CRP) is in vogue for its utility in assessing cardiovascular risk. Elevated plasma CRP level, the prototypic marker of inflammation, has been shown to be strongly predictive of an increased risk of future myocardial infarction and predicts mortality in apparently healthy people as well as in patients with established coronary artery disease. [7] On the other hand, increased CRP is also frequently observed in chronic renal failure patients and is associated with atherosclerosis. Prospective cohort studies showed that CRP is one of the important predictors for mortality in hemodialysis patients. [8] What is more intriguing is that a single determination of CRP is predictive of all-cause mortality and cardiovascular death even after a follow-up period of 4 yr in patients on hemodialysis treatment. [5] However little information is available regarding CRP levels in predialysis renal failure. [9]

Controversy exists over the role of hyperuricemia in renal disease. Hyperuricemia has also been reported to be a risk factor for progression and acceleration of CKD although the mechanism is unknown. [10] On the other hand moderate hyperuricemia frequently occurs early in the course of chronic renal disease. In such patients a positive correlation exists between the serum urate and severity of kidney disease. [11] Recent studies now indicate serum uric acid as a marker of inflammation. Hyperuricemia is detectable in almost all inflammatory diseases including CKD and rather than risk factor it is a risk marker signaling the presence of risk for the development of severe clinical complications. [12]

Either inflammation or hyperuricemia has been related with increased cardiovascular risk and mortality. A hypothetical relationship between serum uric acid levels and CRP has been tested recently in chronic renal disease patients. [13] Hence, with this background, the present study was planned to evaluate the serum C-reactive protein and uric acid levels and correlate them with Glomerular filtration rate (GFR) in patients of chronic kidney disease.

## 2. Materials and Methods

The present study was carried out at Department of Biochemistry, Government Medical College & Hospital Aurangabad. Study protocol was approved by Institutional Ethical Committee and informed consents were obtained from the participants. Total 45 cases of CKD on conservative treatment and End-stage renal disease (ESRD) patients on dialysis for at least 3 months were selected. Patients with acute renal failure, gout, and acute tubular necrosis were excluded from the study. Patients were grouped into the stages according to NKF classification of CKD depending on GFR in mL/min /1.73 $m^2$ of body surface area.

After thorough clinical examination anthropometric measurements for Body mass Index (BMI) were recorded as body weight (Kg)/ Height (m) 2. GFR was calculated by the Cockcroft-Gault equation. [5]

$$GFR = \frac{[(140 - age) * body\ weight\ (kg) * 0.85\ if\ female]}{[72 * serum\ creatinine\ (mg/dL)]}$$

For biochemical investigations 3 ml of blood was collected and after serum separation assayed for CRP by Latex turbidimetry using commercial kit 'CRP- turbilatex' from Spinreact, S. A., Spain. Serum uric acid was estimated by Uricase and Peroxidase method using commercial kit of TECO diagnostics, U.S.A.

**Statistical analysis:**

Statistical analyses were performed using SPSS software, version 10.0. Continuous data are expressed as mean +/- 2 SD or median and categorical data are expressed as percentages. A 'p' value of < 0.05 is considered statistically significant.

## 3. Results:

A total of 45 patients were studied; out of which 24 were men and 21 were women. The mean age was 49.7+/-21.4 years. We could find out patients in only stage 4 and stage 5 chronic kidney disease (CKD).The number of patients in stage 4 CKD was 20 (44%) and 25 patients (56%) were in stage 5 who were shifted on maintenance hemodialysis. The median duration of dialysis was 6 months (range, 0.3 to 1year).

The table 1 shows that mean values of blood urea, serum creatinine, serum uric acid and C-reactive protein are raised above normal in all CKD patients. Further these values are increasing from stage 4 to stage 5 CKD. The mean BMI value of the patient group is within normal range and it is slightly low in stage 5 than stage 4 CKD patients.

**Table 2: Parameters in CKD patients (all patients and stage wise):**

| Age | Ref. value | All patients | Stage 4 CKD | Stage 5 CKD |
|---|---|---|---|---|
| Age (yrs) | - | 49.7+/-21.4 | 43.65+/-22.36 | 54.48+/-16 |
| BMI (kg/$m^2$ BSA) | 18.5-24.99 | 21.8+/-3.8 | 22.6+/-3.8 | 21.17+/-3.6 |
| Bl. Urea (mg/dL) | 15-40 | 103+/-48.4 | 93.7+/-34.4 | 110+/-54.24 |
| Sr. Creatinine (mg/dL) | 0.6-1.4 | 4.75+/-3 | 4.1+/-1.2 | 5.3+/-3.4 |
| GFR (mL/min/$m^2$) | 125 | 14.7+/-8.12 | 18.5+/-4.4 | 11.7+/-4.8 |
| Sr. Uric Acid (mg/dL) | 2.5-6.5 | 8.14+/-1.4 | 7.7+/-1.1 | 8.5+/-1.2 |
| CRP (mg/L) | Upto 6 | 7.68+/-1.8 | 7.1+/-2.3 | 8.2+/-1 |

Table 2 demonstrates correlation of various parameters with each other in stage 4 patients. Serum uric acid shows statistically significant (p=0.044) negative correlation (r= -0.455) with GFR; but without statistically significant correlation with serum creatinine, CRP and BMI. CRP does not show significant association with GFR, serum creatinine and serum uric acid in this stage; but it shows statistically highly significant negative correlation with BMI (r= -0.753/p=0.0001). Both, serum creatinine and blood urea show statistically significant negative correlation with GFR. In stage 4 CKD patients, as GFR decreases, blood urea, serum creatinine and uric acid levels increase significantly.

**Table2. Pearson coefficient of correlation testing relation between various parameters in stage 4 CKD patients:**

| | Stage 4 CKD patients | | | | |
|---|---|---|---|---|---|
| | **GFR** | **Sr. Creatinine** | **Sr. Uric acid** | **CRP** | **BMI** |
| Sr. Uric acid | r= -0.455 | r= 0.034 | _ | r= 0.233 | r= 0.013 |
| | p=0.044 | p= ns* | | p= ns | p= ns |
| CRP | r= -0.387 | r= 0.077 | r= 0.233 | _ | r= -0.753 |
| | p= ns | p= ns | p= ns | | p=0.0001 |
| Sr. Creatinine | r= -0.598 | _ | r= 0.034 | r=0.077 | r=-0.113 |
| | p=0.005 | | p= ns | p= ns | p= ns |
| BMI | r=0.338 | r=-0.113 | r= 0.013 | r= -0.753 | _ |
| | p= ns | p= ns | p= ns | p=0.0001 | |
| Bl. Urea | r= -0.483 | r=0.709 | r=-0.014 | r=0.091 | r=-0.121 |
| | p=0.031 | p= ns | p= ns | p= ns | p= ns |

*** : not statistically significant**

Patients from stage 5 CKD showed statistically significant negative correlation of serum uric acid with GFR (r= -0.529/p=0.007) and statistically significant positive correlation with CRP (r=0.436/p=0.029) without any correlation with serum creatinine and BMI. CRP also shows statistically negative correlation with GFR (r= -0.398 / p=0.049). Serum creatinine does not show significant correlation with GFR, serum uric acid, CRP and BMI. Thus within stage 5 CKD, with decreasing GFR; serum uric acid and CRP level goes on increasing. Further with increase in serum uric acid, CRP levels are also increasing.

**Table3. Pearson coefficient of correlation testing relation between various parameters in stage 5 CKD patients:**

| | Stage 4 CKD patients | | | | |
|---|---|---|---|---|---|
| | **GFR** | **Sr. Creatinine** | **Sr. Uric acid** | **CRP** | **BMI** |
| Sr. Uric acid | r= -0.529 | r= 0.506 | _ | r= 0.436 | r= -0.212 |
| | p=0.007 | p= ns | | p=0.029 | p= ns |
| CRP | r= -0.398 | r= 0.183 | r= 0.436 | _ | r= -0.036 |
| | p=0.049 | p= ns | p=0.029 | | |
| Sr. Creatinine | r= -0.781 | _ | r= 0.306 | r=0.183 | p=nsns |
| | p= ns | | p= ns | p= ns | |
| BMI | r=0.306 | ns | r= -0.212 | r= -0.036 | _ |
| | p= ns | | p= ns | p= ns | |
| Bl. Urea | r= -0.352 | r=0.601 | r=0.260 | r=0.033 | r=0.090 |
| | p= ns | p=0.001 | p= ns | p= ns | p= ns |

Table 4 shows comparison of serum uric acid and CRP levels in two stages and correlate them with GFR, serum creatinine and BMI. Mean serum uric acid in studied patients was found to be elevated (mean 8.1+/-1.4mg/dL) (table 2). After applying unpaired t- test on the data, it is found that the increase in serum uric acid level from mean7.7 mg/dL in stage 4 CKD to mean 8.5 mg/dL in stage 5 CKD is statistically significant ($p < 0.01$). Mean CRP in studied patients was found to be elevated (mean 7.7+/-1.8 mg/L) (table 2). Serum C-reactive protein value was found to be elevated in 80 % of patients in stage 4 and in 88 % of patients of stage 5 chronic kidney diseases. Furthermore increase in mean serum CRP from mean 7.1 mg/L in stage 4 CKD to mean 8.2 mg/L in stage 5 CKD is also statistically significant ($p < 0.05$).

**Table 4: Comparison of studied parameters in two groups:**

| | **Stage 4 CKD** | **Stage 5 CKD** |
|---|---|---|
| GFR | 18.5+/-4.4 | 11.7+/-4.8 |
| ($mL/min/m^2$) | | |
| Sr. Uric Acid | 7.7+/-1.1 | 8.5+/-1.2* |
| (mg/dL) | | |
| CRP | 7.1+/-2.3 | 8.2+/-1* |
| (mg/L) | | |
| Sr. Creatinine | 4.1+/-1.2 | 5.3+/-3.4* |
| (mg/dL) | | |
| BMI | 22.6+/-3.8 | 21.17+/-3.6 |
| ($kg/m^2$ BSA) | | |

* : statistically significant increase from stage 4 to stage 5 CKD

## 4. Discussion:

Kidney failure is a worldwide serious public health problem, with increasing incidence imposing socioeconomic burden. There is substantially higher prevalence of the earlier stages of CKD, with adverse outcomes, including loss of kidney function, CVD, and premature death. [14] To study serum uric acid and CRP in patients of CKD at one point of time was the aim of our study.

CKD patients of only stages 4 and 5 were enrolled in our study as only patients in advanced stages of CKD are referred to the tertiary care Government hospital. Rests of the patients are managed in other healthcare units and majority of the patients of initial stages of disease even remain undiagnosed. Schieppati et al also noted in their epidemiological study that the majority of the individuals at early stage of CKD remained undiagnosed and under treated. [15]

CRP an acute phase reactants is a pentraxin protein synthesized in liver. Elevated plasma concentration of CRP is sensitive marker of underlying systemic inflammation. In our study we observed raised serum CRP levels in the patients of stage 5 CKD over those of stage 4 CKD. This reflects ongoing increased generalized inflammatory process with disease progression. Olimpia Ortega reported elevated serum CRP as strong predictor of morbidity and mortality in dialysis patients. [16] Lily L. Wu stated association of serum uric acid with interlukein-6 (IL-6), tumor necrosis factor-α (TNF-α) and CRP in various inflammatory diseases including ESRD. [12] Angela

Yee-Moon Wang demonstrated usefulness of a single random CRP in predicting all-cause and cardiovascular mortality, independent of other cardiovascular, echocardiographic, dialysis, biochemical, and nutritional parameters in peritoneal dialysis patients showing the rise in CRP levels are associated with adverse prognosis. [8]

Karen Ann Herzing in their prospective observational study demonstrated abnormally elevated CRP level in 58% of peritoneal dialysis population which was associated with increased risk of future myocardial infarction for at least 3 years. The data warrant closer monitoring and extra attention to modifiable cardiovascular risk factors in peritoneal dialysis patients with high plasma CRP concentrations. [17]

Uric acid (2, 6, 8-trihydroxypurine) is the major product of catabolism of the purine nucleosides. Normally two thirds to three fourths of it is excreted by the kidneys, and remaining through the intestines. Renal handling of uric acid is complex. Glomerular filtration of virtually all uric acid occurs in capillary plasma entering the glomerulus followed by reabsorption of about 98 to 100% of uric acid in proximal convoluted tubular. Then subsequent secretion of half of reabsorbed uric acid takes place in distal portion of proximal tubule and post-secretory reabsorption of 40 % of secreted uric acid in distal tubule. [18]

## 5. SUMMARY:

CRP estimation in CKD is helpful in predicting an increased risk of cardiovascular death. Either inflammation or hyperuricemia has been related with increased cardiovascular risk and mortality. Thus the study as a whole can be helpful to assess the deteriorating kidney function and generalized inflammatory state with progression of chronic kidney disease.

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