

# Serum Uric Acid Level in Patients with Chronic Kidney Disease: A Prospective Study

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## Abstract

**Background:** Chronic kidney disease (CKD) is a serious condition associated with premature mortality, decreased quality of life, and increased health-care expenditures. Chronic kidney disease occurs when one suffers from gradual and usually permanent loss of kidney function over time.

**Material and Method:** This is a prospective observational study. In this study, one hundred forty six ckd patients were studied with detailed clinical and laboratory examination and divided (and then compared) into two age groups: one group included 56 ckd patients with raised serum uric acid and another group containing 90 ckd patients with normal serum uric acid. Both groups were age matched.

**Results:** In our study, prevalence of raised serum uric acid in ckd patients was found to be 38.4%. It is observed that, CKD patients with raised serum uric acid were predominantly male and presented mainly in later part of life. There is statistically significant ( $p < 0.05$ ) positive correlation is found between serum uric acid and stages and severity of ckd, hypertension, diabetes mellitus, dyslipidemia, smoking, alcoholism, serum BUN, serum creatinine, CRP, N/L Ratio, urine albuminuria, anaemia, cardiovascular disease, mortality and negative correlation with eGFR and creatinine clearance.

**Conclusion:** In ckd patients, higher serum uric acid levels were associated with higher degree of renal dysfunction, hypertension, diabetes, dyslipidemia, smoking, alcoholism, CRP, N/L Ratio, urine albuminuria, anaemia, cardiovascular disease/events and mortality. It is found that most common cause of mortality in ckd patients with raised serum uric acid was cardiovascular disease/events.

**Key words:** Chronic Kidney Disease, Patients, Uric Acid

## INTRODUCTION

Chronic kidney disease (CKD) is a serious condition associated with premature mortality, decreased quality of life, and increased health-care expenditures. Chronic kidney disease occurs when one suffers from gradual and usually permanent loss of kidney function over time. This happens gradually, usually over months to years.<sup>1</sup>

The lineage of kidney disease as a subject of study generally is traced to 1827, when Richard Bright (1789-1858) described his eponymous disease of the kidneys in albuminuric dropsical

patients who died in kidney failure.<sup>2</sup> By middle of 19<sup>th</sup> century, kidney disease was defined, it's diagnosis by urinalysis was established, and it's structural changes were characterized, but speciality of nephrology went unborn and patients continued to seek urologic care for their hematuria, proteinuria and uremia.<sup>3</sup> It was a return to the roots of nephrology at the turn of the 21<sup>st</sup> century that refocused attention on kidney disease not as a fatal condition requiring replacement therapy, but as a clinical entity that is common, harmful, early to diagnosed and potentially treatable.<sup>4</sup>

It was to meet this need that the initial set of clinical practice guidelines for dialysis care was published in 1997 by the DOQI (Dialysis Outcome Quality Initiative) which was changed to KDOQI (Kidney Disease Outcome Quality Initiative) at the turn of the millennium.<sup>2</sup>

KDOQI (Kidney Disease Outcome Quality Initiative), in 2002, published the Clinical Practice Guidelines for Chronic kidney disease.<sup>5,6</sup>

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Chronic kidney disease (CKD) prevalence is increasing world-wide and the prevalence of end-stage renal disease (ESRD) is expected to rise by 44% from 2000 to 2015.<sup>7</sup>

The pattern of disease morbidity and mortality throughout the world is changing both in the developed and the emerging world. The major cause of end-stage renal failure in most countries worldwide is now diabetes. Countries throughout Asia also have large percentages of their incident end-stage renal failure patients due to diabetes: Pakistan, 42%, Taiwan, 35%, Philippines, 25% and Japan, 37%.<sup>8</sup> India has the largest number of people with diabetes in the world, with the projected figures of 57.2 million cases in 2025. This will make India the reservoir of CKD.<sup>9</sup>

The annual incidence of ESRD differs between developed and developing countries, 34 — 240 per million population (pmp) to 98 — 198 per million populations, respectively.<sup>10</sup>

Agarwal SK, *et al*, (2005), in All India Institute of Medical Sciences New- Delhi, India carried out the first community-based epidemiological study to determine the prevalence of chronic renal failure in India. A total 4,972 subjects were evaluated from whom samples for testing were available in 4,712 cases. CRF was detected in 37 patients (0.785%). CRF prevalence was calculated to be 7,852 per million populations. Hypertension and diabetes were found in 22.8% and 11.1%, respectively. Diabetic nephropathy was possibly the common etiological factor, found in 41% of patients with CRF.<sup>11</sup>

The K/DOQI definition (2002) of CKD was accepted worldwide and given as follows:<sup>5</sup>

#### Criteria for the Definition of Chronic Kidney Disease(CKD)

Kidney damage for ≥ 3 months as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, that can lead to decreased GFR, manifest by either:

- Pathological abnormalities; or
- Markers of kidney damage, including abnormalities in imaging tests
- GFR <60ml/min/1.73m<sup>2</sup> for 3 months, with or without kidney damage

#### Classification of CKD

The K/DOQI guidelines (2002) for classification of ckd by severity are given in the following table.

Classification of ckd<sup>5</sup>

## MATERIALS AND METHODS

The present study is a prospective study carried out on 146 CKD patients in ICU and medicine ward. Ethical

Clearance was obtained from the ethical committee for the study. Patients satisfying the inclusion and exclusion criteria were enrolled into the study. Detailed clinical, biochemical, haematological examinations were conducted to establish the diagnosis and stage of CKD.

The present study was carried out on 146 adult patient of CKD (Chronic Kidney Disease). Out of which 56 ckd patients with raised serum uric acid were placed in study group and also 90 CKD patients with normal serum uric acid with age matched were placed in comparison group.

#### Inclusion Criteria

- 1) All the patients of both the sexes >18 years of age
- 2) All the diagnosed cases of chronic kidney disease.

#### Exclusion Criteria

- 1) All the patients <18 years of age.
- 2) All HIV positive individuals.
- 3) All the patients having history of gout and/or Hyperuricemia.
- 4) Patients who are taking anti tubercular drugs and thiazide diuretics.

#### Diagnostic Criteria

All the patients were evaluated for chronic kidney disease (ckd) as per the K/DOQI criteria (2002) by National Kidney Foundation for diagnosis of ckd.<sup>5</sup>

After confirmation of diagnosis from the above parameters, blood samples are drawn from these patients for the estimation of serum uric acid by Trivedi and Kabasakalian with a modified Trinder peroxidase method using TBHB(2,4,6-Tribromo-3- hydroxybenzoic acid).

The study was designed to include the Demographic, clinical data, biochemical and haematological changes observed in CKD patients. The data was entered into a structured proforma separately. Management was done as per standard guidelines. Patients were discharged after significant improvement in clinical as well as haematological and biochemical parameters.

Detailed clinical examination was done in all CKD patients. All these CKD patients were evaluated clinically for history of fever, easy fatigability, facial puffiness, swelling over extremities, nausea and vomiting, generalized bodyache, breathlessness, altered sensorium, convulsions, decreased urine output, haematuria, haemestemesis/malaena, pallor, pedal oedema, blood pressure and other vitals.

The laboratory investigations done in all CKD patients included a complete haemogram, neutrophil-lymphocytic ratio (N/L Ratio), fasting and postprandial blood sugar level, serum BUN, creatinine, eGFR, creatinine

clearance, serum electrolytes (sodium, potassium, calcium, phosphorus), serum uric acid, liver function test, lipid profile (Total cholesterol, HDL, LDL, Triglycerides), C- reactive proteins(CRP), 24hrs urine albuminuria, HIV, Hepatitis B and C.

Detailed ultrasonography of abdomen and pelvis was done to check the size, shape and echo texture of the kidney. Formal approval of hospital ethical committee and written consent of the CKD patients were obtained for this study.

### Statistical Analysis

Data was analyzed by statistical Product for social service sciences Version-16 (SPSS 16) statistical software. Data was presented in frequency and percent distribution form. Association in between the parameters was tested using Pearson's chi square test or Fishers exact test. Mean values of parameters were compared between normal and raised uric acid levels in ckd patients using unpaired t-test. Mean comparisons of values of parameters in between patients with 5 stages of ckd were done by using ANOVA (Analysis Of Variance Test). The significance level was set at  $p < 0.05$ . P less than 0.05 was considered as significant

## RESULTS

146 patients of documented CKD were taken and divided into 2 groups of which study group included 56 ckd patients with raised serum uric acid levels and comparison group included 90 ckd patients with normal serum uric acid levels. Statistical analysis showing study's result is given as follow:

### Sex

Of 90 CKD patients with normal uric acid level, 58.9% were male and 41.1% were female. Of Raised uric acid CKD patients, 78.6% were males and 23.2% were females. There was statistically significant ( $p < 0.05$ ) difference of male predominance over female in CKD patients with raised uric acid level.

### 3) Prevalence of serum uric acid in CKD

Serum uric acid was raised in 38.4% CKD patients and CRP was raised in 51.4% patients out of 146 having CKD.

### 4) Stages of CKD

In those with raised uric acid level, Maximum i.e. 53.6% CKD patients had stage 5 CKD, 30.4% had Stage 4 and 8.9% had Stage 3 CKD, 5.4% had Stage 2 and 1.8% has Stage 1 CKD. Of Normal uric acid level patients 26.7% were in stage 5, 25.6% were in stage 4 and 16.7% in Stage 3 while 15.6% in Stage 2 and Stage 1. There was

statistically highly significant ( $p < 0.01$ ) difference with higher proportion of patients in higher Stage of CKD in raised uric acid group compared to normal uric acid group.

### 5) Complications of CKD (Anaemia and Cardiovascular Disease)

61.1% raised uric acid CKD patients had cardiovascular disease compared to 38.9% normal uric acid patients. All 56 i.e. 100% patients with raised uric acid level had anemia compared to 76.7% of normal uric acid. There was statistically very highly significant ( $p < 0.001$ ) difference with higher percentage of patient in raised uric acid having cardiovascular disease and anemia in CKD patients.

### 7) Relation With Severity Of CKD:

There was statistically significant ( $p < 0.01$ ) difference with increasing stages severity of duration of illness, BUN, Serum Creatinine, uric acid concentration, potassium, phosphorus, estimated GFR, creatinine clearance and CRP.

### 8) Mortality:

10) Relation of serum uric acid with different biochemical parameters (Tables 1-8).

## DISCUSSION

Previous studies have shown that serum uric acid is having independent role in progression of ckd and is also cause and predictor of associated morbidities in ckd.

Blood samples for measurement of serum uric acid level and other biochemical assessments were obtained immediately after admission. Uric acid concentration expressed in milligrams per deciliters (mg/dl). Male patients with uric acid concentration  $> 7$  mg/dl and female patients with  $> 6$  mg/dl were considered as having raised serum Uric acid. Furthermore for studying correlations of serum Uric acid with other clinical and investigational findings, all ckd patients were divided into two groups out of which one group included all ckd patients with raised uric acid and other group included all ckd patients with normal uric acid. Both groups were age matched.

There were 90 ckd patients studied in ckd with normal UA group and 56 patients were studied in ckd with raised UA group.

Serum UA level of ckd patients done on day of admission in both age matched groups were compared by t-test where its value  $p < 0.05$  is considered as statistically significant. Thus patients who were having raised serum UA level was because

**Table 1: Classification on severity of CKD**

Stage	Description	GFR ml/min/1.73m <sup>2</sup>	Related items	Classification by treatment
1	Kidney damage with normal or i GFR	90	Albuminuria, proteinuria, hematuria	T if kidney Transplant Recipient
2	Kidney damage with mild 1, GFR	60-89	Albuminuria, proteinuria, hematuria	
3	Moderate 1 GFR	30-59	Chronic renal insufficiency or early renal insufficiency	
4	Severe GFR	15-29	Chronic renal insufficiency or late renal insufficiency or pre ESRD	
5	Kidney failure	<15 or dialysis	Renal failure, uremia, ESRD	D if dialysis (hemodialysis or peritoneal dialysis)

of ckd and in both ckd groups derangement of other clinical and biochemical profiles were due to raised serum UA.

The findings which we got in our study are discussed as follows:

### Age

In our study, we found that out of 146 ckd patients maximum that is 53.4% were within age group of 51-70 yrs. and 39.7% ckd patients were in age group of 31-50 yrs. This finding is consistent with findings of the study by Punamyadav *et al*, (2014), Madero *et al*, (2009) and George S. *et al*, (2013). It is observed that incidence of ckd reaches its maximum strength in later part of life.<sup>12-14</sup>

### Sex

In our study, (from Table 2), it is found that 78.6% males and 21.2% females were in ckd with raised UA group which shows statistically significant ( $P < 0.027$ ) difference of male predominance over females in ckd patients with raised UA level. This finding in our study is consistent with findings in the studies by Nacak *et al*, (2014) & Madero *et al*, (2009)

## SERUM URIC ACID LEVELS IN RELATION WITH SEVERITY OF CKD

In our study, (from Table 4, 6 & 9), it is found that, there was statistically significant ( $p < 0.01$ ) correlation of raised serum uric acid with increasing stages of ckd, and it's severity. Serum uric acid was statistically significantly ( $p < 0.001$ ) positively correlated with serum BUN, serum creatinine, and negatively correlated with eGFR, and creatinine clearance. In our study, ANOVA study also showed the statistically significant positive correlation between raised serum uric acid and progressively declining renal functions and severity of ckd. This finding in our study is consistent with the findings of studies by Chen *et al*, (2014), Mostafa Kamel *et al*, (2013)<sup>16</sup>, Nermina Babic *et al*, (2014), J. T. Park *et al*, (2009), where it is found that, there was statistically highly significant positive correlation of serum uric acid with stages and severity of ckd, duration of illness and markers

**Table 2: Sex distribution according to Serum uric acid status of patients with chronic kidney disease**

Sex	Serum uric acid		Total
	Normal	Raised	
Female	37 41.1%	13 23.2%	51 34.2%
Male	53 58.9%	43 78.6%	95 65.8%
Total	90 100.0%	56 100.0%	146 100.0%

Chi-Square tests	Value	Df	P value
Pearson Chi-Square	4.910	1	0.027

**Table 3: Serum uric acid and CRP level of patients with chronic kidney disease**

Parameters	Frequency	Percent (%)
Serum uric acid		
Normal	90	61.6
Raised	56	38.4
CRP		
Normal	71	48.6
Raised	75	51.4
Total	146	100.0

**Table 4: Stage of CKD according to Serum uric acid status of patients**

Stage of CKD	Serum uric acid		Total
	Normal	Raised	
1	14 15.6%	1 1.8%	15 10.3%
2	14 15.6%	3 5.4%	17 11.6%
3	15 16.7%	5 8.9%	20 13.7%
4	23 25.6%	17 30.4%	40 27.4%
5	24 26.7%	30 53.6%	54 37%
Total	90 100.0%	56 100.0%	146 100.0%

Chi-Square tests	Value	Df	P value
Pearson Chi-Square	18.01	4	0.001

of reduced renal functions like serum BUN and serum creatinine and negatively correlate with eGFR.

## HYPERTENSION

In our study, (from Table 10), it is found that, significant proportion of hypertensive patients had come in ckd with raised UA group i.e., 85.7%, and showing

**Table 5: Associated disorders according to Serum uric acid status of patients with chronic kidney disease**

Parameters	Serum uric acid		Total	X <sup>2</sup>	P value
	Normal	Raised			
CKD with cardiovascular diseases					
No	69	23	92	18.767	<0.001
	75%	25%	100%		
Yes	21	33	54		
	38.9%	61.1%	100%		
CKD with anemia					
No	21		21	15.262	<0.001
	23.3%		14.4%		
Yes	69	56	125		
	76.7%	100.0%	85.6%		

statistically significant positive correlation ( $p=0.031$ ) of UA with hypertension, this finding is consistently matched with the findings of studies by J. T. Park *et al*, (2009), Paul *et al*, (2012) and Liu WC *et al*, (2012). It is found that, there is statistically significant higher systolic BP ( $P<0.001$ ) and diastolic BP ( $P<0.001$ ), in raised UA ckd patients than normal UA ckd patients. This findings are consistently matched with findings of studies by B. Satirapoj *et al*, (2010) and Mostafa Kamel *et al*, (2013).

## Diabetes Mellitus

In our study, (from Table 10), it is found that, there was statistically significant positive difference of diabetes ( $p=0.011$ ) in ckd patients with raised uric acid level (44.6%) than normal uric acid level (24.4%) in CKD patients. Also, serum uric acid has statistically significant positive correlation ( $p<0.001$ ) with both fasting and post prandial blood sugar level. This finding in our study is consistently matched with the findings of studies by J. T. Park *et al*, (2009), Adel Gouri *et al*, (2013) and Liu WC *et al*, (2012).<sup>15-30</sup>

## CONCLUSION

In ckd patients, higher serum uric acid levels were associated with higher degree of renal dysfunction, hypertension,

**Table 6: Comparison of mean findings according to severity of CKD. ANOVA**

Parameters	CKD					F	P value
	Stage 1 (n=15)	Stage 2 (n=17)	Stage 3 (n=20)	Stage 4 (n=40)	Stage 5 (n=54)		
Age (yrs)	51.6	51.53	53.0	55.85	57.15	1.279	0.281
Duration of illness	7.00	8.00	7.95	11.18	12.69	11.432	<0.001
BMI (kg/m <sup>2</sup> )	22.20	22.79	22.07	22.01	21.23	1.895	0.115
Sr. BUN (mg/dl)	43.67	47.65	48.68	57.87	60.78	4.149	0.003
Sr. Creatinine (mg/dl)	0.90	1.141	1.975	3.845	5.543	220.14	<0.001
Sr. uric acid (mg/dl)	4.46	4.81	5.35	7.29	7.68	35.545	<0.001
SR.SODIUM (mEq/1)	145.8	145.0	145.15	144.59	143.16	1.180	0.322
SR.POTASSIUM (mEq/1)	4.83	4.39	5.03	4.75	5.27	3.568	0.008
Sr. Calcium (mg/dl)	8.27	8.39	7.29	7.28	7.16	1.826	0.127
Sr. phosphorus (mg/dl)	5.16	5.08	5.50	5.79	6.37	4.395	0.002
eGFR (ml/min/1.73m <sup>2</sup> )	94.95	72.61	40.79	17.68	11.86	813.95	<0.001
Creatinine clearance (ml/min)	74.73	59.06	35.61	16.62	11.37	375.13	<0.001
CRP (mg/l)	4.79	4.88	5.22	6.75	7.33	17.634	<0.001

**Table 7: Outcome according to Serum uric acid status of patients with chronic kidney disease**

Outcome	Serum uric acid		Total
	Normal	Raised	
Alive	90	48	138
	65.2%	34.8%	100%
Dead		8	8
		100%	100%
Total	90	56	146
	61.6%	38.4%	100.0%
<b>Chi-Square tests</b>			
	<b>Value</b>	<b>Df</b>	<b>P value</b>
Pearson Chi-Square	13.602	1	<0.001

**Table 8: Comparison of different parameters in ckd patients with raised and normal serum uric acid**

Parameter	Uric acid		Total	P value
	Normal	Raised		
Age (yrs)	52.97	54.07	55.0	0.604
Sex(% Male)	58.9%	78.6%	65.8%	0.027
SBP on admission (mmHg)	141.76	162.14	149.58	<0.001
DBP on admission (mmHg)	87.8	95.7	90.84	<0.001
HT	70%	85.7%	76%	0.031
Fasting BSL (mg/dl)	102.4	131.46	113.55	<0.001
Postprandial BSL (mg/dl)	170.52	202.9	182.96	<0.001
HbA1C	5.47	7.25	6.15	<0.001
DM	24.4%	44.6%	32.2%	0.011
Smoking	10%	60.7%	29.5%	<0.001
Dyslipidemia	51.1%	69.6%	58.2%	0.027
Urine albuminuria (mg/d)	389.94	1112.32	667.02	<0.001
CRP (mg/l)	5.92	6.98	6.33	<0.001
N/L ratio	2.26	2.81	2.47	<0.001
S BUN (mg/dl)	44.42	72.11	55.04	<0.001
Creatinine (mg/dl)	2.774	4.93	3.59	<0.001
eGFR (ml/min/1.73m2)	44.16	15.15	33.03	<0.001
Anemia risk	76.7%	100%	85.6%	<0.001
Cardiovascular risk	23.3%	58.9%	37%	<0.001
Death	0	14.3%	5.5%	<0.001

diabetes, dyslipidemia, smoking, alcoholism, CRP, N/L Ratio, urine albuminuria, anaemia, cardiovascular disease/events and mortality. It is found that most common cause of mortality in ckd patients with raised serum uric acid was cardiovascular disease/events.

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