Review title:

The role of asymptomatic hyperuricemia in the progression of chronic kidney disease CKD and cardiovascular diseases CVD.

Authors: Yousuf waheed¹#, Fan Yang¹#, Dong Sun¹.²*

Author affiliations:

¹Department of Nephrology, Affiliated Hospital of Xuzhou Medical University, Xuzhou 221002, China

²Department of Internal Medicine and Diagnostics, Xuzhou Medical University, Xuzhou 221002, China

The authors contributed equally to this work.

Corresponding author:

Dong Sun, MD, PhD, Department of Nephrology, Affiliated Hospital of Xuzhou Medical University, 99 West Huai-hai Road, Xuzhou, Jiangsu, 221002, China

Telephone: +8618952186599

E-mail: sundong126@yahoo.com

Running title: The role of hyperurecimia in chronic kidney disease and cardiovascular diseases.

Words count: 5210

Number of tables: 1

Number of figures: 2
Abstract:

In the past decades, questions arose whether hyperuricemia works as an independent risk factor of cardiovascular and renal disease, many evidence cleared this question, that hyperuricemia works as an independent risk factor for chronic kidney disease and cardiovascular diseases.

Hyperuricemia defined as an abnormally high level of uric acid. In general, it's defined as serum urate concentration excess of 6.8 mg/dl. Hyperuricemia, which is commonly thought to be just a complication of chronic kidney disease, seems to play a pathogenic role in the progression of renal diseases. In recent years, more attention has been paid to the link between hyperuricemia and chronic kidney disease. Randomized controlled trials have shown that there may be independent associations between hyperuricemia and the progression of cardiovascular and renal morbidity. It is thought to be mediated by renin-angiotensin system activation, nitric oxide syntheses inhibition, and the development of macro and microvascular diseases. Debate continues regarding serum uric acid concentration as an indirect index of renal vascular disease. To sort out the thread, our literature review focus on the role of asymptomatic hyperuricemia in the progress of chronic kidney disease along with the association between hyperuricemia and cardiovascular diseases and a general review of the physiological metabolism of uric acid.

Key words: hyperuricemia; xanthine oxidase; hypertension; insulin resistance; febuxostat; cardiovascular disease; chronic kidney disease.

Introduction:
The continuous controversy exists regarding the association between hyperuricemia (HUS) and cardiovascular disease (CVD). By the year 2020, CVD is considered one of the most common non-communicable diseases which are suspected to be the major cause of mortality in most developing countries [1].

Uric acid (UA) discovery happened in the early 1700s with the investigating of a bladder stone. Serum uric acid (SUA) is generally elevated in patients with chronic kidney disease (CKD) but has not received enough attention then. However, in recent years, many studies have shown that HUS might be independently associated with the progression of CKD. A 5-year follow-up study of 7078 subjects in Japan found that baseline levels of UA were independent risk factors for CKD after adjusting for age, gender, body mass index, blood pressure (BP), and plasma glucose level [2]. As we know CKD is a worldwide public health problem. Without early intervention, it will progress to end-stage kidney disease (ESRD). Therefore, it is essential to find and block the factors that aggravate the deterioration of renal function. The relationship between HUS and CVD has been established since the early 1900s. In high BP and CVD patients, high SUA is common findings. Furthermore, UA as a CV risk factor has been addressed in numerous randomized trials of prospective cohort studies [3]. In the last decades, there has been a reappraisal of the relationship between elevated SUA levels and the increased risk of CV and renal injury [4-5].

The prevalence rate of HUS has significantly increased with the development of CKD. And the incidence of the population has gradually become younger which is closely caused by westernized lifestyle, environment, and irrational diet [6-7-8]. HUS usually accompanies metabolic syndromes, hypertension (HTN), and CKD. SUA levels are significantly depending on meals, lifestyle, gender, and previous use of medications and diuretics [9].
Previous epidemiologic studies suggested that in earlier stages of CKD patients found a linear relationship for all-cause and CV mortality [10].

The physiological solubility of UA occurs at a range of 6.4 mg/dl. Before reaching the supersaturated condition, the UA-binding proteins help to increases the solubility to near 7.0 mg/dl; at this point, the SUA has the potential to crystallize within the human body which lead to the developing of HUS [11]. Possible mechanisms of high SUA for exacerbating renal injury include oxidative stress, inflammatory reaction, renin-angiotensin system (RAS) activation, nitric oxide synthases (NOSs) inhibition, epithelial-to-mesenchymal transition (EMT) and so on [12-13].

The changes mentioned above may induce renal vascular lesions and tubulointerstitial injury. Specific renal pathological changes include renal arteriosclerosis, glomerular hypertension, glomerulosclerosis, interstitial lesions, and acute renal injury. Besides, kidney damage caused by HUS is often associated with HTN and insulin resistance (IR) [14-15].

Febuxostat a nonpurine xanthine oxidase inhibitor (XOI), a UA lowering agent widely used in controlling and the management of HUS, multiple studies shown that febuxostat compared to allopurinol the most commonly used SUA lowering agent, has no inferiority in reducing SUA [16]. Based on the CARES trial results, which conducted over 6000 patients to evaluate the CV safety of febuxostat compared with allopurinol [17]. The results showed no differences between the two drugs on the CV events but slightly elevated the risk of CV mortality in the febuxostat group. Recently clinical studies have shown that early management of HUS in patients with CKD has a good impact on regulating BP and delaying renal function decline [18].
Febuxostat was first discovered by scientists at the Japanese pharmaceutical company Teijin in 1998. In November 2017, the food and drug administration (FDA) released a warning alert regarding febuxostat and CV safety which showed an increased risk of cardiac-related death associated with the use of febuxostat [19]. And recently another warning by the FDA was released in 2019 of prescribing urate-lowering agent febuxostat [20].

1. Uric acid metabolism

In consideration that HUS could be a CVD risk factor, we should be aware of the metabolisms and the mechanisms of SUA productivity. The fundamental processes that take part in the production of UA might give us a clue about this association between UA and CVD [21].

UA is the final product of purine nucleotides metabolism. The disturbance of purine metabolism or the abnormal excretion of UA in the kidney can affect the level of UA in the blood. According to Alegria-Diaz, A., et al the normal range of plasma UA in male is between 237.9 nmol/l and 356.9 nmol/l, equivalent to 4-6 mg/dl and in female 178.4uml/l and 297.4 UML/l which equivalent 3-5 mg/dl respectively [22]. An interesting finding was that UA has antioxidants, enhancing immunity, maintaining BP, and other functions [23]. As a result, SUA levels in human beings are much higher than in other mammals. Uricase an enzyme that helps to demote UA into allantoin, due to its presence UA leans towards aggregate at the baseline components of DNA and RNA, adenine and guanine are the purines with purine skeletons. However, if the level of UA is too high, it may induce gout, HTN, and other diseases. So the role of UA in the body is contradictory. UA is the product of
xanthine metabolized by xanthine oxidoreductase. Xanthine dehydrogenase (XDH) and xanthine oxidase (XO) are two inter-convertible forms of xanthine oxidoreductase [24].

Xanthine could be degraded into UA and superoxide anion by XO which may have the effect of raising intracellular superoxide anion, leading to cell envelope damage and enhancing mutagenesis [25]. XDH in the form of most XOR in vivo which generates the reduced form of nicotinamide adenine dinucleotide NAD. Xanthine oxidoreductase could be transformed into xanthine oxidase when it is in a hypoxic environment [26] (Figure 1). Moreover, the excessive production of initial reactive oxygen species (ROS) caused by various stimuli may activate XO, which remains the main source of ROS. As an experimental study shows, the initial production of mitochondrial ROS activates XO in cultured human primary glomerular endothelial cells under high glucose concentration. Compared with the allopurinol group, XO is the major source of ROS and leads to endothelial dysfunction and activation [27]. Therefore, UA has the dual role of antioxidant and oxidant depending on the environment where it is in. The process of UA production in patients can in turn, promote the progress of CKD.

Figure. 1 Uric acid metabolism
XO xanthine oxidase, XDH xanthine dehydrogenase, NAD nicotinamide-adenine dinucleotide, 

$O^2_\text{-superoxid}$

As we all know the majority of energy in the human body comes from the adenosine triphosphate (ATP) structure, which centers on the adenine, which moves through multiple converting processes into hypoxanthine, xanthine, and finally, it converts into its last product the UA with the activation of XO and the production of reactive oxygen during metabolism. This reactive oxygen tends to bind with nitric oxide (NO), a vasodilator substance, and inhibits its function, and it is considered one of the factors in the development of a serious CV injury known as arteriosclerosis. During the metabolism of fructose, a large amount of ATP is consumed resulting in an increased amount of UA. Recent increases in the rates of HTN and CVD are mainly caused by the elevated intake of sugars including fructose [28]. Ross EA and Perloff JK found out that in pathological conditions such as heart failure (HF), due to oxygen shortage tends to increase the levels of serum lactic acid an aggravated anaerobic metabolism in tissues occurs. This increases the lactic acid level then intensifies the reabsorption of UA in the kidney, which leads to an increase in the SUA level [29]. SUA levels are also influenced by excretion from the kidney and digestive tract, increased SUA level due to the aggravated production of UA could be a marker of systemic circulatory failure. Medications such as XO inhibitors i.e., allopurinol and febuxostat are effective for the treatment of HUS due to aggravated UA production [30].

1.1. Research on urate transporters

Around 60% of UA is biosynthesized in the body and metabolized through the kidney, so the kidney is the main organ of UA excretion, according to Maiuolo, J, et al, an abnormal secretion or reabsorption of UA considered pathogenesis of HUS [31]. The regulation of the
SUA level is mainly through glomerular filtration, renal tubule secretion, and reabsorption [32]. About 90% of the kidney's filtered UA is reabsorbed by proximal tubules, a process regulated by specific transporters. Several transporters have been confirmed to be involved in the renal proximal tubule transport of UA. Proteins that have been identified currently consist of the glucose transport protein 9 (GLUT9), organic anion transporter (OAT), and urate anion transporter 1 (URAT1) [33]. In 2002, Enomoto and Endon first discovered the SLC22A12 gene encoding URAT1 a new member of the OATs family, which has a unique substrate specificity compared to other OATs [34]. URAT1 is an anion-exchanging uptake transporter localized to the apical membrane of renal proximal tubular cells is one of the organic anion transporters [35-36]. Where it mediates the process of reabsorption of UA from the proximal tubule thereby playing a key role in UA homeostasis, the proximal tubules are responsible for re-absorbing 85% of filtered UA; therefore the UA transports play an important role in the metabolic of UA [37-38-39]. URAT1 was expressed only at the apical brush edge of renal tubular epithelial cells. The driving force for the transport of UA by URAT1 is formed by the exchange of anions in the cell and UA in the lumen. The accumulated anions in the cells were exchanged with the UA located in the cavity under the action of URAT1 affinity, and this electrochemical gradient made the UA complete the reabsorption process. The anions which enter the lumen then pass through the glomerular filtration through the lumen membrane and enter the perivascular capillaries under the OATs of the basolateral membrane to complete the cell metabolism [40-41]. Therefore, when the drug with an affinity to URAT1 acts on the lumen, it can promote the excretion of UA. On the contrary, when used in cells, UA reabsorption is promoted and UA excretion is inhibited, thereby regulating the level of UA in blood. Unlike
other ion transporters, URAT1 has a specific substrate selectivity, which has become a new target for regulating the reabsorption of UA and maybe a new approach to the treatment of HUS in the future.

Circulating UA is necessary to protect against oxidative damage, on the other hand, excess SUA results in CVD. UA handling by the kidney is complex. In simple terms, UA is firstly eliminated into the proximal tubule by glomerular filtration and/or by the active uptake via OAT1 and its eliminated from the proximal cell by the urate channel possibly SLC17A3 then it is reabsorbed from the proximal tubule into the cell by URAT1 and possibly OAT4. Reabsorbed UA is then returned to the blood via another transporter, GLUT9 SLC2A9. The accumulated anions in the cells were exchanged with the UA located in the cavity under the action of URAT1 affinity, and this electrochemical gradient made the UA complete the reabsorption process.[42-43] Therefore when the drug with affinity to URAT1 interacts with the lumen it can promote the excretion of UA.

Several factors are involved in the process of secretion and production of UA, medications have a huge impact on changing the UA levels and like many other factors it complicates the process of identifying and the fluctuations of SUA levels, to come to an agreement regarding of whether the increase of UA over production or under-excretion, UA and other creatinine clearance tests can be used for diagnostic reasons for the underlying disease.

2. Effects of uric acid on incident CKD and risk factors for CKD

Increased levels of UA may cause gout, HTN, CVD, kidney diseases, etc., while decreased levels of UA are associated with neurodegenerative diseases such as multiple sclerosis, Parkinson’s disease, and optic neuritis [44]. At the same time, the concentration of UA as lowered, the ability to clear a large amount of oxygen free radicals generated by exercise is
declined, which also cause damage to renal function. Traditionally, renal diseases caused by HUS include acute and chronic UA nephropathy and kidney stones. However, many evidences show that HUS itself may be associated with the progress of CKD and risk factors for CKD such as HTN and IR [45].

2.1. Hyperuricemia and hypertension

In recent years, studies supporting the close relationship between HUS and CV events such as HTN have increased significantly. A prospective cohort study by Sundstrom [46] found that UA increased by 1 standard deviation, the risk of HTN was 1.17, and the risk of BP progression was 1.11. Mellen's over 9 years follow-up also showed that SUA level was positively correlated with HTN [47]. The mechanism was considered to be associated with RAS activation, inflammatory reaction, oxidative stress, vascular smooth muscle cell VSMC proliferation and IR.

2.1.1. Activation of RAS by uric acid:

The study of animal models by Mazzali suggests that the activation of RAS mediated by HUS is closely related to the pathogenesis of HTN [48]. Recent clinical studies by Doehner and others have also shown that HUS ultimately leads to HTN by activating the RAS. The ONATA study [49] indicates that SUA levels are negatively correlated with insulin sensitivity. HUS is often accompanied by IR, which also causes hyperactivity of the renin-angiotensin-aldosterone system, leading to hyperactivity of the sympathetic nervous system which eventually leads to sodium retention, increased blood volume, and high blood pressure.

2.1.2. Inflammation and oxidative stress induced by uric acid:

It has been proved that HUS is accompanied by an increase in the level of serum high-sensitivity C-reactive protein hsCRP [50], which is an important marker of inflammation.
The increase in the level of serum hsCRP highly suggests that HUS is closely related to inflammation and oxidative stress. Soluble urate can participate in vascular inflammation and oxidative stress reaction by increasing low-density lipoprotein oxidation and lipid peroxidation as well as increasing hsCRP. CRP can mediate vascular endothelial necrosis by activating the complement system, inducing macrophage and other inflammatory cells to enter the vascular endothelium, leading to vascular endothelial injury which ultimately promotes the formation and development of HTN [51].

2.1.3. **Effect of uric acid on the biological behavior of VSMC:**

Johnson RJ's research shows that although VSMCs do not express UA receptors, their expression of the organic anion transporter URAT1 can take up UA [52]. Urate can enter into smooth muscle cells via UA transport channel protein; it will activate specific mitogen-activated protein kinase MAPK and induce cyclooxygenase 2 COX-2 expressions [53]. And then, they will further stimulate the formation of local thrombus, upregulate the expression of platelet-derived growth factor PDGF, the final result in the stimulation of VSMC proliferation and migration [54]. The influence of HUS on VSMC biological behavior can lead to vascular remodeling. It plays an important role in the onset, progression, and intervention of HTN.

2.2. **Hyperuricemia and insulin resistance (IR)**

IR is not only the main cause of type 2 diabetes, but also one of the important risk factors for HTN, dyslipidemia, and coronary heart disease [55]. HUS in patients may be involved in the development of IR. A study of 7483 non-diabetic patients showed that after adjusting the levels of hyperlipidemia, HTN, obesity and blood sugar, the level of SUA is positively correlated with hyperinsulinemia and IR index. IR rat model experiments showed that IR
rats increased the reabsorption of urate by up-regulation of the expression of URAT1 gene in the renal cortex, and reduced the secretion of urate by downregulating the expression of urate transporter gene. The treatment of rosiglitazone can improve both two conditions [56]. The possible mechanism is those elevated SUA can directly damage pancreatic β-cells, resulting in decreased insulin synthesis, reduced receptor sensitivity, and IR, which in turn increases insulin compensatory secretion. Insulin stimulates the synthesis and secretion of endothelin in aortic endothelial cells [57]. ET is the most potent vasoconstrictor currently known, which can increase peripheral vascular resistance, promote renal tubular reabsorption of water and sodium, and promote smooth muscle and myocardium proliferation, causing CV remodeling, leading to elevated BP.

2.3. Hyperuricemia and CKD progression

Many epidemiologic studies have suggested the role of HUS on increased mortality and renal disease, but the data published on CKD is limited. HUS is highly prevalent in CKD which may account for the decrease UA excretion when the renal function declines. CKD in recent years becomes a global public health problem because of its high prevalence and the accompanying increase in the risk of ESRD. Emerging evidence suggests a pathogenic role of HUS in the development and the progression of CKD [58]. According to previous studies, it has been proved that HUS if left untreated it considered a risk factor for the onset of CKD [59-60].

The prevalence of HUS in CKD patients in China is 36.6% to 50%, and the prevalence of HUS is significantly higher with the development of CKD [61-62]. CKD patients when advanced to stage 4-5, the initiation of dialysis will be required, but on the other hand, it will gradually raise the risk of death. In recent years, researchers have found that HUS has
been actively involved in renal dysfunction [63]. A followed up 177570 patients with nephropathy database system in the United States for 25 years. Chonchol, M found that the risk of CKD in patients with the highest UA level was 2.14 times higher than the normal [64]. The mechanism by which the HUS develops CKD is induced by renal inflammation, endothelial dysfunction, and activation of the renin-angiotensin system [65], and several epidemiological studies have linked HUS with the increased risk of CKD. In a simple explanation, HUS would stimulate the rennin-angiotensin system and inhibit the release of endothelial nitric oxide in which renal vasoconstriction will be developed and therefore increasing the BP at the same time the high level of UA will have the pathogenetic role in stimulate inflammation and will cause progression in renal disease [66-67].

Urate which is deposited in the renal tubules and renal interstitium can reduce the expression of NOS in the kidney. Nitric oxide NO plays an important role in regulating the relaxation activity of vascular endothelial cells, maintaining the constant renal vascular tension, regulating renal tissue blood flow, renin secretion, tubuloglomerular feedback, and so on [68]. NOS was inhibited by HUS, endothelial cells can upregulate the angiotensin-converting enzyme activity [69], increasing the production of angiotensin II, and superoxide anions, triggering vasoconstriction, leading to significant and persistent HTN. UA also directly acts on endothelial cells, resulting in a decrease in NO level, which affects the proliferation of VSMC, extracellular matrix deposition, macrophage adhesion and migration of mediation, leading to resistance arteries, arterial remodeling. Eventually resulting in renal dysfunction and renal fibrosis (Figure 2).
Figure 2 Hypothetic mechanisms of renal damage caused by hyperuricemia

NOS nitric oxide synthase, RAS renin angiotensin system, COX-2 cyclooxygenase 2, VSMC vascular smooth muscle cell, EMT epithelial-to-mesenchymal transition

In multiple recent studies suggested that treating HUS may delay or prevent the onset of CKD. Feig et al conducted a randomized double-blinded study [70]. The study found out that treating HUS in adolescents with newly diagnosed HTN was effective at controlling BP. However, there is no evidence to treat CKD with asymptomatic HUS in patients with HTN. Although animal experiments suggest that UA has non-crystalline and crystal deposition damage to the kidney, there is not enough evidence in the human body. The results of observational studies are different, and there is also a lack of large-scale RCT to confirm the benefits of lowering UA. The FEATHER trial (febuxostat vs. placebo randomized controlled trial regarding reduced renal function in patients with HUS
complicated by CKD stage 3) showed no positive results for CKD stage 3 patients with asymptomatic HUS compared with placebo, but only in a small number of subgroups without proteinuria and low serum creatinine SCR [71]. Nonetheless, most studies suggested that lowering UA therapy can delay the progression of CKD. A single-center double-blind, randomized, parallel placebo-controlled study indicates that compared with placebo, lowering UA can slow down the decline of glomerular filtration rate GFR in patients with CKD stages 3 and 4 [72]. Siu randomly divided 54 patients with CKD and HUS into two groups. The experimental group was treated with allopurinol to reduce SUA levels. After a 1-year follow-up, 4 of the 26 patients in the treatment group had renal function deterioration, while the proportion of renal function deterioration in the control group was up to 46.1% [73]. Although the results of the two groups did not have a statistical difference, the decrease of SCR levels in the treatment group was more obvious than that in the control group. In another small scale study concerning the urate-lowering agents in patients complicated with CKD and HUS, they concluded that ULT decreases the inflammation and slow the progression of renal disease in patients moderated with CKD [74]. These studies suggest that lowering UA levels may improve renal function. The clinical trials of UA-lowering therapy are listed in Table 1. The question raised in these studies is whether the benefit of urate-lowering is caused by the reduction in UA itself or by inhibition of XO. Results of two trials indicate that both benzbromarone and febuxostat could reduce the risk of CKD progression and lower SUA levels in CKD patients [75-76]. We suspect that the benefit of urate-lowering therapy mainly comes from the reduction in UA itself, but inhibition of XO maybe amplify its effect and it needs to be evaluated by credible experimental studies.
Although in recent years there has been much evidence supporting HUS as a true risk factor of CKD, there is still no agreement as to whether treating asymptomatic HUS individuals with UA-lowering therapy will offer more renal protection. Large trials are needed for more information regarding this issue.

- **Hyperuricemia and cardiovascular diseases**

  CVD are complex criteria of diseases and have multiple causative ways, of which HUS could be considered an additional component cause. Many studies reported on the relationship between HUS and CVD. This relationship was established since the early 1900s. Elevated SUA has been linked to increase the risk for development of HTN and CVD [77]. According to these studies, the levels of SUA are a common finding in patients with high BP, obesity, and IR. Higher levels of HUS are strongly associated with a wide variety of macrovascular and microvascular diseases, in recent study 15773 participants; NHANES revealed that the mortality and the cardiac mortality gradually increased by increasing the levels of SUA [78].

  Questions and debate regarding the UA whether it’s an independent predictor of CVD arose from early times. Later it was proven that HUS appears to be an independent risk factor for incident HTN, CVD. Many epidemiologic studies confirm the association between HUS and CVD it has been addressed in numerous prospective studies [79]. Multiple studies confirmed that it was more accurate to regard HUS as a consequence of the existence of previously related CV risk factors [80]. A previous study that targeted and analyzed patients with HTN showed that when the level of SUA exceeded 7.5 and 6.2 mg/dl in male and female respectively the CVD risk was significantly increased.
UA raises BP through endothelial cells, and vascular smooth muscle cells [81]. HUS would contribute to renal vasoconstrictions and elevate the BP levels by stimulating the renin-angiotensin system and inhibit the process of releasing endothelial NO [82]. A previous study that targeted and analyzed patients with HTN showed that, when the level of SUA exceeded 7.5 mg/dl and 6.2 mg/dl in male and female respectively, the CVD risk was significantly increased [83]. A sub-study, by Alderman MH, he showed that a 1 mg/dl increase in SUA level can be a potential in increasing the cholesterol levels by 20 mg/dl and elevate the systolic BP by 10 mmHg [84]. More common findings were reported by the PIUMA study, When the SUA exceeded 6.2 and 4.6 mg/dl in males and females respectively, the CVD onset was significantly increased [85]. The NHANES III study findings were similar as well, it showed that CVD onset was significantly increased when the SUA level elevated and passed 6.0 mg/dl in both genders [86].

A large number of observational studies revealed an increase in the risk of HTN with the increase of the UA levels and this link is an independent risk factor. In other studies, other CVD than HTN, a 3 years cohort study the J-CAD, were conducted in Japan, targeting patients with coronary artery disease. The 3 years’ study findings were similar to NHANES III findings as an increasing the onset of CVD events but included death when the SUA surpassed 6.8 mg/dl [87]. SUA is also linked to being associated with the incidence of atrial fibrillation [88-89] coronary artery disease [90] and heart failure (HF) mortality [91]. Finally, patients suffering from HF, the morbidity and mortality of both acute and chronic heart failure patients can significantly be predicted when the SUA levels are elevated [92].

The current evidence and studies were able to demonstrate that around 40% HF patients experience an increase in the levels of SUA; which previously liked this due to pro-
inflammatory HF and beside oxidant stress, which might decline and worsen the clinical symptoms. Furthermore, there been a percentage of HF patients with HUS significantly reported having renal function decline. Most of these trials suggested that UA and CV effects are due to its intracellular effects [93]. Taking that into consideration, viable conclusions concerning that relationship are that: using xanthine oxidase inhibitors for treatment might be most potent in lowering the intracellular UA due to the fact that these agents will block intracellular production accompanied by decreasing in the extracellular levels. In addition to that is febuxostat a non-purine xanthine oxidase inhibitor previously confirmed to be potent in reducing the levels of SUA in patients suffering from HUS [94]. However, it has the potential and risk of developing CVD.

The sex difference in SUA and its association has been reported in multiple studies previously [95-96], it has been reported that women in their premenopausal age tend to have a lower SUA than men, probably due to the uricosuric effects of estrogens [97]. And this tends to increase during the postmenopausal age; this has been linked to the influence of sexual hormones [98]. The sex difference has led to different metabolic syndromes such as CVD, cancer, and so on [97].

Previous studies have analyzed the association between SUA and CV events under the consideration of gender differences of SUA. Some studies regardless of sex pointed out that the SUA level is an independent risk factor for CV mortality [99-100]. And some other studies confirmed a difference between men and women [101-102]. So the association between SUA and the mortality of CV according to sex factor is still a huge argument. Niskanen, et al reported that the level of SUA is a strong predictor for CV mortality in middle-aged men [103].
In a recent retrospective observational study [104], in Gunma, Japan they studied 12,029 participants to evaluate the association of UA with the risk of HTN among different age and different sex, the results of that study showed that older men had lower UA, whereas older women had higher UA, compared to young age participants. They found out that men participants under ≤50 years of age had a significant association of UA with the incidence of HTN, while above ≥50 years old of age participants did not have any association. On the other hand women, participants over ≥40 years of age had a significant association between UA and HTN whereas under ≤40 years old did not show any significant association. Their data suggest that UA level is an independent indicator for HTN among middle-aged men under ≤50 years of age and in older women above ≥40 years of age.

In another recent observational study [105], were done to assess the sex-specific association of SUA with all-cause mortality in 40 years old patients, the study conducted 27,490 participants, the study results showed that a lower SUA was an independent risk factor for all-cause mortality in men than women, also they found out that the SUA levels were lower in women than in men. As the participant’s age increased, SUA in women increased significantly and declined in men, this was also proven by previous studies [106-107].

> **Conclusion**

HUS is clinically significant in the role of CKD, Many studies have suggested that UA itself may harm patients with CKD by increasing inflammation and the progression of CKD, high SUA may cause kidney damage not only through a crystal dependent pathway, but also through a non-crystal dependent mechanism such as inflammation, oxidative stress, and hemodynamic. Most clinical studies suggest that early treatment of HUS is beneficial to the
control of CKD, HTN, and other chronic diseases. As a nontraditional risk factor to CKD, the close association between HUS and CKD needs more intensive inquiry. HUS and the prevention of CKD progression and more importantly the CV events is a promising topic and large studies are expected in the near future. A preexisting CVD in patients complicated with HUS and CKD needs appropriate attention, the levels of SUA in patients at high risk for developing CVD needs to be tracked and investigated for any signs. Diet, poly-pharmacy, and lifestyle issues are very important aspects to discuss with patients especially in countries where medications can be bought without any prescription since UA can be altered by many medications; special attention should be given to specific contraindications to certain drugs. Febuxostat is a drug choice for the treatment of patients with HUS and it proved its effectiveness in preventing the progression of CKD but we should pay close attention to its adverse reaction on the CV system. Although several studies focused on UA and CVD have been recently reported, future large-scale studies are expected.

- **Acknowledgments**

  We are grateful to Prof. Sun Dong our director of the postgraduate course, at the Xuzhou medical university, Xuzhou Medical Affiliated Hospital, department of nephrology for sharing his knowledge and guiding and caring, and our second commendations go to our dear colleagues and the staff of our department with their great support and assistance.

  This study was supported by funding from a project of Jiangsu Provincial Post Graduate Innovation Plan (SJCX17_0560).

- **Conflicts of Interest**

  The authors declare that there are no conflicts of interest.
### Table 1. Randomized controlled trials of uric acid-lowering therapy on renal function

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>At risk (n)</th>
<th>Uric acid-lowering therapy</th>
<th>Finding on kidney function</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siu</td>
<td>2006</td>
<td>SCr 1.35-4.50 mg/dL (n = 54)</td>
<td>12 months of allopurinol</td>
<td>Slowed progression of CKD</td>
<td>Limited by the concomitant use of antihypertensive drugs.</td>
</tr>
<tr>
<td>Kanbay</td>
<td>2007</td>
<td>eGFR &gt;60 mL/min (n = 69)</td>
<td>3 months of allopurinol</td>
<td>Increased eGFR from 79 to 92 mL/min</td>
<td>Small sample size and relatively short follow-up.</td>
</tr>
<tr>
<td>Goicoeceha</td>
<td>2010</td>
<td>CKD 3 (n = 113)</td>
<td>24 months of allopurinol</td>
<td>Slowed decline in eGFR</td>
<td>Not designed in a double-blinded fashion, all patients were advised about the dietary composition, concomitant use of statins, antiplatelet, and RAAS blocker drugs.</td>
</tr>
<tr>
<td>Momeni</td>
<td>2010</td>
<td>T2DM (SCr &lt;3.0 mg/dL) (n = 40)</td>
<td>4 months of allopurinol</td>
<td>Reduced proteinuria</td>
<td>Small sample size and relatively short follow-up.</td>
</tr>
<tr>
<td>Pai</td>
<td>2013</td>
<td>CKD 3, 4 (n = 183)</td>
<td>2 years of allopurinol</td>
<td>Reduced blood pressure and progression of CKD</td>
<td>Not designed in a randomized control, double-blinded fashion. Limited by the concomitant use of statins, antiplatelet and RAAS blocker drugs.</td>
</tr>
<tr>
<td>Sezer</td>
<td>2014</td>
<td>CKD (n = 96)</td>
<td>6 months of allopurinol</td>
<td>Decrease in GFR in control patients</td>
<td>Patients were advised about the dietary composition of their food. Small sample size and short duration of follow-up, a relatively homogeneous population. Single tertiary medical center, differential prescription practices for urate-lowering agents, insufficient to yield statistically reliable information.</td>
</tr>
<tr>
<td>Sircar</td>
<td>2015</td>
<td>CKD 3, 4 (n = 93)</td>
<td>6 months of febuxostat</td>
<td>Slowed the decline in eGFR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment with either allopurinol, febuxostat, or benzbromarone</td>
<td>Lower risk of ESRD with febuxostat or benzbromarone</td>
<td></td>
</tr>
<tr>
<td>Chou</td>
<td>2017</td>
<td>CKD (n = 874)</td>
<td>6 months of febuxostat</td>
<td>Maintain renal function</td>
<td>Open-labeled, small sample size and relatively short follow-up.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>eGFR 20-60 mL/min (n = 66)</td>
<td></td>
<td></td>
<td>GFR was estimated rather than measured, and patients with stages 4 and 5 CKD were excluded. Small sample size, few female patients, and short duration of follow-up.</td>
</tr>
<tr>
<td>Yu</td>
<td>2018</td>
<td>CKD 3 (n = 467)</td>
<td>108 weeks of febuxostat</td>
<td>NO decline in kidney function</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu</td>
<td>2019</td>
<td>CKD 3-5 (n = 208)</td>
<td>6 months of febuxostat or allopurinol</td>
<td>Slowed progression of renal function</td>
<td></td>
</tr>
</tbody>
</table>

SCr serum creatinine, CKD chronic kidney disease, eGFR estimated glomerular filtration rate, ESRD end-stage renal disease, RAAS renin-angiotensin-aldosterone system, GFR glomerular filtration rate
References:


[14]. Ilundain-Gonzalez, A.I.; Gimeno-Orna, J.A.; Saenz-Abad, D.; Pons-Dolset, J.; Cebollada-Del Hoyo,


[27] Eleftheriadis, T.; Pissas, G.; Antoniadi, G.; Liakopoulos, V.; Stefanidis, I. Allopurinol protects human glomerular endothelial cells from high glucose-induced reactive oxygen species generation,


Kirca, M.; Oguz, N.; Cetin, A.; Uzuner, F.; Yesilkaya, A. Uric acid stimulates proliferative pathways in vascular smooth muscle cells through the activation of p38 MAPK, p44/42 MAPK and PDGFRbeta.


[93]. Schlesinger N. Management of acute and chronic gouty arthritis: present state-of-the-art. Drugs 2004;64:2399-2416


