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Editorial

Hyperuricemia: A non-traditional risk factor for development and progression of chronic kidney disease?



The historical association between hyperuricemia and kidney disease has been well-recognized from ancient times [1]; however, uric acid has been regarded as a marker rather than a risk factor for the development of renal disease since a decrease in glomerular filtration rate (GFR) *per se* induces an elevation in serum uric acid level despite compensatory increases in urinary and gastrointestinal excretions of urate [2]. In the past decade, substantial data from epidemiological and interventional studies has provided evidence that uric acid has a causative role in the development and/or aggravation of renal disease. In this issue of *Kidney Research and Clinical Practice*, Kim et al. reported that where hyperuricemia was already present at the time of diagnosis of immunoglobulin A (IgA) nephropathy, this was associated with a higher rate of renal progression [3]. Although this observational study did not address whether uric acid *per se* caused an aggravation of renal disease, hyperuricemia was an independent risk factor for IgA nephropathy on multiple regression analysis adjusted to age, gender, blood pressure, and proteinuria. It has been reported already that uric acid at the time of kidney biopsy is one of the independent risk factors determining renal prognosis in IgA nephropathy [4]. Furthermore, treatment of asymptomatic hyperuricemia with allopurinol delayed the renal progression with a lesser increase in blood pressure in patients with IgA nephropathy [5]. In this editorial, recent understanding regarding the role of uric acid in chronic kidney disease (CKD) will be highlighted, together with a review of potential mechanisms by which renal disease might be induced by uric acid, and a reappraisal of hyperuricemia as a novel risk factor for renal progression in CKD.

Causes of elevated serum uric acid level

Uric acid is a waste product resulting from the biological oxidation of purines, including adenine and guanine – components of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and adenosine triphosphate (ATP). Approximately two-thirds of total body urate is produced endogenously, while the remaining third is accounted for by dietary purines (present in fatty meat, organ meats, and seafood). The primary site of excretion of uric acid is the kidney. The normal urinary urate excretion is 250–750 mg per day, approximately 70% of the daily urate production [2]. Although urate is freely filtered in the glomerulus, there is evidence that both reabsorption

and secretion occur in the proximal tubule, and as a consequence the fractional urate excretion is only 8–10% in a normal adult. After molecular identification of urate transporter URAT01 (SLC22A12), several transmembrane molecules for urate handling have been detected and are still under investigation. Serum uric acid level is determined by the balance between generation and excretion of uric acid. Obesity, insulin resistance, hypertension and use of diuretics have led to decreased renal excretion of uric acid, and so they can be confounding factors in determining the clinical significance of hyperuricemia in vascular and renal disease.

Role of hyperuricemia in CKD: lessons from epidemiological studies

Bellomo et al. demonstrated that a higher uric acid level was associated with subsequent worsening of kidney function, and that this remained significant after adjustment for body mass index (BMI), blood pressure and proteinuria in a prospective cohort of 900 healthy, normotensive adults [6]. A recent study of more than 21,000 healthy participants also revealed that increased uric acid independently increased the risk for new-onset kidney disease [7]. In addition, the Atherosclerosis Risks in Communities and the Cardiovascular Health Study collected data from 13,338 participants with intact kidney function and analysis demonstrated that increased serum uric acid level is a modest, independent risk factor for incidental kidney disease in the general population [8]. Several epidemiological studies performed in large populations have shown that uric acid level was a major predictor for the development of incident kidney disease [9–11].

An increased uric acid level is also associated with impaired GFR in type 1 diabetes without proteinuria or prehypertension [12]. However, other studies have shown conflicting results, especially regarding the role of uric acid in the progression of established kidney disease or in kidney transplant patients [13,14]. Neither the Modification of Diet in Renal Disease Study nor the Mild to Moderate Kidney Disease Study considered uric acid to be a risk factor [15,16]. Therefore, it is still controversial whether hyperuricemia can be considered a risk factor for the progression of CKD. A recent study in middle-aged and elderly Taiwanese people has shown that elevated uric acid increased the risk of renal disease after an adjustment for gender, BMI, cholesterol, triglycerides, blood pressure

and blood sugar [17]. An interesting finding from this study was that serum uric acid was independently associated with estimated GFR (eGFR) only in stage 3 CKD, not in stages 4 or 5.

Role of hyperuricemia in CKD: lessons from clinical interventional studies

There have been a few observational and interventional studies to examine the association of uric acid with renal progression or the effect of uric acid lowering in the progression of IgA nephropathy [4,5,18]. In a recent randomized, prospective study in 113 patients with a GFR < 60 mL/minute, allopurinol (100 mg/day) treatment resulted in a slowing of the progression of renal disease after a mean time of 23.4 ± 7.8 months [18]. No changes in blood pressure or in albuminuria induced by allopurinol have been observed. Interestingly, allopurinol treatment also reduces cardiovascular and hospitalization risk in these subjects. Although this study may suggest a beneficial effect of allopurinol in the progression of renal disease, it is not certain whether the effect is related to uric acid lowering or another effect of allopurinol as an inhibitor of xanthine oxidase and/or as an antioxidant. These results have to be confirmed in larger prospective trials and a comparison study undertaken to see the effect of uricosuric agents.

Mechanism of uric acid induced renal disease

Most understandings about the mechanism of renal disease associated with uric acid emerged from the data in an animal model of hyperuricemia using a uricase inhibitor. Hyperuricemic rats showed preglomerular arterial disease, renal inflammation, and hypertension via an activation of the renin-angiotensin system (RAS) and COX-2 [19,20]. Once thickening of the afferent arterioles and macrophage infiltration in vessel wall has been induced, preglomerular vasculopathy may potentiate renal injury by causing ischemia to the postglomerular circulation. The reduction in the lumen could also provide a stimulus for the increase in the observed expression of renin, and might also contribute to the development of the marked hypertension in these rats, with an ineffective autoregulation and increased transmission of systemic pressures to the glomerulus. Uric acid also induced the proinflammatory cytokine, monocyte chemoattractant protein-1 (MCP-1), and the *de novo* expression of C-reactive protein (CRP) in vascular cells, which was further shown to be due to direct entry of uric acid into cells with activation of mitogen activated protein (MAP) kinase and nuclear transcription factor (NF- κ B) [21,22]. In addition, uric acid can become pro-oxidative under certain circumstances, in contrast to its natural antioxidant activity.

Consistent with experimental data, there has been some evidence that uric acid is associated with endothelial dysfunction in patients with cardiovascular disease. Zoccali et al. demonstrated an inverse relationship between uric acid and acetylcholine-stimulated vasodilatation in patients with untreated essential hypertension, even after adjusting for differences in traditional cardiovascular risk factors [23]. Furthermore, allopurinol treatment yields potentially beneficial effects on peripheral or cerebrovascular endothelial function in patients with chronic heart failure, type 2 diabetes and metabolic syndrome [24,25].

Conclusions

Evidence has been accumulating to support the hypothesis that hyperuricemia may be a genuine risk factor for CKD rather than an incidental finding related to declining glomerular filtration, and this is well grounded in recent epidemiological, clinical, and experimental observations. Nonetheless, there are still controversies regarding the causative role of uric acid in the development or aggravation of CKD. Considering the worldwide epidemic of CKD, it is critical to identify modifiable, novel risk factors for the disease and treat them adequately. Uric acid may be one of the ignored risk factors for CKD. In this sense, the clinical significance of hyperuricemia as a therapeutic target for CKD progression needs to be investigated by performing large randomized clinical trials to evaluate the effect of uric acid reduction on renal progression, cardiovascular disease, and mortality in CKD patients.

Conflict of interest

None to declare.

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