The Role of Hyperuricemia in the Pathogenesis and Progressivity of Chronic Kidney Disease

Gede Wira Mahadita*, Ketut Suwitra

Department of Internal Medicine, Nephrology and Hypertension Division, Faculty of Medicine, Udayana University, Sanglah General Hospital, Denpasar, Bali, Indonesia

Abstract

In humans, the end product of purine metabolism is uric acid. Over 70% of uric acid is excreted through the kidneys. When renal function is impaired, uric acid secretion is also impaired. This directly correlates the prevalence of hyperuricemia with the severity of chronic kidney disease (CKD). It has been reported that the prevalence of hyperuricemia in patients with Stage I-III CKD is 40–60% and up to 70% in patients with Stage IV-V CKD. Some studies found a link between serum uric acid levels and decreased glomerular filtration rate (GFR), an independent risk factor for CKD development. Because CKD and serum uric acid levels are related, the relationship between the two frequently generates controversy. As such, this review of the literature discusses the role of uric acid in the pathogenesis and progression of CKD.

Introduction

The uric acid level in the serum is usually high in patients with chronic kidney disease (CKD). In patients with CKD, whether hyperuricemia is caused by impaired renal function or by hyperuricemia alone commonly arises. Although both conditions may have a reciprocal relationship, most research performed recently showed that uric acid is one of the independent predictors for CKD. Uric acid is considered a potential risk factor that plays a role in the progressivity of CKD.

Hyperuricemia and gout are two overlapping conditions. However, these two terms have distinct definitions and boundaries. Hyperuricemia is defined as serum uric acid level >7 mg/dl in males and >6 mg/dl in females [1]. Meanwhile, gout is a disorder in purine metabolism or uric acid excretion through the kidneys, which are indicated by: (a) Hyperuricemia; (b) accumulation of monosodium urate in the whole body with a predilection for the joints, joint cartilages, bones, bursas, subcutaneous tissues, and kidneys; (c) nephropathy; and (d) nephrolithiasis. On the other hand, CKD is defined as renal failure or glomerular filtration rate (GFR) <60 ml/min/1.73 m² for 3 months or more regardless of the cause. Renal failure is indicated by microalbuminuria, that is, the ratio between albumin and creatinine is >30 mg/g on 2 out of 3 urine specimens.

Gout’s prevalence continues to rise each year, and it has become the most frequent inflammatory arthropathy. The prevalence of gout in the United States is estimated at approximately 3.9% and is primarily found in males rather than females (6.1 million vs. 2.2 million people) [2]. The most current prevalence of gout and hyperuricemia in Indonesia was 1.7% and 24.3% [3]. A similar fact is also found in CKD, where the global prevalence is 8–16% and 14% in the United States. On the other hand, the prevalence of CKD in Indonesia in 2005 was around 12.5%, and in 2012, the number of new end-stage CKD patients was 19,621 people [4].

Uric acid is the final product of purine metabolism in humans. Reduced GFR contributes to hyperuricemia, which is typically encountered in patients with CKD [5]. The kidneys secrete 70% of uric acid, with the rest coming from the gastrointestinal tract. More than 90% of hyperuricemia cases occurred due to disorders in renal secretion function. The prevalence of hyperuricemia is parallel with the reduction of GFR, 40–60% occurred in Stage I-III CKD patients, and 79% occurred in Stage IV-V CKD [6].
The largest study to date on the relationship between hyperuricemia and CKD with a 25-year follow-up period, which used samples from the US Renal Data System, discovered that subjects in the highest quartile of uric acid had the highest hazard ratio of around 2.4 to develop CKD [7], [8]. Bellomo et al. [9] found the relationship between uric acid and GFR reduction in a prospective cohort study that involved 900 normotensive subjects. Increased uric acid levels were associated with deterioration of renal function, and this connection remained significant after adjustment for BMI, blood pressure, and urine albumin-creatinine ratio factors. Another study, which included 21,475 healthy people (no comorbidities) with a median follow-up of roughly seven years, found that uric acid level in the serum was an independent risk factor for new-onset renal disease [10]. Atherosclerosis risk in communities and the cardiovascular Health Study, which included 13,338 samples with normal renal function, revealed that increased uric acid level was an independent risk factor for CKD [11].

Initially, it was assumed that the only mechanism linking hyperuricemia and CKD was the development of uric acid crystals on the surface of kidney epithelial cells and the promotion of inflammatory processes that would eventually accelerate the deterioration in kidney function [12]. However, even without forming uric acid crystals, hyperuricemia acts as a risk factor for CKD development. It accelerates the progression of patients with CKD by activating the renin-angiotensin system (RAS) and increasing oxidative stress associated with glomerular hypertension and renal autoregulation failure [13]. Among gout patients, 25% have proteinuria, 50% notice a decrease in renal function, and 25% develop end-stage renal failure. The autopsy and biopsy revealed arteriosclerosis, glomerulosclerosis, and tubulointerstitial fibrosis [12].

This literature review was conducted to explore the role of uric acid in CKD events and underline that serum uric acid, through its different processes, acts as an independent risk factor for CKD, not just as a marker for impaired uric acid excretion function through the kidneys in CKD.

After introduction should be method, the part below should be merged in introduction.

**Pathophysiology of Hyperuricemia**

Uric acid is a weak acid trioxopurine that is primarily synthesized in the liver, muscles, and gastrointestinal tract. It is composed of a substructure of pyrimidine and imidazole with oxygen molecules [14]. The precursor to uric acid is xanthine, converted to uric acid through the xanthine oxidoreductase enzyme. Exogenous uric acid is obtained through meals, particularly fatty meats and internal organs, whereas endogenous purines are synthesized within the human body. Hyperuricemia is caused by insufficient excretion, excessive production, or a combination of the two. Uric acid homeostasis is presented in Figure 1.

**Pathophysiology of Kidney Damage in Hyperuricemia**

Chronic gout and severe hyperuricemia are associated with the accumulation of uric acid crystals in the renal medulla. However, some research
suggests that chronic hyperuricemia (without going through the formation of uric acid crystals in the kidneys) can cause chronic kidney injuries through RAS activation and induce oxidative stress, resulting in glomerular hypertension and impaired renal function autoregulation [18]. In the extracellular environment, uric acid plays a role as an antioxidant, but inside the cells, uric acid has a pro-oxidant effect which causes endothelial and mitochondrial dysfunction.

Uric acid can cause CKD either directly or indirectly. It can directly cause CKD through the formation of uric acid crystals or RAS activation and increases oxidative stress, which results in glomerular hypertension, auto-regulation failure of the kidneys, and endothelial and mitochondrial dysfunction. Uric acid can indirectly cause CKD by secondarily decreasing kidney function through obesity and insulin resistance.

**Direct mechanism of relationship between hyperuricemia and CKD**

Uric acid can cause preglomerular artery disease, inflammation of the kidneys, and hypertension through activation of RAS and cyclooxygenase-2 (COX-2). In hyperuricemia, smooth muscle cells multiply, indicating that uric acid has a mitogenic effect on smooth muscle cells [19]. Uric acid, through COX-2, angiotensin II, and thromboxane, has been shown in animal studies to promote the proliferation of smooth muscle cells in blood vessels, ensuing in hypertension and progressive CKD [20]. Uric acid can cause vasculopathy in the systemic blood arteries and the kidneys by activating COX-2, angiotensin II, and thromboxane. Thickening of afferent arterioles and macrophage infiltration on the walls of blood vessels will increase preglomerular vasculopathy, which will eventually cause ischemia, thus initiating chronic injuries in the kidneys. Vasculopathy also results in ineffective autoregulation function in the kidneys and increases systemic pressure transfer in the glomerulus (Figures 3 and 4) [19].

Uric acid can activate phospholipase A2 and nuclear transcription factor-κB (NF-κB), which causes increased production of pro-inflammatory cytokines, resulting in inhibition of cellular proliferation of proximal tubules in vitro [21]. Increased uric acid will be accompanied by increased production of pro-inflammatory cytokines, such as tumor necrosis factor-α, c-reactive protein, and expression of various local chemokines, such as monocyte chemotactic protein-1 in the kidneys and COX-2 in blood vessels [19], [22]. Monocyte chemotactic protein-1 can also help increase the transport of uric acid directly into the smooth muscle cells of blood vessels to re-activate transcription factors NF-κB and mitogen-activated protein kinase [23].

Discontinuation of drugs that can lower uric acid was related to the increased urinary transforming growth factor-β1 in CKD patients with hyperuricemia [24]. This series of processes underlie the relationship of hyperuricemia in causing chronic inflammation of the kidneys. Uric acid is known to directly affect tubule cells by inducing the transition of epithelial cells into mesenchymal cells or referred to as epithelial-to-mesenchymal transition (EMT). EMT is the initial stage in the process of fibrosis in the kidneys [25]. EMT will accelerate the occurrence of glomerular hypertension and vascular lesions, and therefore resulting in proteinuria and renal failure in conjunction with worsening of glomerulosclerosis condition and tubulointerstitial disease [19].
Indirect mechanisms of the relationship between hyperuricemia and CKD through metabolic syndrome (MS)

Increased uric acid levels can result in oxidative stress and endothelial dysfunction, resulting in glomerular and systemic hypertension, which resulted in increased vascular resistance and decreased kidney perfusion [26]. Increased uric acid will stimulate the oxidation of low-density lipoprotein, resulting in lipid peroxidation. Specifically, oxidative stress due to hyperuricemia reacts and lowers nitric oxide (NO) levels, resulting in failure of NO release response to acetylcholine and decreased endothelial vasodilation ability [27].

Obesity and MS are the main risk factors for CKD. They are strongly associated with hyperuricemia as a consequence of insulin resistance, which has an impact on decreasing urate excretion through the kidneys [26]. Uric acid inhibits NO synthase, lowering the NO level, which contributes to the development of MS. A high level of uric acid is often found in people with hypertension. Increased uric acid levels can result in initial salt-insensitive hypertension, which is reversible when the uric acid level becomes normal [28].

Hyperuricemia with chronic and low-grade inflammatory effects can affect the phosphorylation of insulin receptors in threonine residue instead of tyrosine residue, thus triggering a decrease in insulin receptor sensitivity, which eventually leads to insulin resistance. Insulin resistance is associated with aciduria, which will accelerate the formation of nephrolithiasis due to uric acid [27].

Manifestations of Kidney Disease in Hyperuricemia

Manifestations of kidney disease concerning hyperuricemia include uric acid nephrolithiasis, urate nephropathy, and chronic uric acid nephropathy. In gout patients, the primary abnormality which affects the formation of uric acid stones in the kidneys is an increase in the acidity of urine that can trigger the formation of uric acid crystals [29]. Increased acidity of urine is associated with an increased risk of the construction of uric acid stones and a decrease in ammonium excretion. MS is comorbid and is considered strong enough to play a role in the incidence of uric acid nephrolithiasis since insulin resistance can increase the degree of acidity of the urine.

Urate nephropathy is defined as the deposition of uric acid crystals at physiological pH in the renal medulla. The accumulation of uric acid crystals will trigger inflammatory processes and fibrosis in the surrounding tissues [29]. The pathological spectrum associated with urate nephropathy can be heavy arteriosclerosis, glomerulosclerosis, and interstitial fibrosis. On the other hand, impaired renal function associated with chronic hyperuricemia can also occur without uric acid crystals. Hyperuricemia itself can be a de novo risk factor for CKD [10]. In the broader terminology, this condition is referred to as chronic uric acid nephropathy [29]. Impaired renal function is found in 30–50% of patients who have been suffering from gout for several years, and in 90% of patients, changes of the histological image were found in kidney biopsies. The most common histological findings are arteriosclerosis, focal or global glomerulosclerosis, and chronic tubulointerstitial disease.

Diagnostics of Kidney Damage Due to Hyperuricemia

Chronic uric acid nephropathy is characterized by mild proteinuria, less urine sediment, and minor tubular dysfunction (usually in the form of failure of urine concentrating, which is manifested as isosthenuria). The possibility of urate nephropathy diagnosis should be considered when it is found that serum uric acid increase is disproportional with decreased renal function level, as presented in Table 1 [29]. Uric acid levels higher than those shown in Table 1, which correspond to serum creatinine (SC) levels, can be suspected as chronic uric acid nephropathy. However, it is not a confirmed diagnosis.

Table 1: SC and uric acid levels in CKD [29]

<table>
<thead>
<tr>
<th>SC (mg/dl)</th>
<th>Serum uric acid (µmol/l)</th>
</tr>
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<tbody>
<tr>
<td>&lt;1.5</td>
<td>&lt;132</td>
</tr>
<tr>
<td>1.5–2</td>
<td>132–176</td>
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<tr>
<td>&gt;2</td>
<td>&gt;176</td>
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</table>

SC: Serum creatinine.

Symptoms of hyperuricemia that cause gout, such as joint pain, usually on the fingers, should also be explored. The joints appear to have swelling, redness, and pain that will get worse. Gout can also occur on the ankles, knees, and wrists [15]. When performing a physical examination, a thorough examination should be made to see any presence of pain in the joints. Anamnesis should be done in detail on the pain and inflammation to ensure that hyperuricemia originates from gout, and serum uric acid levels should be tested.

From the histopathological aspect, the most found histological images are arteriosclerosis, focal or global glomerulosclerosis, and chronic tubulointerstitial disease. Uric acid crystals are sometimes found in the tubules and interstitium (Figure 5), especially in the outer medulla.
patients with mild to moderate CKD were followed during the study period. A study by Feig et al. [18] demonstrated increased renin and intrarenal RAS activation levels in human subjects [37]. The study also showed that decreased uric acid levels were associated with improvement of GFR [31]. In an RCT conducted by Siu et al. [38], which involved 1072 patients with gout, uric acid >8 mg/dl with normal SC levels or in the range of 1.5–2 mg/dl, the subjects in this study were randomized into three groups, that is, the group who received febuxostat (with dose up to 240 mg/day) and allopurinol (100–300 mg/day) or the group who received placebo. It was found that the febuxostat group has a higher percentage of subjects with an impaired renal function who achieved the uric acid targets compared to those who received allopurinol. In general, hyperuricemia conditions associated with CKD are divided into (a) lowering uric acid to treat gout in CKD and (b) lowering uric acid to manage CKD. Guideline from American College of Rheumatology (ACR) in 2012 emphasized the importance of pharmacological and non-pharmacological management of gout in CKD. According to this recommendation, the target level of uric acid should be 6 mg/dL [7].

The drugs of choice for lowering uric acid levels are allopurinol and febuxostat. Febuxostat does not require dose adjustment in CKD patients. However, its safety profile on CKD patients in stage 4 and above is still minimal. The recommended initial dose of allopurinol in CKD is no more than 100 mg/day. Then the dose can be titrated up to 300 mg/day. ACR recommends giving prophylactic when initiating uric-acid-lowering drugs in gout patients to prevent exacerbations. The first drug of choice for this purpose is low-dose colchicine (0.6 mg twice daily, with lower doses for moderate to severe CKD (GFR 15–59 ml/min/1.73 m²). The use of NSAIDs should be avoided in CKD patients [7].

The research results on the relationship between CKD and hyperuricemia showed that
the decrease in uric acid levels is related to the improvement of CKD progressivity. Most of the research data presented above in the previous section of discussions are observational studies, and some are clinical trial studies with relatively small samples. As the final part of this literature review, we tried to conduct a systematic review of the PubMed database on the studies of hyperuricemia and CKD interventions and their benefits. We found five studies relevant to this topic, as presented in Table 2.

### Conclusion

Hyperuricemia is often found in CKD patients. Various studies have found that uric acid plays a role in the pathogenesis and progressivity of CKD. Uric acid can directly or indirectly cause CKD. Uric acid directly induces CKD through the formation of uric acid crystals or the activation of RAS. It increases oxidative stress, which results in glomerular hypertension, autoregulation failure of the kidneys, and endothelial and mitochondrial dysfunction. Uric acid indirectly causes CKD by decreasing kidney function secondarily through obesity and insulin resistance. This series of pathogenesis processes results in several manifestations of kidney disease in conjunction with hyperuricemia, including uric acid nephropathy and/or chronic uric acid nephropathy.

In patients with chronic uric acid nephropathy which accompanied by manifestations of hypertension with mild renal function disorders, mild proteinuria, less prominent urine sediment, and minor tubular dysfunction (usually in the form of failure of urine concentrating, which manifests as isostenuria). The possibility of a diagnosis of urate nephropathy should be considered when a disproportion was found between the increase of serum uric acid and the decrease in renal function. From the histopathological aspect, the most common histological images are hyperuricemia frequently observed in patients with CKD. Numerous studies have established that uric acid plays a role in the pathogenesis and progression of CKD. Uric acid can cause CKD either directly or indirectly. Uric acid causes CKD directly by precipitating uric acid crystals or activating the RAS and increasing oxidative stress, resulting in glomerular hypertension, kidney autoregulation failure, and endothelial and mitochondrial dysfunction. Uric acid indirectly contributes to CKD by impairing kidney function secondary to obesity and insulin resistance. This cascade of pathogenesis events results in various kidney disease manifestations in association with hyperuricemia, including uric acid nephropathy and chronic uric acid nephropathy, arteriosclerosis, focal or global glomerulosclerosis, and chronic tubulointerstitial disease. Uric acid crystals are sometimes found in the tubules and interstitium, especially in the outer medulla.

Allopurinol should be used carefully in the treatment of hyperuricemia in patients with CKD. Accumulation of xanthine in the kidneys can occur during the administration of xanthine oxidase inhibitor allopurinol and this deposition of xanthine can also trigger the occurrence of acute renal disorders. To minimize this condition, the recommended initiation dose of allopurinol is 50–100 mg/day, and then increased to 200–300 mg/day after a few weeks if it is well-tolerated.

### References


PMid:21784838

PMid:23192770

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PMid:22573200

PMid:18192841

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