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Study of Serum Uric Acid in Different Stages of Chronic Kidney Disease

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Authors' contributions

This work was carried out in collaboration among both authors. Author SA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author ASMR managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Hyperuricaemia is a metabolic marker of decreased renal function in chronic kidney disease (CKD). It increases cardiovascular, cerebrovascular and mortality risk in patients with CKD.
Objectives: To estimate serum uric acid level in different stages of CKD.
Methods: The present study was a cross sectional analytical study and was conducted in the Department of Physiology, Dhaka Medical College, Dhaka from July 2012 to June 2013 on 300 participants. They were divided into group A (150 control healthy participants) and group B (150 diagnosed cases of CKD). Serum creatinine and serum uric acid levels were measured by auto analyzer in Department of Pathology, Dhaka Medical College. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine level by Modification of Diet in Renal Disease (MDRD) equation. For statistical analysis unpaired Student "t" test, one way ANOVA test, Bonferroni test, Pearson's correlation coefficient (r) test and Linear regression were performed using SPSS for windows version 20.
Result: In this study, serum uric acid level was significantly ($p<0.05$) higher and eGFR were significantly lower in study groups than that of control group. There was gradual rise of serum uric acid level in CKD subjects from stage I to V. A significant inverse correlation was observed

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between serum uric acid level and eGFR. Serum uric acid level increased 0.048 mg/dl for each ml/min/1.73m^2 decrease of eGFR.

Conclusion: This study concludes that serum uric acid level increases gradually in accordance with the higher stages of CKD. There is a negative correlation of serum uric acid with eGFR in all stages of CKD which was statistically significant ($p<0.05$). Screening of serum uric acid level in different stages of CKD may be beneficial for assessing renal damage as well as prediction of co-morbidities associated with it.

Keywords: Cardiovascular health; cerebrovascular health; CKD; hyperuricaemia; uric acid.

1. INTRODUCTION

All patients with evidence of persistent kidney damage for ≥ 90 days are considered as having chronic kidney disease (CKD). Kidney damage refers to any renal pathology that has the potential to cause reduction in renal capacity. This is most usually associated with a reduction in GFR [1].

The prevalence of CKD is increasing worldwide as a consequence of rise in the prevalence of disorders that damage kidney, such as hypertension and diabetes mellitus [2]. Based on the data derived from 26 studies of different countries of the world, the researchers have found that, the average worldwide prevalence of CKD was 7.2% in persons aged > 30 years [3].

In Bangladesh there are about 20 million people suffering from CKD. And among them 20,000 people die of end stage renal disease (ESRD) in each year [4]. The level of kidney function is predicted most commonly by measuring serum creatinine concentration. But it can be affected by various factors such as age, gender, ethnicity, muscle mass, dietary habit and specific drug use. To overcome this limitation, some creatinine-based GFR estimation equations have been developed. Some studies showed that among all the equations, Modification of Diet in Renal Disease (MDRD) equation was more precise and accurate to estimate GFR [5].

Kidney plays essential role in the maintenance of homeostasis. As kidney function diminishes, its excretory, regulatory and endocrine function is gradually lost and complications develop in every organ system [6]. Common complications of CKD are anemia, cardiovascular disease, hyperparathyroidism, metabolic acidosis, salt and water retention, renal osteodystrophy, dyslipidemia etc [7,8].

Hyperuricaemia is a metabolic derangement that may develop in CKD. It is usually defined as serum uric acid level > 7 mg/dl [9]. It runs in parallel with deranged renal function [10]. Hyperuricemia may develop as a consequence of either over production or under excretion or both. But in most cases, it occurs as a result of under excretion [11]. In normal condition, kidney excretes about two thirds of the daily uric acid produced from the body. Renal handling of uric acid involves four subsequent steps. Glomerular filtration, tubular secretion, reabsorption and post secretory reabsorption. Defect in any one of the above steps may raise serum uric acid level [9].

Uric acid has diverse biological properties. It is considered as a major anti-oxidant in human blood that may protect against aging and oxidative stress. But despite of this protective property, elevated serum uric acid is strongly associated with cardiovascular disease, kidney disease, hypertension and increased risk of mortality [12]. There is three to five fold increased risk of both coronary artery and cerebrovascular disease in hyper-uricaemic subjects than normo-uricaemic subjects [13].

High serum uric acid level may lead to uric acid crystal formation which may adhere to the surface of the renal epithelial cells. Uric acid crystals are directly pro-inflammatory and may cause further reduction of the glomerular filtration rate [14]. Uric acid mediates inflammation, endothelial dysfunction and oxidative stress in subjects with CKD [15]. It may reflect decrease in renal blood flow and may be an indicator of early nephrosclerosis [16]. In a prospective cohort study it was shown that, CKD subjects with increased serum uric acid level were associated with greater incidence of end stage renal disease (ESRD) [17].

Several researchers have found significantly increased level of serum uric acid in subjects with CKD [18-23]. Some researchers also noticed that serum uric acid level rose gradually in accordance with the higher stages of CKD and the level correlated negatively with eGFR [18,21-23].

On the contrary, some studies did not find significant rise of serum uric acid level in subjects with CKD [24,25]. Again, some researchers found that serum uric acid level increased in subjects with CKD, but the level did not correlate with GFR [26,27].

Several studies have been done abroad to observe the level of serum uric acid in different stages of CKD. But less published data has been available regarding this topic in our country. Furthermore, we need our own standard baseline from which we can compare these parameters in our population. The current study thus aimed to delineate the level of serum uric acid and its association with different stages of CKD.

2. MATERIALS AND METHODS

This was a cross sectional descriptive study done in the Physiology Department of Dhaka Medical College from July 2012 to June 2013. After gaining informed written consent, 150 diagnosed patients suffering from different stages of CKD and 150 age matched healthy controls were enrolled in the study by purposive sampling. The control group was labeled as group A and the CKD patients group was labelled as group B which was subdivided into B1 to B5 based on five stages of CKD. Patients on dialysis, those who have gouty arthritis, pregnant women, history of regular alcohol consumption, history of taking some drugs eg. Furosemide, Thiazide and Allopurinol were excluded from the study. Chronic kidney disease was defined as either kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of kidney, with or without decreased glomerular filtration rate (GFR) (which is manifested by pathological abnormalities or markers of kidney damage including abnormalities in composition of blood or urine or abnormalities in imaging tests); or GFR < 60 ml/ min/ 1.73 m2 for ≥ 3 months, with or without kidney damage [1].Determination of estimated glomerular filtration rate (eGFR) was done from serum creatinine level by modification of diet in renal disease equation and Staging of CKD was done according to KDOQI (Kidney disease quality initiative) guideline [28]. Hyperuricaemia was defined as serum uric acid level more than 7 mg/dl [9]. Hypertension is defined as systolic blood pressure ≥ 140 mm hg and or diastolic blood pressure ≥ 90 mm Hg [29].All the parameters were expressed as Mean ± SD (standard deviation). Comparison between the groups was done by one way ANOVA test. Pearson's correlation-coefficient (r) test was performed to observe relationship between study parameters. Linear regression was performed to observe rate of change of serum uric acid for each unit change of eGFR. P value of <0.05 was accepted as level of significance. Statistical analysis was performed by using a computer based statistical program SPSS (statistical package for social science) Version 20.

3. RESULTS

General characteristics of the subjects of different groups are shown in Table 1.

3.1 Age

The mean (±SD) age of control group A and study subgroups B1 to B5 were 50.21±3.96, 48.8±2.72, 48.9±2.5, 49.8±3.2, 51.1±3.70 and 54.2±2.86 years respectively and there is no statistically significant difference among the groups. So, all the groups were matched for age.

3.2 Body Mass Index (BMI)

The mean (±SD) BMI of control group A and study groups B1-B5 were 23.28±1.55, 23.82±1.22, 22.99±1.05, 22.5±1.23,21.46±0.66 and 20.31±0.85 kg/m2 respectively and there is no statistically significant difference between the groups. So, all the groups were matched for BMI.

3.3 Blood Pressure

The mean (±SD) systolic blood pressure of control group A and study subgroups B1-B5 were 113.21±10.37, 131.93±12.4, 130.50±10.03, 135.93±7.44, 146.07±4.51 and 150.50±08.02 mm Hg respectively.The mean (±SD) diastolic blood pressure of control group A and study subgroups B1 to B5 were 71.34±6.46, 84.03±13.82, 85.07±7.96, 87.50±4.68, 93.43±3.87 and 99.37±2.81 mm Hg respectively.

Estimated glomerular filtration rate (eGFR) are shown in Table 2. and III and Fig. 1.

The mean (±SD) eGFR of the group A, group B1 to group B5 were 117.25±10.52, 92.90±2.33, 72.60±8.74, 36.60±5.68, 20.20±3.96 and 10.70±2.23 ml/min respectively. The mean (±SD) eGFR in all the subgroups of group B were lower than that of group A which was statistically significant (p <0.05).

Results are expressed as mean±SD. Figures in parenthesis indicate range.

Serum uric acid levels are shown in Table 2. and IV and Fig. 2.

The mean (±SD) serum uric acid level of the group A, B subgroups B1 – B5 were 3.43±0.49, 6.34±0.43, 7.32±0.73, 8.52±0.53, 9.48±0.45 and 11.13±0.32 mg/dl respectively. Mean (±SD) serum uric acid level in all the subgroups of group B were higher than that of group A which was statistically significant ($p < 0.05$). Serum uric acid level increased gradually in the study groups. Uric acid level was higher in B5>B4>B3>B2>B1 group.

Table 1. General characteristics of the subjects of different groups (n=300)

Groups	Age (years)	BMI (Kg/m^2)	SBP (mm Hg)	DBP (mm Hg)
A	50.21±3.96	23.28±1.55	113.21±10.37	71.34±6.46
(n=150)	(41-55)	(20.1-26.9)	(90-130)	(60-80)
B_1	48.8±2.72	23.82±1.22	131.93±12.4	84.03±13.82
(n=13)	(44-52)	(20.1-24.3)	(110-150)	(60-100)
B_2	48.9±2.5	22.99±1.05	130.5±10.03	85.07±7.96
(n=37)	(44-53)	(20.4-24.2)	(110-145)	(70-96)
B_3	49.8±3.2	22.5±1.23	135.93±7.44	87.5±4.68
(n=32)	(44-55)	(20.1-24.3)	(120-145)	(80-95)
B_4	51.1±3.7	21.46±0.66	146.07±4.51	93.43±3.87
(n=35)	(48-56)	(22.1-24.5)	(140-152)	(90-100)
B_5	54.2±2.86	20.31±0.85	150.5±8.02	99.37±2.81
(n=33)	(43-55)	(20.3-23)	(140-160)	(95-105)

Results are expressed as mean±SD. Figures in parenthesis indicate range

Group A : Control (Adult healthy subjects)

Group B : Study group (Adult subjects with CKD)

Group B_1 : Subjects with CKD in stage I

Group B_2 : Subjects with CKD in stage II

Group B_3: Subjects with CKD in stage III

Group B_4: Subjects with CKD in stage IV

Group B_5: Subjects with CKD in stage V

n = Number of subjects

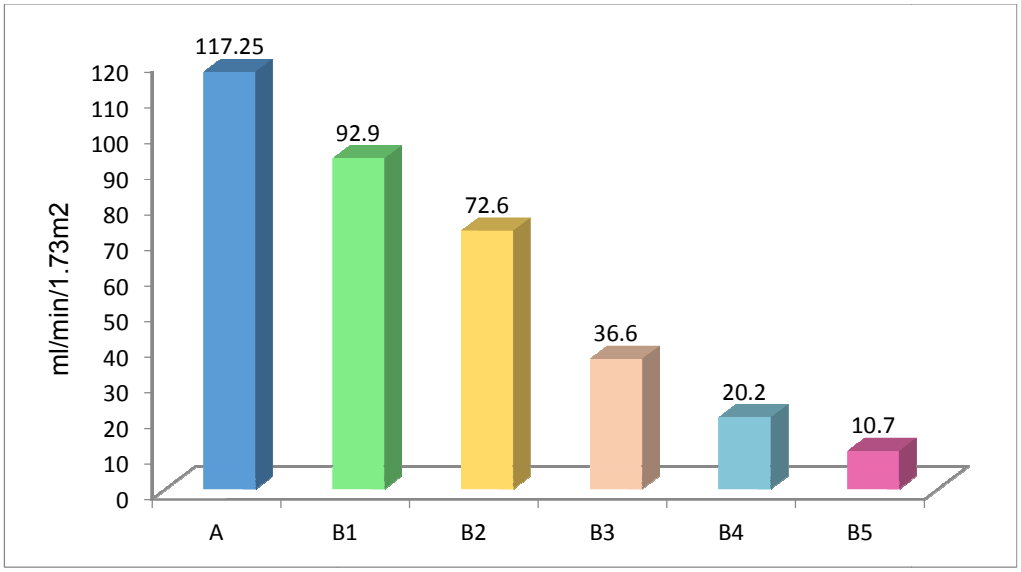

Fig. 1. Mean estimated glomerular filtration rate (eGFR) in different groups (n=300)

Table 2. Study parameters in different groups (n=300)

Groups	eGFR (ml/min/1.73m^2)	Serum uric acid (mg/dl)
A	117.25±10.52	3.43±0.49
(n=150)	(100-136)	(2.6-4.3)
B_1	92.9±2.33	6.34±0.43
(n=13)	(90-96)	(5.5-6.8)
B_2	72.6±8.74	7.32±0.73
(n=37)	(61-86)	(6.1-8.3)
B_3	36.6±5.68	8.52±0.53
(n=32)	(30-49)	(7.2-9.2)
B_4	20.2±3.96	9.48±0.45
(n=35)	(15-29)	(8.6-10.1)
B_5	10.7±2.23	11.13±0.32
(n=33)	(8-14)	(10.4-11.6)

Group A : Control (Adult healthy subjects)

Group B : Study group (Adult subjects with CKD)

Group B_1 : Subjects with CKD in stage I

Group B_2 : Subjects with CKD in stage II

Group B_3: Subjects with CKD in stage III

Group B_4: Subjects with CKD in stage IV

Group B_5: Subjects with CKD in stage V

n = Number of subjects

Table 3. Estimated glomerular filtration rate (eGFR) in different groups (n=300)

Groups	A (n=150)	B_1 (n=13)	B_2 (n=37)	B_3 (n=32)	B_4 (n=35)	B_5 (n=33)
eGFR (ml/min/1.73m^2)	117.25±10.5 (100-136)	92.9±2.33 (90-96)	72.6±8.74 (61-86)	36.6±5.68 (30-49)	20.2±3.96 (15-29)	10.7±2.23 (8-14)

Statistical Analysis

Groups	A Vs B_1 Vs B_2 Vs B3 Vs B_4 Vs B_5				
P value	0.001				
Groups	A Vs B_1	A Vs B_2	A Vs B_3	A Vs B_4	A Vs B_5
P value	<0.001	<0.001	<0.001	<0.001	<0.001
Groups	B_1 Vs B_2	B_1 Vs B_3	B_1 Vs B_4	B_1 Vs B_5	B_2 Vs B3
P value	<0.001	<0.001	<0.001	<0.001	<0.001
Groups	B_2 Vs B4	B_2 Vs B5	B3 Vs B_4	B3 Vs B_5	
P value	<0.001	<0.001	<0.001	<0.001	

Results are expressed as mean±SD. One way ANOVA followed by Bonferroni test was performed to compare among different groups. The test of significance was calculated and p value < 0.05 was accepted as level of significance.

Table 4. Serum Uric Acid (SUA) level in different groups (n=300)

Groups	A (n=150)	B_1 (n=13)	B_2 (n=37)	B_3 (n=32)	B_4 (n=35)	B_5 (n=33)
SUA (mg/dl)	3.43±0.49 (2.6-4.3)	6.39±0.84 (4.6-7.8)	7.4±1.37 (6.1-10.3)	8.69±2.2 (5.2-12.8)	9.14±2.1 (6.1-12.8)	11.1±3.2 (6.3-16.6)

Statistical analysis

Groups	A Vs B_1 Vs B_2 Vs B3 Vs B_4 Vs B_5				
P Value	<0.001				
Groups	A Vs B_1	A Vs B_2	A Vs B_3	A Vs B_4	A Vs B_5
P Value	0.005	<0.001	<0.001	<0.001	<0.001
Groups	B_1 Vs B_2	B_1 Vs B_3	B_1 Vs B_4	B_1 Vs B_5	B_2 Vs B3
P Value	0.03	<0.001	<0.001	<0.001	<0.001
Groups	B_2 Vs B4	B_2 Vs B5	B3 Vs B_4	B3 Vs B_5	B4 Vs B_5
P Value	<0.001	<0.001	<0.001	<0.001	<0.005

Results are expressed as mean±SD. One way ANOVA followed by Bonferroni test was performed to compare among different groups. The test of significance was calculated and P value < 0.05 was accepted as level of significance.

Group A : Control (Adult healthy subjects)
Group B : Study group (Adult subjects with CKD)
Group B_1 : Subjects with CKD in stage I
Group B_2 : Subjects with CKD in stage II
Group B_3: Subjects with CKD in stage III
Group B_4: Subjects with CKD in stage IV
Group B_5: Subjects with CKD in stage V

n = Number of subjects

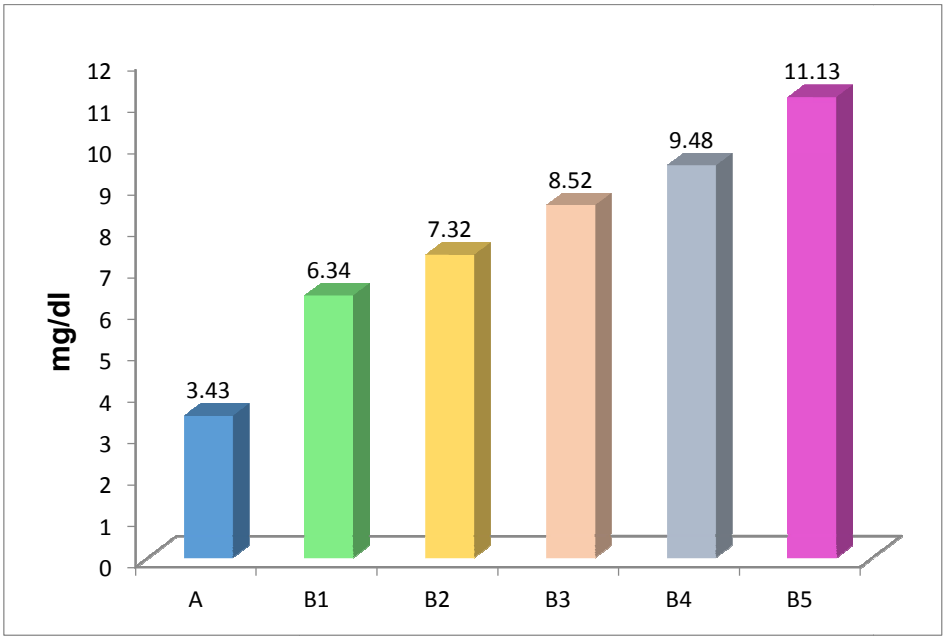

Fig. 2. Mean serum uric acid level in different groups (n=300)

Group A : Control (Adult healthy subjects)
Group B : Study group (Adult subjects with CKD)
Group B_1 : Subjects with CKD in stage I
Group B_2 : Subjects with CKD in stage II
Group B_3: Subjects with CKD in stage III
Group B_4: Subjects with CKD in stage IV
Group B_5: Subjects with CKD in stage V

n = Number of subjects

Correlation of serum uric acid level with estimated glomerular filtration rate (eGFR) in different study groups were analyzed by Pearson's correlation coefficient (r) test and is shown in Table 5.

In group B_1 Serum uric acid level showed negative correlation (r = - 0.247) with eGFR which was statistically not significant. In group B_2 Serum uric acid level showed negative correlation (r = - 0.488) with eGFR which was statistically significant ($p < 0.05$). In group B_3 Serum uric acid level showed negative correlation (r = - 0.621) with eGFR which was statistically significant ($p < 0.05$). In group B_4 Serum uric acid level showed negative correlation (r = - 0.532) with eGFR which was statistically significant ($p < 0.05$). In group B_5 Serum uric acid level showed strong negative correlation (r = - 0.780) with eGFR which was statistically significant ($p < 0.05$).

Pearson's correlation coefficient (r) test was performed to compare relationship between serum uric acid level and eGFR in different study groups. The test of significance was calculated and p value <0.05 was accepted as level of significance.

Linear regression was performed to observe the change of serum uric acid level with unit change of eGFR in the study group. The results are shown in Table 6. and Fig. 3. Serum uric acid level increased 0.051 mg/dl for each unit (1ml/min/1.73m^2) decrease in eGFR in the study group which was statistically significant ($p<0.05$).

Regression analysis was performed to measure change of serum uric acid level for unit change of eGFR. The test of significance was calculated and p value < 0.05 was accepted as level of significance.

Study group: Adult subjects with CKD
b = Change of serum uric acid level for each unit change of eGFR
n = Number of study subjects

Table 5. Correlation of serum uric acid level with estimated glomerular filtration rate (eGFR) in study groups (n=150)

Groups	n	r	P
Group B_1	13	-0.247	0.188
Group B_2	37	-0.488	0.005
Group B_3	32	-0.621	0.002
Group B_4	35	-0.532	0.004
Group B_5	33	-0.780	0.001

Table 6. Linear regression between serum uric acid level and estimated glomerular filtration rate (eGFR) in the study group (n=150)

b	r^2	p
-0.051	0.882	0.001

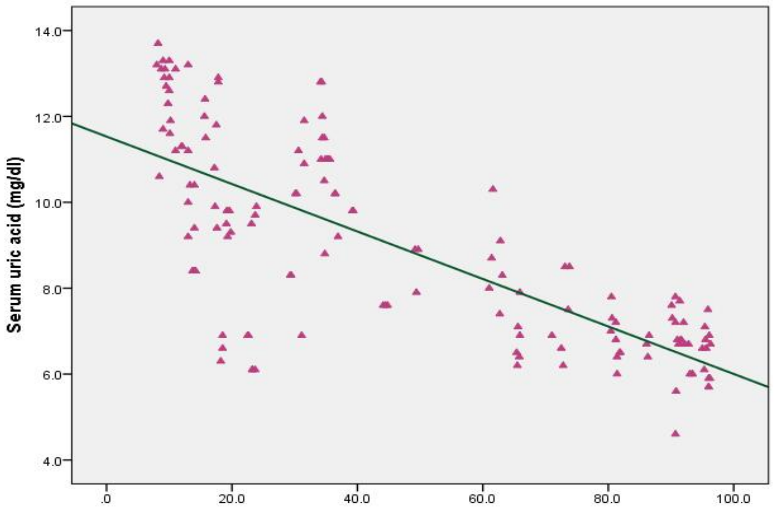

Fig. 3. Linear regression between serum uric acid level and estimated glomerular filtration rate (eGFR) in study group (n= 150)

eGFR (ml/min/1.73 m2)
Study group: Adult subjects with CKD
p= 0.001
n = Number of study subjects

4. DISCUSSION

The present study was undertaken to assess serum uric acid level in adult subjects with chronic kidney disease (CKD) in different stages (stage I-V). For this, 150 subjects with diagnosed chronic kidney disease were considered as study group and 150 age matched apparently healthy subjects were included in control group for comparison. Study subjects were divided into 5 subgroups according to stages (I - V) of CKD.

In our study, serum creatinine level was estimated in the study group for determination of estimated GFR. Staging of CKD was done based on eGFR. Estimation of serum uric acid level was done to observe its association with renal function in different stages of CKD.

Distribution of study subjects of all the groups by serum uric acid level was also observed in our study. Again, correlation of serum uric acid level was done with eGFR to find out their relationship in different stages of CKD.

Moreover, linear regression was performed between serum uric acid level and eGFR to measure the rate of change of serum uric acid level for each unit change of eGFR in the study group. In the present study, all the parameters in adult healthy subjects were within reference values and were consistent with the findings of various investigators from different countries of the world [20,29].

In the present study, the mean serum uric acid level was higher in study group than that of healthy control group and the result was statistically significant ($p < 0.05$). Hyperuricaemia was found in stage II to stage V of CKD subjects. Serum uric acid level in stage I was within normal range, but it was close to the higher limit of the range. This finding in stage III to stage V was in consistent with studies of many researchers of different countries [21,23]. No such study was found to compare the result in stage I and stage II of CKD.

On the contrary, some researchers did not find any significant rise of serum uric acid level in subjects with CKD [24,25]. The researchers suggested that increase in compensatory gastric excretion of uric acid might be the possible cause for this.

Also in this study, a gradual rise of serum uric acid level was observed in the study groups in accordance with the higher stages of CKD which was statistically significant ($p < 0.05$).

This finding was also in agreement with some other researchers [21,23].

In this study, an inverse correlation was found between serum uric acid level and eGFR in group B_1 ($r = -0.12$), in group B_2 ($r = -0.64$), in group B_3 (($r = -0.62$), in group B_4 (($r = -0.53$), in

group B_5 ((r = -0.92). The result was statistically significant in group B_2, B_3, B_4 & B_5 ($p < 0.05$).

Similar type of observations were made by some other researchers of different countries [21,30]. Yet, some other researchers did not find any significant correlation between serum uric acid and eGFR level in subjects with CKD [24,25].

We have found that, serum uric acid level increased by 0.051 mg/dl for 1ml/min/1.73 m^2 decrease in eGFR (r^2= 0.882), which was statistically significant ($p < 0.05$).

Similar report by other researcher have been published that serum uric acid level increased 0.33 mg/dl for 1 ml/min/1.73m^2 decrease in eGFR level [31]. Another study found that uric acid level increased 0.2 mg/dl for each unit decrease of eGFR [32].

5. CONCLUSION

Our study has revealed that, serum uric acid level increases in all stages of chronic kidney disease and there is a significant positive correlation between serum uric acid level and decline of renal function. As serum uric acid level is inversely correlated with eGFR and thereby it is directly related with severity of the disease, estimation of serum uric acid level may be a baseline investigation to assess severity of renal damage as well as prediction of other co-morbidities associated with it. It may also provide information about prognosis of CKD.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Ethical review committee approved the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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