HYPERURICEMIA IN PRE-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS. A SINGLE CENTRE EXPERIENCE

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ABSTRACT

Objective: To determine the prevalence of hyperuricemia in predialysis CKD patients in a tertiary care hospital and analyze its relationship with various socio-demographic factors.
Study Design: Descriptive cross sectional study.
Place and Duration of Study: Pak Emirates Military Hospital, Rawalpindi, from 1st Jun 2017 30th Nov 2017.
Material and Methods: The sample population comprised of 200 predialysis CKD patients, stage 1-5, of a tertiary care hospital in Rawalpindi, Pakistan. Fasting serum uric acid level was obtained from the patients. Relationship of age, gender, education status, marital status, smoking history, dietary history, BMI, eGFR, lipid profile and blood pressure (systolic and diastolic) was assessed with the serum uric acid level.
Results: Out of 200 patients, 62.5% had hyperuricemia and 37.5% had normal levels. After applying the logistic regression we found that presence of increased systolic blood pressure, raised cholesterol level, increasing age, lowe GFR and smoking history had significant association with the hyperuricemia.
Conclusion: This study showed a high prevalence of hyperuricemia in predialysis CKD patients. Special consideration should be remunerated to the predialysis CKD population having risk factors like hyperlipidemia, high systolic blood pressure along with hyperuricemia as propitious management can procrastinate the progression of CKD and eventually paring down the cardiovascular morbidity and mortality.

Keywords: CKD, Predialysis, Uric acid.

INTRODUCTION

Chronic kidney disease is a major worldwide health problem and its burden has exponentially increased in the last few decades. Afflicting about 14% of US population[1] and its prevalence also has increased in developing country like Pakistan[2-4]. Cardiovascular disease is a leading cause of morbidity and mortality in CKD patients of all stages[4]. Multiple epidemiological studies have elaborated various conventional and novel risk factors hastening the cardiovascular mortality and morbidity in CKD patients, and hyperuricemia is one of such novel risk factor. Recent experimental and epidemiological data have refuelled the longstanding debate of this risk factor putative reltaionship with hypertension, cardiovascular events and renal disease progression[2-4]. In meta-analysis involving 13 observational trials revealed hyperuricemia as independent predictor for development of CKD[2]. This fact highlights the need to size up its burden accurately first and then make endeavours in implementing more relevant strategies to lessen urate levels so as to arresst the progression of CKD.

Uric acid, which is the end product of purine metabolism, usually accumulate in patients with kidney impairment as kidneys are responsible for about two-thirds of its daily excretion. The prevalence of HUA, defined as uric acid level greater than 7mg/dl, increases with GFR decline in parallelism, accounting for about 40-60% in CKD patients with stages I to III and 70% with CKD stage IV or stage V according to one of the study[5,6]. Age, hypertension, increase cholesterol level, etiology of CKD all have been linked to hyperuricemia, accelerating the progression to ESRD by activation of RAAS, production of reactive oxygen species, inhibition of neuronal

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nitric oxide synthase, and expression of COX 2 in the vascular wall[7].

The aim of this study was to determine prevalence of hyperuricemia and its relationship with socio-demographic factors in our predialysis CKD populace because literature review has revealed that no such studies have so far been conducted in our population before, and also to take step to conduct large RCTs with more diverse cohort in evaluating the impact of lowering uric acid on renal and cardiovascular outcomes, so ultimately reducing the robust financial burden in these patients especially in developing countries like Pakistan where people can't bear the burden of renal replacement therapy.

Definition of Variables:

Hyperuricemia was defined as serum uric acid level >7.0 mg/dl.

Obesity was defined as BMI >29.9 kg/m^2[14].

Estimated GFR was used to stage CKD as stage 1 (GFR of ≥90 ml/min), stage 2 (GFR of 60–89 ml/min), stage 3 (GFR of 30–59 ml/min), stage 4 (GFR of 15–29 ml/min) and stage 5 (GFR<15ml/min) 200 mg/dl.

Dyslipidemia was defined as any or combination of the following: total cholesterol >200 mg/dl, high density lipoprotein cholesterol >135 mg/dl and triglycerides >150 mg/dl.[16]

Arterial hypertension: blood pressure >140/90 mm of Hg.

Smoking was defined as the use of smoking tobacco during the last 1 month prior to the consultation.

MATERIAL AND METHODS

This descriptive cross sectional study that included 200 predialysis CKD stage 1-5 patients, age 18-65 years, who reported to Nephrology Outdoor Patient Department, Pak Emirates Military Hospital, Rawalpindi was conducted between 1st June to 30th November 2017. Exclusion criteria were the CKD patients on dialysis, pregnant patients, HIV positive patients, Non-consenting predialysis CKD patients, Patients with gouty arthritis and patients who are already taking aspirin or xanthine oxidase inhibitors.

Subjects were provided with a detailed description of the study and were inducted into the study after written informed consent. Socio-demographic variables including age, gender and education, eating habits including smoking, consumption of meat and vegetables, of patients were obtained. History of hypertension, diabetes mellitus, joint pains, joints swelling, and use of aspirin and xanthine oxidase inhibitors were also obtained. The cause of CKD was established for each patient. About 10 ml of fasting venous blood was obtained from patients to perform biochemical tests which included serum uric acid, serum creatinine, and fasting serum lipids. Glomerular filtration rate (GFR) was estimated using Chronic Kidney Disease Epidemiology (CKD-EPI) equation. Those having BMI more than 24 were regarded as overweight. Bio-chemical markers were studied according to the internationally accepted ranges. The socio demographic data of the full sample of subjects participating in the research was entered in a structured Performa.

Statistical Analysis

Socio-demographic characteristics of parti-cipants were described by using the descriptive statistics. Continuous variables were presented as means and standard deviation while discrete variables as frequency and percentages. Chi-square was used to determine between-group variances in categorical correlates. Binary logistic regression analysis was done to evaluate factors correlation with uric acid level. All statistical analysis were performed using Statistics Package for Social Sciences version 20.0. Chi-square test was used and differences between groups were considered significant if *p*-values were less than 0.05.

RESULTS

A total of 220 patients of predialysis CKD undergoing dialysis were approached to

participate in the study. Seventeen refused participation and 03 were ineligible due to the exclusion criteria leaving 200 patients consisting of 169 males and 31 females. The mean age was 35.5 years and the extremes were 29 to 70. The age group 60-70 years represented 49% of the cases. About education, 13 (6.5%) people were uneducated, 66 (33%) under matric and 121

Table-I: Characteristics of the study group and their uric acid levels.

Socio-Demographic Factors Total	Uric Acid Level >7mg/dl N % 4431.4	Uric acid Level <7mg/dl N % 9668.6	χ^2	*p*-value
Age <40 yrs	18	22		
40-60yrs	36	26	9.886	0.007
>60yrs	71	27		
Gender				
Male	105	54	0.064	0.801
Female	20	11		
Cause				
Hypertension	11	15		
Diabetes	48	17		
DM/HTN	23	17	11.678	0.039
Chronic GN	14	13		
ADPKD	3	3		
Others	26	10		
Smoking				
Yes	125	64	19.4	0.000
No	0	11		
Education Status				
Uneducated	5	8		
Under-matric	44	22	3.699	0.157
Above matric	76	45		
Diet				
Vegetarian	70	40		
Protein	2	0	1.455	0.483
Vegetarian/protein	53	35		
BMI				
18.5-24.9	60	44		
25-29.9	54	28	2.962	0.227
>30	11	3		
Systolic BP				
100-139	81	59	8.379	0.015
140-159	33	16		
>160	11	0		
Diastolic BP				
60-89	99	64	1.170	0.280
90-110	26	11		
eGFR				
>90	0	3		
60-90	13	21		
30-59	58	35	20.06	0.000
15-29	45	14		
<15	9	2		
Lipid profile				
Normal	60	56	13.68	0.000
Increased	65	19		

(60.5%) patients had done matriculation. 110 (55%) patients had vegetarian diet, 2 (1%) had protein diet and 88 (44%) had both vegetarian and protein diet. Eleven (5.5%) patients gave history of smoking. The common etiologies of CKD in this study were hypertensive nephropathy, followed by diabetic/hypertensive nephropathy, chronic glomerulonephritis, diabetic nephropathy and others. The mean BMI was 23.8 ± 3.9kg/m^2 with majority of patients having BMI between 18.5-24.5 kg/m^2. The prevalence of hyperuricemia in the CKD subjects was 62.5%, with 79 (39.5%) patients having uric acid level between 7-9 and 11 (5.5%) patients with uric acid level between 11-13mg/dl The mean uric acid level was 65.4 ± 12.8 mg/l. As shown in table-I, increasing age, smoking history, high systolic blood pressure and increased cholesterol level had significant association with psychiatric morbidity when chi-square was applied. Table-II shows that increasing age, smoking history, high systolic blood pressure and increased cholesterol level were strongly associated with hyperuricemia when regression analysis was done.

Table-II: The correlated factors relating to hyperuricemia: The binary logistic regression.

	B	*p*-value	OR (95% CI)
Age (ref. is >60 years)	2.359	0.022	10.585 (1.405-79.723)
Gender (ref. is female)	0.804	0.226	0.236 (0.608-8.214)
Cause of CKD (hypertension)	2.835	0.002	0.0059 (0.011-0.307)
Diet (ref. is protein diet)	-0.659	0.143	0.517 (0.214-1.250)
Smoking (ref. is smoker)	19.857	0.035	0.000
Education (ref. is above matriculation)	0.201	0.689	1.223 (0.456-3.280)
Systolic B. (ref. is >160mmHg)	1.150	0.055	3.159 (0.977-10.208)
Diastolic B.P (ref. is 90-110mmHg)	0.875	0.243	2.398 (0.551-10.42)
BMI (ref. is 24.5 or less)	-0.548	0.626	0.578 (0.064-5.231)
Lipid Profile (ref. is raised cholesterol level)	-1.616	0.001	0.199 (0.078-0.509)
eGFR (ref. is CKD 3)	1.174	0.017	3.236 (0.362-28.963)

DISCUSSION

Chronic kidney disease is a worldwide health problem effectuating a robustious encumbrance on health care budget[8,9]. This fact emphasizes the urgent need to search for risk factors leading to progression of CKD. Uric acid and its association with the progression of CKD, which has been considered a dead subject previously, now considered an independent risk factor and many experimental and epidemiological evidence as well as a number of clinical trials done proclaiming its relationship with CKD progression but data still scarce to provide a recommendation thaturic acid lowering treatment might delay progression. The prevalence of hyperuricemia in our study was which was this prevalence was higher than 19.6% reported by Siu *et al*[10]. In addition, a direct relationship between the level of uric acid and the prevalence of metabolic syndrome leading to increased cardiovascular morbidity and mortality had been documented[11].

Various studies in past concluded that increasing age has a congruous correlate with hyperuricemia among the patients of CKD. The mean age of the CKD patients in this study was 35.5 years with the age group 60-70 years represented highest prevalence of hyperuricemia, the results of which is concordant with many local and foreign studies conducted so far[12,13] and may be due to lifestyle convenance by this group and also showing CKD affects the economically productive group in our setup like Pakistan with behemothic loss to the economy of the nation.

There was no significant difference observed between male and female hyperuricemia prevalence in CKD population which may be because of low estrogen level that has a role in renal clearance of uric acid level[14].

The common etiologies of CKD in this study were hypertensive nephropathy, followed by diabetic/hypertensive nephropathy, chronic glomerulonephritis, diabetic nephropathy and others, this is similar to the previous studies which showed high prevalence of hyperuricemia in hypertensive population compared to others[15,16]. Majority of the CKD patients who had hyperuricemia in our study were in stage 3 which is in accordance with the previous local and international studies showing that hyperuricemia may accelerate the progression of CKD. Kuo CF followed 63,758 subjects for 12 years, who had eGFR >60 ml/min/1.73 m^2 and established that patients with hyperuricemia had an accelerated decline in eGFR compared to patients without hyperuricemia[17-19].

The plasma uric acid level in smokers was significantly lower than in nonsmokers which is in congruence with the results of past literature showing negative correlation because of reduction of antioxidants leading to increased oxidative stress[20].

Our study and literature review revealed that Hypertension (systolic pressure), hypercholesterolemia, both independent risk factor, by effecting endothelial function, platelet aggregation and adhesion, had positive correlation with serum uric acid level[21].

There was no statistically significant association between hyperuricemia, obesity, diastolic blood pressure and dietary habits in our study which is not consistent with the previous studies[22]. This might be due to ethnic or environmental factors, but the large scale study involving CKD patients to confer negative correlation between hyperuricemia and increase BMI and diastolic blood pressure is proposed to find the real cause and confirm the findings of our study.

Our study has several important limitations. It is single center short duration study without external validation targeting small number of specific group of patients instead of randomized sample of all chronic kidney disease patients including dialysis population as well at various hospitals of Pakistan. Another limitation is the possibility of data collection errors which cannot be ruled out and is mainly indigent on interviewees' reminiscence capacity. Furthermore, lack of comparison and questionnaire deficient of specific data on purine content of food, medication historyetc, could not be evaluated because of methodological issues. Lastly, the cause and effect relationship remains evasive due to the cross-sectional study method and futher future studies using more representative sample size and longitudinal epidemiological data to delve into these associations are recommended.

CONCLUSION

Hyperuricemia although common in CKD predialysis population but the robust relationship between them is till shrouded in disputation. Special consideration should be remunerated to the predialysis CKD population having risk factors like hyperlipidemia, high systolic blood pressure along with hyperuricemia as propitious management can procrastinate the progression of CKD and eventually paring down the cardiovascular morbidity and mortality.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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