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Research Article

SERUM URIC ACID LEVELS IN CHRONIC KIDNEY DISEASE PATIENTS IN INDIANS

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ABSTRACT

Both serum uric acid (SUA) and chronic kidney disease (CKD) are associated with the risk of cardiovascular disease. Hyperuricemia has been attracting attention at the clinical level as a risk factor for the progression of kidney dysfunction. Several epidemiological studies have demonstrated as association between higher serum uric acid (SUA) levels and greater risk of CKD incidence. Hyperuricemia probably causes kidney damage by a mechanism involving systemic and glomerular hypertension. Tubulointerstitial fibrosis, which might be readily associated to the direct proinflammatory effects of soluble urate, is independent from the precipitation of monosodium urate crystals in the kidney. In CKD patients, higher serum uric acid levels are associated with higher degree of renal dysfunction, hypertension, diabetes, dyslipidemia, smoking, CRP, urine albuminuria,anaemia, cardiovascular disease/ events and mortality. The most common cause of mortality in ckd patients with raised serum uric acid was cardiovascular disease/ events.

Keywords:- Uric acid; Biomarker, Chronic kidney disease, Epidemiology.

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INTRODUCTION

Serum uric acid is commonly elevated in subjects with chronic kidney disease (CKD), but was historically viewed as an issue of limited interest. Recently, uric acid has been resurrected as a potential contributory risk factor in the development and progression of CKD. Most studies documented that an elevated serum uric acid level independently predicts the development of CKD. Raising the uric acid level can induce glomerular hypertension and renal disease as noted by the development of arteriolosclerosis, glomerular injury and tubulointerstitial fibrosis. Studying the role of uric acid in chronic kidney disease (CKD) is very difficult since uric acid is excreted primarily by the kidney, and hence a decrease in the glomerular filtration rate (GFR) is inevitably accompanied by a rise in the serum uric acid level. As such, studies in experimental animals in which serum uric acid can be modulated are critical to understanding if there is a role for uric acid in the causation or progression of kidney disease [1-4].

Hyperuricemia may be directly pathogenic rather than simply acting as a marker for other associated risk factors [1–3].It has recently been reported that hyperuricemia can cause hypertension and plays a role in the progression of end-stage renal disease (ESRD) [4]. Several studies have suggested a positive association between hyperuricemia and ESRD [3, 5–8], macro-cardiovascular diseases [5, 9] and mortality [10]. However, whether serum uric acid (SUA) is independently associated with chronic kidney disease (CKD) is still undetermined in relation to cardiovascular risk factors.

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CKD becoming a global health care burden so identification of modifiable risk factors, such as hyperglycemia, hypertension, hyperuricemia and implantation efforts to control these factors are imperative for CKD prevention. An elevated uric acid level is commonly observed in CKD patients. Hyperuricemia cause kidney injury including afferent arteriolopathy, glomerulosclerosis and tubuloin terstitial fibrosis.

Material and Methods:

This is a cross-sectional, prospective, randomized study was carried out in the Department of General Medicine, SLIMS, Puducherry. The study was comprised of 100 patients of either sex and age 18 years or above CKD patients attending medical indoor or Intensive care unit and dialysis unit for treatment. After selection of patients, General information and relevant history were asked by questionnaire methodology and clinical examination, renal function test, serum uric acid , lipid profile, CRP(qualitative), complete hemogram, liver function test, serum electrolytes, blood sugar and ultrasonography of abdomen and pelvis was done to check the size, shape andecho texture of kidney. GFR calculated by Modification of Diet in Renal Disease (MDRD) study. In this study all the patients of either sex>18 years of age were included and those were less then18 years of age, had history of gout and hyperuricemia due to other cause and taking antitubercular or thiazide drugs were excluded from this study. After explaining details of this study, patent informed consent were taken.

Statistical Analysis:

All values were expressed as Mean ± Standard Deviation (SD). The statistical analysis were done by using one way analysis of variance (ANOVA) using SPSS for windows version 11.5 (SPSS, Inc.,Chicago).Statistical significance was considered at $p<0.05$.

Results:

Table -1.Distribution of Patients according to age group

Age Group (Yr.)	No. of Pts.	Percentage (%)	Mean± S.D.
< 25	2	1.33	56.46 ±10.48
26-40	4	2.66	
41-55	60	40	
56-70	80	53	
>70	04	2.6	

Table-2 Stage of CKD according to serum uric acid status of patients

STAGE OF CKD	SERUM URIC ACID NORMAL	SERUM URIC ACID RAISED	p value
1	14 (16 %)	2 (1.5%)	<0.01
2	14(16 %)	2 (1.5%)	
3	16(17 %)	6 (10 %)	
4	22(25 %)	18 (30 %)	
5	24(26 %)	32 (57 %)	
TOTAL	90(100 %)	60 (100 %)	

Table-3 Complications in CKD patients and correlation with serum uric acid level

COMPLICATION	SERUM URIC ACID NORMAL	SERUM URIC ACID RAISED
Diabetes Mellitus	26	42
Cardiovascular Disease	20	36
Severe anemia	22	40
Dyslipidemia	26	28
Tuberculosis	2	4

Table -1.Distribution of Patients according to age group

150 patients of documented CKD were taken in which 65% were male and 35 % were female. The mean age of study population was 56.46 years and maximum number of patients 80 (53%) belongs to age group 56-70 years followed by 41-55 years of age group.

Table-2. Stage of CKD according to serum uric acid status of patients

There is statistically significant ($p<0.01$) correlation of raised serum uric acid with increasing stage of CKD and its severity. There are 1.67% patients in stage 1,1.67% in stage 2 , 8.12% in stage 3, 30% in stage 4 and 57.89% in stage 5 with raised uric acid level as compared

to 16% in stage 1, 16% in stage 2, 17.% in stage 3, 25.% in stage 4 and 26% in stage 5 with normal uric acid level.

Table-3. Complications in CKD patients and correlation with serum uric acid level

Raised serum uric acid level is very important prognostic factor in CKD. In this study we observed that those patients having raised level of serum uric acid level associated with more fatal complications in comparison to normal uric acid level.

Discussion:

Serum uric acid is eliminated principally by the kidneys, and while there is a compensatory increased removal by the gut in the setting of renal insufficiency, this is not completely effective, and serum uric acid increases as the GFR falls, with approximately half of the subjects becoming hyperuricemic by the time dialysis is initiated [11]. This makes it very difficult to assess the role of uric acid in the progression of renal disease in subjects with CKD based on epidemiological studies. In addition, the experimental studies suggest that uric acid may cause kidney disease primarily by causing systemic and glomerular hypertension, but in renal disease this mechanism may become less relevant as systemic hypertension commonly develops as a consequence of sodium and water retention. As such, it is not surprising that, in subjects with established CKD, serum uric acid has often [12, 13] not been found to predict progression. Nevertheless, some studies have found an elevated uric acid level to predict progression in subjects with established CKD, especially in diabetes and IgA nephropathy [14, 15].

Thus, an elevated uric acid is strongly associated with the development of CKD, but not always with the progression of CKD. In addition, an elevated serum uric acid level has been associated with both the presence of intrarenal arteriolar lesions [16,17] and with an increased risk for cardiovascular mortality in subjects with CKD [18,19]. The observation that hyperuricemia frequently precedes the development of CKD suggests that factors other than renal insufficiency are likely involved in the pathogenesis of the elevation in uric acid. Studies suggest that a variety of mechanisms may be operative. One of the most common risk factors for CKD is obesity and metabolic syndrome, which is strongly associated with hyperuricemia likely as a consequence of insulin resistance and the effects of insulin to reduce urinary urate excretion [20]. Hypertension is also commonly associated with renal vasoconstriction which also leads to uric acid retention [21]. However, more recent studies suggest that the rise in serum uric acid also precedes these conditions and hence may not represent the underlying cause of hyperuricemia [22]. Furthermore, one study found uric acid to be minimally elevated in secondary hypertension [23], a condition in which renal vasoconstriction is also present.

Hyperuricemia probably causes kidney damage by a mechanism involving systemic and glomerular hypertension. Tubulointerstitial fibrosis, which might be readily associated to the direct pro inflammatory effects of soluble urate, is independent from the precipitation of monosodium urate crystals in the kidney. In CKD patients, higher serum uric acid levels are associated with higher degree of renal dysfunction, hypertension, diabetes, dyslipidemia, smoking, CRP, urine albuminuria, anaemia, cardiovascular disease/ events and mortality. The most common cause of mortality in ckd patients with raised serum uric acid was cardiovascular disease/ events.

Low-level intoxication of lead and cadmium can also raise serum uric acid levels, likely by blocking the renal excretion of uric acid. Chronic low levels of lead have also been strongly associated with the development of CKD [24]. The renal pathology in chronic lead intoxication is associated with the development of microvascular disease, glomerulosclerosis and interstitial fibrosis similar to what is observed in subjects with gout [25]. Furthermore, the administration of lead to animals with CKD is associated with the development of hyperuricemia and an acceleration of the renal disease [26]. In these animals, the administration of allopurinol could reduce the systemic hypertension, but renoprotection was unable to be assessed due to the toxicity from treatment as a consequence of the deposition of allopurinol and xanthine crystals [26].

We found statistically significant ($p<0.01$) correlation of raised serum uric acid with increasing stages of CKD and its severity in comparison to other 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 could be attributed to the fact that recently, serum uric acid was proposed as a potential risk factor for new onset of kidney disease. From patho-physiological perspective, hyperuricemia result in progression of renal dysfunction through preglomerular arteriolopathy characterized by hyalinosis and wall thickening.

Elevation in the uric acid level persists throughout childhood and adolescence and is associated with endothelial dysfunction and the development of hypertension [27–29]. The mechanism for the hyperuricemia is unknown but may result from genetic and familial factors [30]. Higher SUA levels increased the risk of CKD, suggesting that at least part of the reported association between SUA and cardiovascular disease may be connected to CKD. This result establishes the importance of monitoring SUA and GFR and supports timely screening to access changes.In our study it is found that, significant proportion of hypertensive and diabetic

patients had come in CKD with raised serum uric acid group.

Conclusion:

Complications like cardiovascular diseases, diabetes mellitus, dyslipidemia, anemia are more common in Chronic kidney disease patients with raised serum uric acid level as our study suggests that most of the CKD patients attend hospitals in stage 5 with raised uric acid level. This highlights need of early investigation and treatment of high serum uric acid level so that complications do not occur. Hyperuricemia is strongly associated with CKD, but we still need large clinical trials before we should embrace the lowering of uric acid therapy in management. However, we are better off than we were 20 years ago when uric acid was a dead subject. Given the relatively ineffective current treatments for CKD, a new therapy would be greatly beneficial.

The need for large clinical trials, more studies are required to better understand the biology of uric acid. Does uric acid have the primary role in causing kidney disease, or is it the activation of xanthine oxidase which also produces oxidants in addition to uric acid? Does lowering uric acid provide any additional benefit over ACE inhibitors in subjects with CKD? Would it be more effective to alter diet, or chelate lead, as opposed to reducing uric acid itself in these subjects? Clearly there are more questions than answers.

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