



## Hyperuricemia and Urologic Disease

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Gout is a disease that causes painful inflammatory arthritis related to hyperuricemia, due to the incorrect metabolism of uric acid. Decreased renal excretion of urate is thought to be the major hyperuricemic mechanism. Most genes responsible for the serum uric acid (SUA) level encode uric acid transporters or related regulatory proteins. The acquired effects can also modulate SUA level and uric acid excretion, which can result in acute gout. Interestingly, kidney related comorbidities in gout, such as hypertension, chronic kidney disease (CKD), and urolithiasis, all have a fairly high prevalence. Recent advancements in genetics and molecular physiology have greatly improved our understanding of renal reabsorption and secretion of filtered uric acid. Furthermore, the baseline SUA level appears to be established by a net balance between absorption and secretion through the epithelium of the kidneys and intestines. There have also been considerable progress in the management of gout patients with CKD. Increased prevalence of gout with CKD can be balanced by an expanded spectrum of treatment options for this important disease. Another issue is that lowering of the uric acid level can reduce the incidence of cardiovascular disease, renal disease, and urological complications. Basic research and clinical studies on these mechanisms might be helpful in determining the appropriate treatment for hyperuricemic patients. Based on currently existing literature, there have been improvements associated with medications that lower uric acid, particularly xanthine oxidase inhibitors. Here, we review the pathogenesis and epidemiology of hyperuricemia, specific diseases related to uric acid, and up-to-date perspectives on their management.

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## INTRODUCTION

Uric acid has long been regarded as an inert end product of purine catabolism. However, many studies have demonstrated that chronic hyperuricemia is associated with the accumulation of uric acid crystals in the body, onset of hypertension, metabolic syndrome, chronic kidney disease (CKD), and cardiovascular (CV) disease. Moreover, it has been reported that hyperuricemia could be an etiological

factor for hemospemia or prostatitis that can be easily managed by allopurinol [1].

The average level of serum uric acid (SUA) in the general population has been increasing [2]. This is mainly due to changes in diet, body mass index (BMI), and prolonged life expectancy in the general population as well as in those with CKD or congestive heart failure. Thus, hyperuricemia and related pathological conditions have become very common.

Hyperuricemia induces many metabolic diseases. It also protects against diseases. Unlike gout and related diseases, hyperuricemia clearly has protective effect on neurologic diseases, including Parkinson's disease, multiple sclerosis, and Alzheimer's disease [3,4]. Higher uric acid levels can decrease the risk of Parkinson's disease and lower the risk of disease progression [5]. Although the underlying mechanism might be heterogeneous, most theories have suggested that such protective effect of uric acid is due to its antioxidant effect [6]. A similar mechanism might explain the apparent protective effect of hyperuricemia on patients with end-stage renal disease, who are on hemodialysis. Higher SUA has been shown previously to be associated with lower risk of all-cause mortalities and CV deaths [7].

Hyperuricemia, in adults, is defined as having a plasma uric acid level of greater than 7 mg/dl [8]. The frequency of hyperuricemia varies worldwide, ranging from 8% in Saudi Arabia to 35.2% in Seychelles [9,10]. This present descriptive review evaluates the role of hyperuricemia in several pathological conditions, particularly CV, renal disease, and urological disease. It emphasizes the importance of measuring SUA in daily clinical practice. This article also provides considerations for using appropriate SUA value as a basis for defining clinical hyperuricemia and some suggestions on proper treatments.

## BIOCHEMICAL ASPECTS OF URIC ACID

Uric acid is the final product of purine metabolism. Purines are produced in two ways: (1) the de novo synthesis from

non-purine compounds modulated by phosphoribosyl-pyrophosphate synthetase and (2) the purine salvage process controlled by hypoxanthine-xanthine phosphoribosyl-transferase. Uric acid is eliminated by excretion through the kidneys and intestines. Renal and intestinal transporters of urate have been reported in the last decade [11]. Insufficient renal excretion of uric acid has been found to be the major cause of primary and secondary hyperuricemia in patients with gout [12]. Decreased intestinal excretion of urate is also associated with *ABCG2* gene polymorphisms that appear to contribute to 'pseudo-over-production' phenotype [13].

## ENVIRONMENTAL FACTORS AFFECTING SERUM URIC ACID LEVEL

Environmental factors, such as diet and administered drugs, can affect the levels of SUA. SUA levels are also affected by various CV risk factors. Various drugs can lower the SUA level. Such effects may accumulate in patients, especially in those with hyperuricemia. Uricosuric drugs, such as probenecid, sulfinpyrazone, and benzbromarone, as well as xanthine oxidase inhibitors, such as allopurinol and febuxostat, can all directly affect the levels of SUA. Several other drugs have secondary effects on the SUA levels, including cholesterol-lowering agents, anti-hypertensives, steroids, non-steroidal anti-inflammatory drugs, and antimicrobials (Table 1). Diets known to increase SUA levels include meat, seafood, sodium, fructose, and alcohol. Factors known to lower SUA levels include consumption of ascorbic acid, coffee, and dairy products.

**Table 1.** Drugs that affect uric acid levels

Name	Effect on serum uric acid level	Magnitude of effect (%)	Mechanism of action
Losartan	Down	20-25	Uricosuric effect
Diuretics	Up	6-19	Uric acid reabsorption in proximal tubule
Beta-blockers	Up	6-9	Unclear
ACE inhibitors	Stationary (but attenuates rise caused by diuretics)	-	Uricosuric effect
Calcium channel blockers	Down	3-10	Uricosuric effect
Alpha blockers	Stationary	-	-
HmG CoA reductase inhibitors <sup>a)</sup>	Down	3.6-12.0	Uricosuric effect
Fenofibrate	Down	20	Presumed inhibition of URAT 1 transporter
Acetylsalicylic acid	Up at low doses, down at higher doses	6 with low doses	Low dose: uric acid retention High doses: uricosuric

A class effect is assumed, except for where individual drug names are given.

ACE: angiotensin-converting enzyme, URAT 1: urate transporter 1, -: not available.

<sup>a)</sup>Most powerful evidence for atorvastatin, but also supports mild effect of simvastatin and rosuvastatin.

## EPIDEMIOLOGICAL ASPECTS OF URIC ACID

The definition of hyperuricemia varies by study, and thus, difficult to compare them. Very high incidence rates of hyperuricemia and gout have been reported in certain Aboriginal people in the Pacific region, with Taiwanese indigenous people having the highest incidence rates (hyperuricemia, 41.4%; gout, 11.7%) [14]. The prevalence of hyperuricemia in the United States (US) has been estimated to be about 23%, with African Americans having higher prevalence than non-African American populations (25.7% vs. 22.1%) [14]. A recent Italian survey study has reported a clear pattern of increasing prevalence of hyperuricemia with time given the cut-off value of 6 mg/dl (360  $\mu$ mol/L) (8.5% in 2005 vs. 11.9% in 2009) [15]. Therefore, understanding the epidemiology of hyperuricemia is very important because it is closely related to CV and/or CKD, including components of the metabolic syndrome.

## THE KIDNEY AND URIC ACID

Crystallization of uric acid will form urate, which precipitates in the body. However, hyperuricemia can affect vascular endothelium, vascular walls, and kidney parenchyma, even in the absence of crystallization or deposition. Uric acid has intracellular pro-oxidant effect and is involved in the extracellular antioxidant activity. As a result, hyperuricemia has a deleterious effect on the vascular endothelium. It promotes endothelial dysfunction, which can be improved by the administration of xanthine oxidase inhibitors, but not by using uricolytic drugs [16]. It appears that the deleterious effect of hyperuricemia is mediated by the oxidative stress produced by xanthine oxidase activity, as well as uric acid.

Approximately 14% of the adult population in developed countries suffers from CKD, while two-thirds of the population over the age of 80 years has reduced glomerular filtration rate (GFR), defined as an estimated GFR of less than 60 ml/min per 1.73 m<sup>2</sup> [17]. The association between hyperuricemia and kidney disease has been known for a long time. Early observations have suggested that uric acid might play a role in the pathogenesis of CKD. However, this was considered obsolete by the 1970s and 1980s, when

hyperuricemia was regarded as an indicator for CKD, but not as a risk factor or pathophysiologic factor for CKD. Indeed, large studies, such as the German Chronic Kidney Disease Study and the National Health and Nutrition Examination Survey, have shown an increase in the incidence of hyperuricemia with reduced GFR [18,19]. Previous studies have shown that hyperuricemia, regardless of deposition, is related to the degree of albuminuria. Furthermore, 18 prospective cohort studies using 431,000 patients have shown that hyperuricemia can predict the rate of CKD as well as the rate of deterioration in renal function [20].

Research on the role of SUA in CKD have been hampered by confounding factors such as hypertension. Hypertension can cause CKD. Consequently, a reduction in GFR can lead to hyperuricemia. Moreover, administration of diuretics for hypertension management can increase the levels of SUA. However, this issue has been addressed in several recent studies investigating the association between SUA and the onset of renal disease in healthy populations. A seven-year prospective study of 21,475 healthy volunteers has revealed that SUA is associated with incident diseases (estimated GFR < 40 ml/min per 1.73 m<sup>2</sup>) [21]. An analysis of 656,108 patients in Taiwan, with a long-term follow-up, has revealed that uric acid deposition is associated with an increase in the incidence of end-stage renal disease.

Kang et al. [22] have shown that hyperuricemia is associated with hypertension. It also causes COX-2 mediated thromboxane-induced vascular disease with related changes in renal histology, using 5/6 kidney resection model and a series of well-planned experiments [22]. Moreover, their study suggested that lowering uric acid may hinder the progression of kidney disease. These preclinical data are consistent with new epidemiological data. A five-year follow-up of 900 healthy and normotensive patients with normal renal function has revealed a correlation between SUA levels and the likelihood of reduced estimated GFR [23]. The effect was seen at SUA concentration of 5.5 mg/dl in males and 5.0 mg/dl in females. The prevalence of CKD was significantly higher in patients with hyperuricemia (odds ratio, 2.55; 95% confidence interval, 1.71-3.85;  $p < 0.001$ ) [24]. These data indicate that the cut-off value of hyperuricemia based on the solubility of uric acid in physiological conditions should be reconsidered. The question is whether these preclinical and new epidemiological data suggest that

lowering SUA may effectively slow down the progression of CKD and reduce proteinuria. One small trial has suggested that this might be true. In this prospective study, 113 patients with CKD were randomized and their estimated GFRs were around 40 ml/min per 1.73 m<sup>2</sup>. They took either the placebo or xanthine oxidase inhibitor for two years [25]. Similar to the results by Kang et al. [22] using an animal model, this treatment slowed the progression of CKD in the treatment group, while the placebo group lost about 10% of their initial kidney function. In addition, the rate of proteinuria was decreased with an improvement of GFR. In one prospective, randomized, and controlled study of hyperuricemic patients with CKD [26], the effect of allopurinol on the progression of CKD was evaluated over twelve months. The treated patients showed a significant reduction in the SUA level. They preserved their renal function for 12 months. In an open-label Febuxostat/Allopurinol Comparative Extension Long-Term (EXCEL) study, the effect of xanthine oxidase inhibitor on renal function was confirmed in 551 patients with gout, who had taken febuxostat for up to 4 years [27]. In this study, the continuous reduction of SUA level was related to a slower decrease of renal function ( $p < 0.001$ ). This study showed that a sustained reduction of 1 mg/dl of SUA was correlated with the preservation of 1.15 ml/min of GFR [27]. However, ongoing prospective trials are needed to confirm the effect of febuxostat on the decline of GFR over an extended period in patients with CKD and hyperuricemia without deposition [28].

Therefore, hyperuricemia is common in the CKD population. It is often accompanied by decreased GFR and increased proteinuria. Data from observational studies have indicated that the increasing levels of SUA can predict the progression of CKD. The results of several interventional studies have suggested that effective pharmacologic treatment of hyperuricemia in patients with CKD may delay the progression of CKD, slowing down or even preventing dialysis.

## URIC ACID STONES

Although uric acid stones are uncommon forms of kidney stones, they are common amongst those with metabolic syndrome. Uric acid stones are comprised of 8-10% of all renal stones in the US. They account for 25% of stones

in certain areas of Germany, and 16% of stones in Okinawa, Japan [29]. Their prevalence is considerably higher in some subsets of those with stones. Stone formers and type 2 diabetes mellitus have been found to have uric acid stones more frequently than others with stones [30-32]. The higher prevalence of uric acid stones in obese patients has also been reported [33,34]. In addition, higher BMI and diabetes are independent risk factors for uric acid stones [30]. A recent study has found that a significant proportion of patients with uric acid stones are affected by various features of metabolic syndrome [35,36]. In short, metabolic syndrome and individual characteristics are associated with uric acid nephrolithiasis. Patients with uric acid stones have shown diverse pathogenesis, including congenital, acquired, or idiopathic [29]. In patients with uric acid stones, three important urinary abnormalities have been identified: acidic urine, hyperuricosuria, and low urine volume. Decreased urine volume (less than 2 L/d) increases urine saturation associated with stone forming ingredients, contributing to the development of all types of stones, including uric acid stones. Conditions associated with hyperuricosuria include indiscreet diets (such as purine-rich diets) [37], use of drugs that prevent reabsorption of uric acid in the renal proximal tubule (high doses of salicylates, losartan, and probenecid), and increased purine catabolism (hemolytic diseases and myeloproliferative disorders) [29]. Overly acidic urine is an important pathogenic mechanism associated with the occurrence of uric acid nephrolithiasis.

Low 24-hour urine pH ( $< 5.5$ ) has been observed in most patients with uric acid stones. Many of these patients have been found to have normal uric acid excretion [35,38]. Conditions that can contribute to aciduria include increased endogenous acid production and chronic diarrhea [39]. However, most patients with uric acid stones do not have these features. They are classified as idiopathic uric acid nephrolithiasis, formerly called "gouty diathesis."

## NUTRITIONAL AND PHARMACOLOGICAL MANAGERMENTS OF URIC ACID STONES

In patients with uric acid stone, the initial treatment consists of a medical dissolution therapy, which is a non-invasive approach that has been successful in most cases [40]. Medical therapies have been focused on correcting the underlying three metabolic abnormalities that

lead to stone formation, including low urine volume, hyperuricosuria, and acidic urine. Calibration of urine pH is the cornerstone of treatment in patients with uric acid nephrolithiasis. It disintegrates existing stones and prevents recurrent stone formation. Reducing animal protein intake has been shown to be helpful; it should be recommended to all patients [41]. However, pharmacotherapy with potassium citrate is the most commonly chosen one in this setting [40]. Sodium bicarbonate is also used in patients who cannot tolerate or are unsuitable for potassium citrate because of renal insufficiency or hyperkalemia. Calibration of a low urine volume is usually done by increasing water intake to maintain a urine volume of about 2 L per day. In addition, some fruit juices (such as orange juice and lemon juice) might also be used as they provide alkaline, while increasing urine volume and urine pH levels [42].

In summary, the correction for hyperuricosuria can be achieved by pharmacotherapy, such as allopurinol, and lifestyle changes, such as a balanced diet and reduction of purine-containing diet. Dissolution therapy is usually effective, and many patients have obtained reliable results with long-term alkali treatment. Urological intervention is rarely used to treat uric acid nephrolithiasis. It may be performed on patients with urinary tract obstruction, progressive renal insufficiency, unbearable pain, and/or poor response to medication.

## CHRONIC PROSTATITIS AND URIC ACID

Chronic prostatitis is a disease that causes substantial morbidity in men with a constellation of lower urinary tract symptoms, sexual dysfunction, and chronic pelvic pain [43]. Although epidemiologic studies of chronic prostatitis have rarely been published, available studies have shown that this condition is common [44-47].

There are diverse types of prostatitis with various features and available treatments. Among these, the etiology of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is particularly unknown. Various therapies for CP/CPPS partially reflect this knowledge gap. Although there are many hypotheses about the causes of CP/CPPS with many innovative therapies, there has not been any consensus to date on a treatment considered to be effective or therapeutic. The absence of safe and effective therapy for this mysterious condition has frustrated patients and doctors.

One proposed etiology is a reflux of urine into the prostate ducts, causing prostatitis through high-enriched metabolites, including purine and pyrimidine bases in the prostatic fluids [48]. Interestingly, a previous study has reported their experience with hemospermia and its relationship to hyperuricemia [49]. These theories have led to the use of allopurinol in the treatment of CP/CPPS to lower uric acid levels of prostate and improve prostatitis-like symptoms. However, some scholars have criticized that this concept of treatment is premature [50]. To date, only one randomized trial that used allopurinol as a treatment for CP/CPPS has shown the positive effects of allopurinol on CP/CPPS. In addition, they showed that allopurinol is safe to use for CP/CPPS. The authors of this study recommend the use of drugs for each event of non-bacterial prostatitis to relieve symptoms. However, their research is somewhat limited due to the small sample size, absence of statistical validations, and non-standard analysis. Given these points, their conclusions and proposals are still immature. However, this question remains highly interesting. It can be tested in the future whether high concentrations of purine- and pyrimidine-based metabolites in prostatic secretions can lead to prostatic inflammation via urine reflux into the prostatic ducts. To confirm whether allopurinol is effective, additional trials of allopurinol therapy using highly validated and standardized outcome measures and analysis are required.

## WHEN SHOULD WE START URATE-LOWERING THERAPY?

Nowadays, there is no evidence to treat asymptomatic hyperuricemia worldwide based on randomized controlled trials. However, the two well-known xanthine oxidase inhibitors are permitted in some countries for the treatment of hyperuricemia [51]. In most countries, urate lowering therapy (ULT) has not been approved to treat asymptomatic hyperuricemia. However, data suggesting the efficacy of ULT in cases other than gout are increasing. This means that we can consider it as a treatment even when there is no overt gout if hyperuricemia is concurrent with other CV risk factors.

Large-scaled controlled studies are required to perfectly establish the effect of ULT on CV, renal, and other urological morbidities. Febuxostat study is ongoing in patients with

cerebral and cardiorenovascular events. We are looking forward to seeing the results by the end of 2017. Unfortunately, there has not been any study to date on xanthine oxidase inhibitor with urological end points.

## CONCLUSIONS

There have been tremendous advancements in the molecular physiology of hyperuricemia over the last few decades. In clinical practice, CKD is thought to be a frequent complication of gout that may be an important basis for treatment. At this point, a rapidly evolving treatment option for CKD and gout is considered essential. It is also clear that improving the target SUA is important for nephrologist and urologists. In addition, the target SUA should be developed for patients with urological specific diseases, such as uric acid stone and CP/CPPS.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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