

Role of Uric Acid in the Progression of Chronic Kidney Disease

Kidney plays an important role in uric acid excretion through a complex process involving filtration, reabsorption and tubular secretion and can be affected in a number of ways by abnormal uric acid metabolism^{1,2}. The solubility of uric acid depends upon both pH and concentration of uric acid in the filtered fluid. As the concentration of uric acid increases in tubular fluid and further it is exposed to low pH of the filtrate, the likelihood of the precipitation of uric acid increases several fold. The crystallization of uric acid within the tubules, collecting system or outflow tract leads to acute uric acid nephropathy and deposition of uric acid within the interstitium causes inflammation and interstitial nephritis.

Uric acid stones and attendant obstructive uropathy is a well-recognised entity. A strong association has been observed between uric acid nephrolithiasis and various clinical conditions such as diabetes, obesity and hypertension³. Epidemiologic studies provide strong evidence that states of insulin resistance such as type-2 diabetes and obesity underlie normouricosuric uric acid nephrolithiasis⁴. Cross sectional data demonstrated that patients who formed idiopathic uric acid stones have many features of metabolic syndrome, including obesity, dyslipidemia and glucose intolerance. All these conditions are linked to insulin resistance⁶. More than half of the patients who form uric acid stone exhibit glucose intolerance or type 2 diabetes mellitus⁵. Conversely, patients with obesity or type 2 diabetes mellitus have a higher proportion of uric acid stones than do lean or non diabetes persons.

Recent experimental and clinical studies have supported a causal relationship between hypertension and hyperuricemia. In an experimental study in rats, hypertension developed when hyperuricemia was established by inhibition of endogenous uricase⁷. In this study, BP correlated with rise in serum uric acid levels and decreased when uric acid levels were brought down with xanthine oxidase inhibitor or with a uricosuric agent. Further renal vasoconstriction resulted from a reduction in nitric oxide levels in endothelium and activation of renin angiotensin system and thereby causing microvascular disease and interstitial inflammation. In a randomized, double blind placebo controlled trial, Feig and colleagues reported that treatment with xanthine oxidase inhibitor allopurinol significantly lowered blood pressure⁸.

Whether sustained and chronic hyperuricemia as observed in patients with chronic kidney disease contributes to progressive decline in renal function or is a silent bystander still remains a topic of interesting debate. In children with familial juvenile hyperuricemia, a sustained hyperuricemia, chronic interstitial nephritis and progressive decline in renal function have been observed⁹. It has been postulated that uric acid regulates critical proinflammatory pathways in vascular smooth muscles. In experimental studies conducted in rats, hyperuricemia induced by uric acid inhibitor oxonic acid resulted in hypertension, intrarenal vascular disease and renal injury^{10,11}. In another experimental study, hyperuricemia was linked to high systemic blood pressure and cyclooxygenase mediated thromboxane induced vascular disease¹². Further in mice with systemic knock out of the Glut 9 urate transporter a state of hyperuricemia, hyperuricosuria, renal injury with interstitial inflammation, uric acid stone and progressive interstitial fibrosis was observed¹³. In a small randomized trial, use of allopurinol in 113 patients with CKD indicated an approximately 50% slowing of progression of kidney function decline and a trend towards fewer events in allopurinol treated patients^{14,15}.

In a study conducted at Amritsar (North India), published in this issue authors have observed a strong association between diabetic nephropathy and raised serum uric acid level. Whether raised serum uric acid level is just a benign bystander or only plays an important role in the progression of chronic kidney disease is yet to be seen in a large randomized trial. In

a large, double blind, placebo controlled randomized study (REENAL study), examining the renoprotective effects of losartan administered along with conventional blood pressure lowering drugs in proteinuric type 2 diabetic patients, concluded that use of losartan reduced the incidence of doubling of serum creatinine (taken as index progression of diabetic nephropathy) by 25%¹⁶. This beneficial effect of losartan was initially attributed to the inhibition of renin-angiotensin system but later on it was observed that losartan also reduces the serum uric acid through its uricosuric effect. Losartan has greater affinity for urate/anion exchanger and causes inhibition of urate reabsorption in the proximal tubules¹⁷. The uricosuria is associated with concomitant decrease in serum uric acid level in normal subjects, hypertensive subjects, and in patients with renal disease and kidney transplantation¹⁸. Losartan also increases urinary pH, which protects against crystal nucleation¹⁹. Therefore, renoprotective effect of losartan in diabetic nephropathy as seen in REENAL trial would have been not only due to renin angiotensin inhibition but lowering of serum uric acid level would have also contributed to this effect.

Though there are enough clinical and experimental evidences to suggest that raised uric acid level causes renal injury and may be partly responsible for the progression of CKD, but in the absence of a large randomized trial it is difficult to recommend routine use of uric acid lowering agents in patients with CKD.

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