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# Uric Acid and Atherosclerosis in Patients with Chronic Kidney Disease: Recent Progress, Mechanisms, and Prospect

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**Keywords**
Chronic kidney disease · Atherosclerosis · Uric acid

**Abstract**
***Background:*** Chronic kidney disease (CKD) is a prevalent global health concern, significantly linked to increased cardiovascular morbidity and mortality. Among various risk factors, uric acid (UA) has emerged as a potentially modifiable contributor to cardiovascular complications in CKD patients. ***Summary:*** Elevated serum uric acid levels frequently occur in individuals with CKD and are associated with the development of atherosclerosis (AS). Uric acid has been demonstrated to exacerbate inflammatory processes, promote oxidative stress, and cause endothelial dysfunction, which are critical factors that drive the formation of atherosclerotic plaques. Furthermore, high uric acid levels can worsen renal function, establishing a detrimental cycle that amplifies cardiovascular risk. ***Key Messages:*** This review investigates the complex interconnection between UA and AS in patients with CKD, highlighting the underlying mechanisms and therapeutic considerations. A more profound comprehension of this relationship is essential for enhancing cardiovascular health and outcomes in this vulnerable population.



## Introduction

Uric acid (UA), which functions as an important accelerator in the evolution of the human stress response, intelligence, and upright walking [1], is now mainly considered as an antioxidant. However, the overaccumulation of UA can lead to serious consequences [2], such as chronic kidney disease (CKD), diabetes mellitus (DM), coronary heart disease, hypertension, and stroke. Elevated UA level coincides with CKD progression. Meanwhile, poor kidney function will also result in hyperuricemia.

As a leading cause of death and disability worldwide, atherosclerosis (AS) can supervene with many other common diseases and aggravate the risk of them. In previous studies [3–6], there is strong evidence of a link between higher UA level and AS progression. Furthermore, the risk of premature death in CKD patients mainly comes from cardiovascular diseases, which obviously includes AS. Life quality of CKD patients also decreases as the GFR declines [7]. Given the concern about the rising prevalence and incidence of CKD, it is necessary to investigate the relationship between UA levels and AS in patients with CKD. In this review, we will discuss recent progress, mechanisms, prospect of UA level, and AS in patients with CKD, to guide prevention, diagnosis, and long-term treatment.

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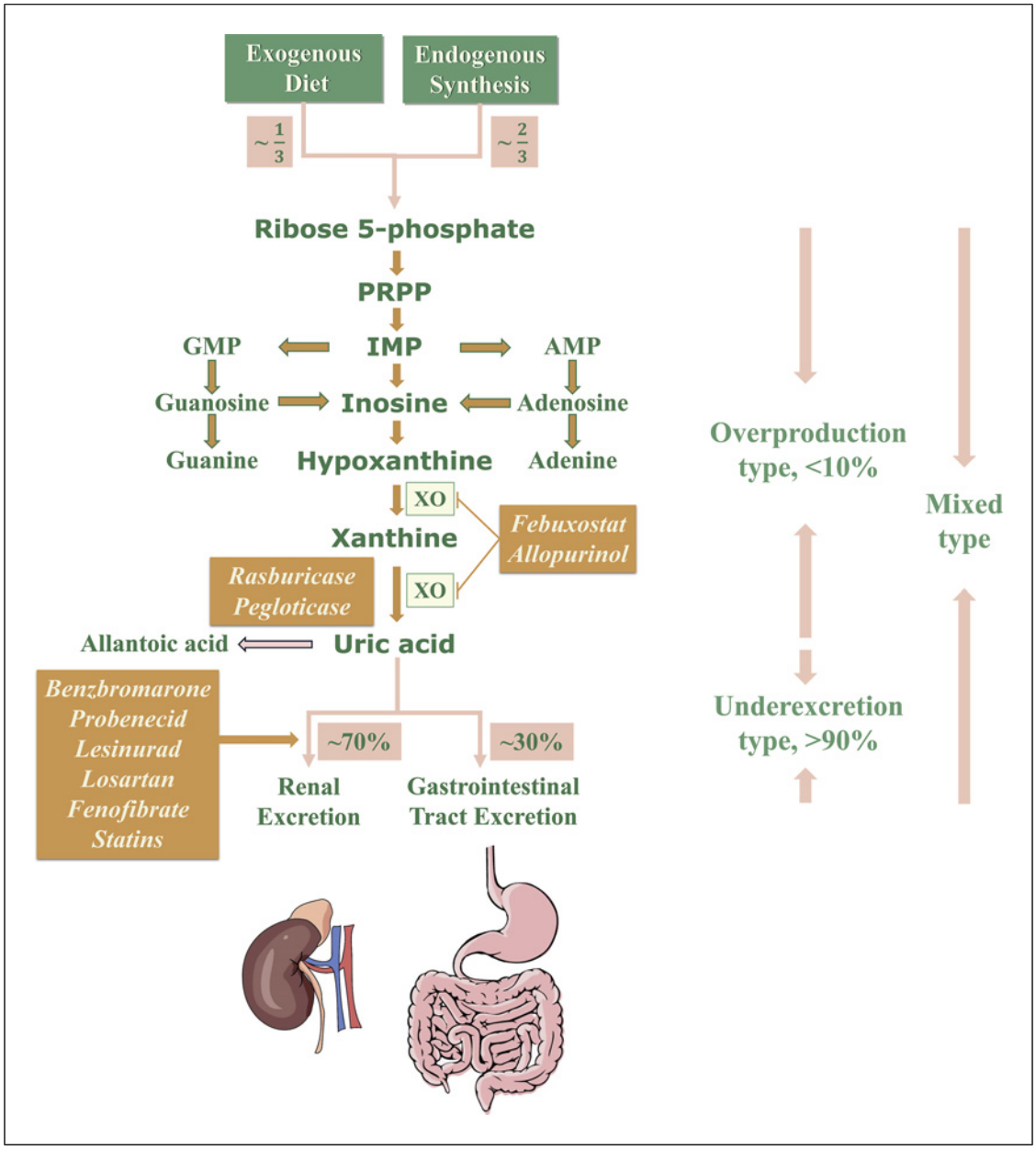


**Fig. 1.** UA metabolism. 5-Phosphoribosyl 1-pyrophosphate (PRPP) can be transformed into inosine monophosphate (IMP). IMP, adenosine monophosphate (AMP), and guanosine monophosphate (GMP) can be transformed into each other. XO is the enzyme that catalyzes the oxidation of hypoxanthine to xanthine, and xanthine to UA. It is inhibited by allopurinol and febuxostat. The gene for uricase has been inactivated in humans. Rasburicase and pegloticase can restart the process, transforming UA into allantoic acid, a more soluble form.

### Uric Acid Metabolism in CKD Patients

UA is the final product of purine metabolism in human body. Figure 1 shows the metabolic pathway of UA. There are two sources of UA: 1/3 from the exogenous diet and 2/3 from the endogenous synthesis. UA is produced primarily in the liver, with a portion coming from the small intestine. Purine metabolism occurs mainly in the liver, and xanthine oxidase (XO) encoded by the xanthine oxidoreductase (XOR) gene is the key rate-limiting enzyme in this process. Hypoxanthine produced by purine metabolism can be sequentially oxidized by XO to form xanthine and

UA. In mammals, uricase is present in the liver, which further breaks down UA into more soluble allantoic acid for excretion. In all, 70% of the UA synthesized by the body is reabsorbed and excreted by the renal tubules after glomerular filtration, and the remaining 30% is excreted from the gastrointestinal tract (shown in Fig. 1).

UA homeostasis is composed of the interaction and balance of routine intake, de novo synthesis, recycling, degradation of XO, and excretion of kidney and gastrointestinal tract. Once the balance is disturbed, hyperuricemia will probably follow. When UA concentration exceeds 380 μmol/L, the risk of UA crystallization and precipitation rises [8]. Hyperuricemia can be divided into 3 types based on different pathogeneses: overproduction type, underexcretion type, and mixed type (shown in Fig. 1). More than 90% hyperuricemia patients belong to the underexcretion type, suffering from renal insufficiency [9, 10]. Diseases, drugs, and hereditary factors can lead to decreased renal excretion of UA, resulting in hyperuricemia.

Glomerular filtration or tubular secretion dysfunction may be present in approximately 90% of patients with hyperuricemia and gout [11]. In CKD patients, damage to the renal vascular endothelium, tissue ischemia, and hypoxia, resulting in increased expression of hypoxanthine and purine oxidase, causing increased production of UA. Elevated lactate level decreases UA excretion. Decreasing glomerular filtration rate and impaired tubular function lead to hyperuricemia because of abnormal UA filtration, reabsorption, and secretion. Diuretics, which reduce blood volume, lead to hyperuricemia by increasing the net reabsorption of UA.

Epidemiological evidence suggests that renal underexcretion is the main cause of hyperuricemia [12]. Disruption of UA homeostasis leads to fluctuations in UA levels, making it more likely to cause hyperuricemia. When mounting evidence shows that hyperuricemia is one of the independent risk factors for CKD, cardiovascular disease, and DM, it is urgently necessary to address the importance of UA homeostasis.

In recent studies, hyperuricemia is noted as a key risk factor associated with AS. Among patients with CKD, the increased risk of premature mortality mainly comes from AS. Considering the worldwide high occurrence and mortality of AS and CKD, more attention should be paid to maintaining UA homeostasis, especially in CKD patients.

### Relationship and Recent Progress between Uric Acid and Atherosclerosis in CKD Patients

As mentioned above, more than 90% of patients with hyperuricemia have kidney problems. The reason may lie in some harmful physiological effects of UA, including but not limited to oxidative stress, adipose inflammation, vascular smooth muscle cell (VSMC) proliferation, inhibition of nitric oxide (NO) production, and endothelial dysfunction [13–17]. Despite the direct pathophysiological mechanism, hyperuricemia can also worsen hypertension and DM [18, 19], which are well-known correlation factors of CKD and AS. Besides, CKD will decrease the excretion of UA, and its connection with hyperuricemia is complicated and intimate. There is a significant overlap in population affected by the two diseases. Approximately half of patients with CKD developed hyperuricemia when they started dialysis [20]. The prognosis is highly correlated with the existence of AS in CKD patients. Considering the strong correlation between the UA level and AS, the findings in this network seem to matter.

The prevalence of cardiovascular morbidity and mortality is higher in patients with CKD, especially those with end-stage renal disease, than in the general population. Numerous factors are believed to contribute to an acceleration of the atherogenic process in patients with CKD. In addition to the frequent presence of traditional factors for AS (such as age, smoking, and dyslipidemia), the effects of uremia-specific factors need to be considered. For example, studies in past 10 years have shown that a direct association can be found between serum cholesterol level and AS-related mortality in general population. However, 2 randomized controlled trials in patients on hemodialysis failed to show a significant improvement in AS outcomes, although serum cholesterol levels have been effectively reduced by statins [21, 22]. This suggests that the same risk factor may have different or even opposite effects in different populations. It should be noted that asymptomatic AS was made apparent by the progress of CKD, through increasing number of plaques. Despite the large number of clinical studies between the two populations, specific differences in AS and UA between the populations remain elusive because of the number of confounding factors.

UA-lowering therapy is a conventional treatment [23] for hyperuricemia in patients with or without CKD, and many studies [24, 25] have shown improvements in slowing of CKD progression and reduced risks of cardiovascular events [26] after the therapy. A cohort study noted that the extent of coronary artery calcification was proportional to the concentration of circulating UA. According to many studies, elevated serum UA levels are a traditional predictor for the presence and progression of AS [27–31]. UA-lowering therapy can delay AS progression [32, 33].

In patients with CKD, many clinical trials [34–36] reported that the use of allopurinol can significantly lower

the risk and mortality of AS in patients with CKD. 3 clinical trials evaluated the effect of reducing serum UA level of CKD patients and found a 60% reduction in cardiovascular events compared with the control group [35–37]. In a large-scale cohort study conducted in Kailuan that included 27,707 patients with CKD, Li found that a higher concentration of UA was associated with a higher risk of myocardial infarction, heart failure, and all-cause mortality among individuals with CKD, following a dose-response manner [38].

Some specialists found that UA-lowering therapy hits the target not by reaching a proper UA concentration [32], but by a great reduction in serum UA levels [33]. That suggests that a change of UA level may be more important than a simple concentration of serum UA in AS management. Nonetheless, scientists [6, 34, 39–42] have failed to reach an agreement on whether there are exact benefits brought to patients with CKD directly by a reduction in serum UA level through small or large trials of various qualities. Most Western specialists do not recommend treating asymptomatic hyperuricemia in patients with CKD, whereas Asian experts in China, Japan, and Korea recommend active treatment [43].

Serum UA level in early CKD patients can be used to estimate the ischemic heart disease occurrence, even in stages earlier than G3a [44]. In moderate CKD stage, AS also got an increased prevalence [45–47], which is closely related to high serum UA levels [48]. The serum UA level in patients with CKD may take part in various pathways that lead to AS [49, 50].

## Potential Mechanisms Linking Uric Acid to Atherosclerosis in CKD Patients

### *Oxidative Stress*

UA plays a major physiological role in extracellular antioxidation and intracellular net pro-oxidation. Under physiological conditions, UA is an important antioxidant in the blood. But when the level of serum UA exceeds the physiological concentration, it activates the oxidative stress response and promotes the occurrence and development of cardiovascular diseases. Excessive levels of UA can be rapidly taken up by endothelial cells, promoting the production of angiotensin II (Ang II) and the expression of Ang II type 1 receptor, activating the renin-angiotensin system (RAS), which in turn induces oxidative stress, causing senescence and apoptosis of endothelial cell [14], and proliferation of VSMC via MAPK/ERK pathway [51]. This effect can be inhibited by the angiotensin-converting enzyme inhibitor captopril and the Ang II receptor blocker (ARB) losartan [13]. RAS plays an important role in the enhanced susceptibility to AS seen across the spectrum of CKD [52], which suggests that hyperactivated RAS and high serum UA levels may promote AS progression together in patients with CKD [13, 14, 53].

PI3K/Akt pathway regulates the distribution of the UA secretory protein adenosine triphosphate (ATP)-binding cassette superfamily G member 2 (ABCG2) in cells. High serum UA level aggravates the accumulation of UA in endothelial cells by activating oxidative stress in endothelial cells, inhibiting the phosphorylation of Akt, and decreasing the membrane translocation of ABCG2 and UA efflux [54].

In the process of UA metabolism, which involves redox reactions, XO plays an important role in the conversion of purine to UA. Normal cellular function and damaging effects may be impacted by the dynamic equilibrium of reactive oxygen species (ROS) [55] that take part in cellular signaling pathways, inflammatory regulation [56], vasoconstriction, and dilation [57]. Expression of XO increases during serum UA level elevation, which directly induces oxidative stress through a series of reactions. In the end, these reactions would thereby participate in the onset and progression of many cardiovascular diseases [55]. XO inhibitor, allopurinol, can suppress the formation of foam cell and AS [55]. Hence, in the internal environment of oxidative stress in patients with CKD, antioxidant ability of UA may change into stimulating oxidative stress, which facilitates the formation and progression of AS.

### *Inflammation*

Chronic inflammatory response is a key component of AS. Elevated serum UA levels will stimulate the release of inflammatory cytokines, exacerbating chronic systemic inflammation that is already present in CKD patients. Cross-sectional studies [31] have already found that serum UA levels are probably associated with many inflammatory indicators, such as C-reactive protein (CRP) and interleukin-6 (IL-6) [58]. Except for the direct effects of serum UA, several studies have discovered that UA may be related to the translation of CRP mRNA in endothelial cells [59]. Additionally, serum UA levels in CKD patients starting dialysis rise every time CRP and intercellular cell adhesion molecule-1 (ICAM-1) elevates [60], indicating the relevance of UA to inflammation in patients with CKD.

Macrophage and endothelial cells are central to AS because they regulate cholesterol traffic and inflammation in the arterial wall. CKD affects macrophage function

both directly and indirectly. Direct effects include the upregulation of scavenger receptors and decreased cholesterol efflux via the NF-κB pathway. Indirect effects include inflammatory [61] and oxidative insults to the endothelium that cause increased recruitment, trapping, and decreased egress of arterial macrophages [52].

In macrophages, a study of Harvard University found a novel mechanism by which the uremic toxin indoxyl sulfate (IS) induces proinflammatory activation of macrophages and accelerates AS in CKD. Specifically, in patients with CKD, IS has been demonstrated to cause AS by activating macrophage inflammation via the organic anion-transporting polypeptide 2B1 (OATP2B1)-ubiquitin-specific protease 5 (USP5)-Delta-like 4 (Dll4)-Notch signal pathway [62]. Meanwhile, high UA levels take part in enhancing the activity of Notch signal pathway [63]. It can be postulated that elevated UA levels in patients with CKD contribute to an increased susceptibility to AS.

In endothelial cells, UA promotes the phosphorylation of RAS and ERK by upregulating renin receptors, which promotes the production of inflammatory mediators and monocyte adhesion. Probenecid could block the inflammation via this pathway [53]. UA can induce the nuclear translocation and activation of NF-κB, stimulating the production of chemokines and adhesion factors, including MCP-1, IL-8, VCAM-1, and ICAM-1. These chemokines and adhesion factors finally promote the migration and adhesion of monocytes to endothelial cells [64]. High-mobility group box 1(HMGB1) is an inflammatory mediator released during cellular damage. UA activates endothelial cells causing nuclear HMGB1 acetylation initiating its translocation and release. Once released, HMGB1 may further stimulate its own release while also exacerbating the endothelial cell inflammatory response [65]. IS, a uremic toxin, induces a proinflammatory response in endothelial cells via Nox4 and aryl hydrocarbon receptor (AhR) and leads to AS. In this network, IS would inhibit the production of NO through Nox4 and accelerate chronic inflammation via the AhR-RB/E2F axis by releasing MCP-1, IL-8, E-selectin, and ICAM-1 [66]. The combined effect of IS and UA may result in an increased risk of AS in CKD patients, particularly in the context of renal function deterioration.

In VSMC, Price et al. [67] found that urate transporter 1 (URAT1), a UA transporter expressed on the VSMC membrane, rapidly takes up extracellular UA, which could be the reason for UA promoting VSMC proliferation. UA increased cyclooxygenase 2 (COX-2) and MCP-1 levels via the NF-κB and ERK1/2 (p44/42 MAPK) and p38 MAPK pathways in time-dependent patterns, thus inducing the inflammation of VSMC [68]. In studies on rats with CKD, it has been demonstrated that elevated serum lipopolysaccharide binds to the TLR-4 (Toll-like receptor-4) present on the VSMCs. This binding activates NF-κB and NLRP3 (NACHT, LRR, and PYD domain-containing protein 3) inflammasome signals, which ultimately leads to the process of calcification of VSMCs. The presence of UA in CKD patients may contribute to the acceleration of AS through the NF-κB pathway.

Inflammasomes, including NLRP1 (NACHT, LRR, and PYD domain-containing protein 1), NLRP3, IPAF (NLR proteins ICE protease-activating factor), and AIM2 (absent in melanoma 2) inflammasome, play an important role in the progression of AS. UA can activate oxidative stress and NLRP3 inflammasome by activating ROS and K+ efflux and further induce endothelial cells injury and proliferation of VSMC in the early stage of CKD [69, 70]. In human peripheral blood mononuclear cells, high serum UA levels can activate AS progression and inflammation by suppressing the AMP-activated protein kinase pathway and stimulating the secretion of IL-1β meditated by NLRP3 [71]. In CKD patients, endotoxins interact with TLR on innate immune cells, leading to the NF-κB-and-MAPK-dependent overproduction of proinflammatory factors [72]. The CANTOS trial of canakinumab has shown that inhibiting NLRP3-IL-1-IL-6 pathway can be beneficial in CKD patients with AS [73]. As a part of the upstream of this pathway, UA would participate in the AS progress of patients with CKD. Once serum UA levels exceed 6.8 mg/dL, monosodium urate would be formed. Studies have found that monosodium urate triggers the inflammation, and may also contribute to the pathogenesis of AS [50].

Chronic, low-grade inflammation is recognized as a major pathogenic mechanism that underlies the association of CKD. Treatment effect of statins varies in AS patient with or without CKD, which suggests that the higher residual inflammatory risk in CKD patients still play an important role in prognosis of AS patients. The inflammatory risk was measured by the level of a number of inflammatory predictors, including CRP and IL-1 to IL-6 [74]. Using UA-lowering agents may provide some novel thoughts about decreasing level of inflammation.

*Endothelial Function*

Normal endothelial function is important for the balance of vasoconstriction and dilatation. NO, a molecule closely related to endothelial function, is released less during CKD progression that results in endothelial dysfunction, cardiovascular, and kidney damage [75]. Normal endothelial function maintenance relies on NO

produced by endothelial nitric oxide synthase (eNOS) [76], including regulating vessels tone and controlling cell inflammation and thrombosis [77]. The NF-κB pathway is deeply involved in this process [78]. Endothelial dysfunction has an impact on early development of AS, even earlier than the morphology change in the vascular wall [79].

When the bioavailability of NO decreased, endothelial dysfunction followed and the risk of AS increased. UA will decrease the NO bioavailability in different ways. For instance, some achievements suggest that AS may be caused and mitigated by serum UA levels through different pathways. Therefore, a variety of pharmacological options are available from different prospects for the prevention and treatment. UA can react rapidly and irreversibly with NO to produce 6-amino uracil, which consumes large amounts of NO [80]. Moreover, endothelial cells possess transporters of UA [81], allowing UA to be generated from endothelial cells, and cause inflammation by releasing cytokines like PDGF and MCP-1. What follows is the stimulation of LDL oxidation. After that, UA may deposit in plaque where sediment could be foci for calcification, accelerating AS. Moreover, UA deposits themselves can accelerate AS [20]. UA activates protein kinase C, phosphorylates and inactivates Thr495, the inhibitory site of eNOS, and prevents it from the NO synthesis [82]. Insulin can promote the phosphorylation and activation of eNOS and the production of NO via the phosphatidylinositide3-kinase-protein kinase B pathway. UA blocks the downstream signal of insulin by promoting the phosphorylation of Ser307, the inhibitory site of insulin receptor substrate 1, reducing NO synthesis [83]. There is more than one metabolic pathway involved. UA induces the activation of transcription factor nuclear factor-κB and upregulates its target gene miR-155, causing a decrease in the mRNA stability of eNOS and a decrease in the NO production [84]. Arginase is an enzyme, which can compete for L-arginine [85]. In endothelial cells, UA increases the affinity of arginase for L-arginine and consequently reduces NO synthesis by promoting urea production [86]. Energy metabolism also plays an important role in it. Synthesis of ATP decreases, which is the consequence of inhibiting the tricarboxylic acid cycle by UA, resulting in impaired endothelial function [87]. Endothelial dysfunction can also be triggered by mitochondrial calcium overload due to the activation of mitochondrial $Na^+/Ca^{2+}$ exchanger (NCXmito) by a high concentration of UA [88].

AhR, which is also known as the dioxin receptor, may act as an endogenous effector for IS [89]. Previous reports have demonstrated that the AhR plays a role in mediating IS-induced expression of the endothelial cell adhesion molecule E-selectin [90]. AhR activation induces Notch1 and Notch2 in lymphoid cells [91]. Furthermore, evidence suggests that the AhR pathway is activated in patients and mice with CKD [92]. An in vitro study conducted on a breast cancer cell line demonstrated that the antioxidant effect of UA facilitated the scavenging of ROS, thereby reducing AhR expression. It has been demonstrated that UA stones form in the bladders of AhR knockout mice in the laboratory of Fujii-Kuriyama in an increasingly large quantity. It is postulated that AhR affects nucleic acid degradation in bladder cells, leading to the formation of UA stones [93]. Despite the absence of renal lesions and normal blood UA levels in the mice, the relationship between AhR and UA may have a different impact on CKD patients. This suggests that UA may act on the AS process in CKD patients from multiple signal pathway loci and multiple cells. AS is the most common underlying complication driven by low-density lipoproteins (LDLs), disturbing vascular integrity. Carbamylation of lysine residues, occurring primarily in the presence of CKD, affects functional properties of LDL. Typically, carbamylation of LDL induces endothelial dysfunction via lectin-like-oxidized LDL receptor-1 activation and increased ROS production, leading to eNOS uncoupling [94]. This indicates that a new mechanism may be responsible for AS development and progression in patients with CKD and hyperuricemia.

The evidence implies that different concentrations of serum UA can have very different consequences. Maybe hyperuricemia can play an opposite role in various stages of AS.

*Immune Response*

White blood cells are responsible for the elimination of cholesterol-accumulative cells [78]. Train immunity, a concept put forward to describe the phenomenon of innate immune cells developing persistent hyperreactive phenotype after brief stimulation of pathogenic microorganism and endogenous molecules, such as virus and UA [95]. UA can be recognized as a dangerous molecule by pattern-recognition receptors, the sentinels of the innate immunity. Dendritic cell maturation and activation of resting T cells immediately follow downstream signaling of these receptors, which can also trigger the inflammasome and induce the secretion of proinflammatory cytokines [96]. This process may be mediated by TLR4, under the co-induction of RAS. Chronic tubular damage comes after the interaction between hyperuricemia, RAS, and innate immunity, blunting the protective effect of RAS inhibition [97]. Secretion of inflammatory

mediators from innate immunity could cause irreversible damage to kidney, which is proved to relate to the cross talk between the kidneys and other organs, such as the gut. Growing evidence suggests that administration of probiotics, postbiotics, and symbiotics can ameliorate the renal inflammation and improve the renal function [98–100]. Recent researches [101, 102] have shown that hyperuricemia is capable of inducing long-term proinflammatory activation of innate immune cells, which suggests that there may be many undiscovered therapeutic targets in the immune system. These effects of UA and CKD on the inflammatory state of immune cells, although not yet directly linked to AS, suggest a possible direction.

*Others*

There have been a lot of Japanese researches, showing the increasing prevalence of metabolic syndrome based on serum UA levels [49]. Obesity, insulin resistance, and hypertension are all related to the increased risk of AS. A study conducted by Stanford (CA) University Medical Center shows that insulin resistance and UA concentrations are significantly related, even with the consideration of age, sex, and obesity. For this reason, the effect of UA on AS can also be achieved through insulin resistance. Patients with CKD are more likely to have hyperuricemia than those without CKD, which subsequently triggers or worsens AS [103]. In addition to the above content, AS occurred in CKD patients can be attributed to anemia, coagulopathy, metabolic disturbance, and calcium-phosphate metabolism disturbances [104]. First, chronic inflammation, which may be caused by CKD and hyperuricemia, can promote the secretion of hepcidin in the liver and disturb the absorption iron by intestine and the utilization of iron by monocytes and macrophages. As a result, iron for hemoglobin is not enough in patients with CKD. The anemia is hard to correct by erythropoietin [105, 106]. At the same time, lipid peroxidation products, which are common in patients with AS, can lead to intensification of anemia by inducing the expression of COX-2 [107]. Second, high serum UA levels can increase plasma viscosity, activate platelets, and affect exogenous coagulation [108]. Activation of platelets subsequently causes vascular remodeling and plaque formation. Once the plaque ruptures, coagulation will be disturbed again, forming a vicious circle. Third, metabolic disturbance, which will cause chronic inflammation, is positively correlated to a range of serum UA level [49]. The metabolic disturbance is proved to increase the risk of AS [109]. At last, calcium-phosphate metabolism disturbances, such as hyperphosphatemia, can accelerate the formation of AS [110, 111]. A correlation between urinary calcium and phosphorus excretion and urinary UA excretion has been found in the studies of patients with CKD, suggesting that UA excretion may compete with calcium and phosphorus [112]. The diseases mentioned above also happen to be complications of CKD, further suggesting a complex association between UA and AS in CKD population.

Ultimately, serum UA levels may influence AS development and progression in many ways, including but not limited to oxidative stress, inflammation status, endothelial function, and immunological response. More clinical trials in CKD patients are needed to demonstrate the efficacy of each element and guide further prevention, screening, and treatment.

## Current UA-Lowering Treatments and Their Effects on Atherosclerosis in CKD Patients

*Nonpharmacological Treatments*

A balanced, healthy diet is important to control serum UA, especially for patients with kidney disease [113]. Fresh vegetables, eggs, low-fat, or skim milk are recommended. In the meantime, food rich in purines should be limited.

Drinking enough water to maintain 2,000–3,000 mL daily urine output are necessary for patients whose cardiac and renal functions are normal. But in patients with CKD, this advice should be altered. Patients are allowed to consume fruits with low fructose contents, such as strawberries, pineapples, watermelons, and peaches.

Alcohol should be limited for the effect of increasing risk of hyperuricemia, and beer, yellow rice wine, and spirits should be forbidden [114, 115]. Smoking and passive smoking should both be avoided. Meanwhile, regular physical activity is beneficial for hyperuricemia patients [116]. The patients should take at least 150-min moderate aerobic exercise each week. Additionally, the body mass index should be maintained between 18.5 and 23.9 $kg/m^2$ as the obesity increases the risk of hyperuricemia [117–119].

*Pharmacological Treatments*

When the effect of nonpharmacological treatments is not satisfactory, pharmacological treatments will be applied. Treatments for lowering UA are summarized in Table 1. There are two kinds of commonly used UA-lowering drugs: UA production inhibitors and UA reabsorption inhibitors. Except for these two classes of

**Table 1.** Available UA-lowering therapies

| | Types | Specific recommendations or drugs |
|---|---|---|
| Nonpharmacological treatments | | Fresh vegetables, eggs, low-fat or skim milk, limited food rich in purines<br>Adjusting water intake according to the kidney disease<br>Fruits with low fructose contents, such as strawberries, pineapples, watermelons, and peaches<br>Avoid alcohol and smoking (both active and passive smoking)<br>At least 150-min moderate aerobic exercise each week and maintain a proper BMI |
| Pharmacological treatments | UA production inhibitors | Febuxostat, allopurinol |
| | UA reabsorption inhibitors | Benzbromarone, probenecid, RDEA594 (lesinurad), RDEA-3170 (RDEA684), SHR4640, verinurad, URC-102, and SAP-001 |
| | Uricase | Rasburicase, pegloticase |
| | Urine alkalization | Sodium bicarbonate, citrate preparations |
| | Others | Losartan, fenofibrate, statins, and SGLT-2 inhibitors |

BMI, body mass index; SGLT-2, sodium-dependent glucose transporters 2.

drugs, uricase and agents for urine alkalization are also important in UA-lowering therapy. Uricase decomposes the UA into smaller soluble molecules so that the kidney could excrete them. Agents for urine alkalization can increase the solubility of UA in urine, which is also a recommended way for hyperuricemia treatment.

Uric Acid Production Inhibitors

Traditional UA production inhibitors include allopurinol and febuxostat, collectively called xanthine oxidase inhibitors (XOIs). They block the synthesis of UA by inhibiting the XO. Allopurinol can cause renal injury. Care should be exercised with starting dose and maintenance dose in renal insufficiency patients. This drug is contraindicated in patients with estimated glomerular filtration rate (eGFR) < 15 mL/min (G5). The safety data of febuxostat in CKD patients are better than allopurinol because it is cleared through liver. But it should be used with caution in patients with eGFR <30 mL/min (G4-G5).

Febuxostat achieves the serum UA target in a more effective and faster way than allopurinol. Both drugs are safe and well tolerated. Allopurinol can improve the endothelial function of patients with heart failure [120]. But in patients with CKD (G3) and hyperuricemia, allopurinol treatment did not change the endothelial function and oxidative stress level [121]. This is probably a consequence of the different effects of allopurinol on AS in different diseases. European clinical research explains that allopurinol and febuxostat can maintain the stability of arterial stiffness in patients with hyperuricemia [122]. However, there is evidence from Japanese studies [32] that febuxostat does not delay the carotid AS progression, compared with nonpharmacological care. A random compared trial shows that the febuxostat treatment group developed higher cardiovascular-related mortality than the allopurinol treatment group in 6,190 gout patients with cardiovascular disease [123]. This difference may arise from the different frequency of gout attacks, which in turn exacerbates AS. However, the evidence in support of this view is still lacking. The mechanism underlying this risk of death is unclear. This trial suggests that traditional first-line therapy could have yet undiscovered causal links to many related diseases. The patients involved in this trial are with gout and cardiovascular disease, being stratified according to the kidney function. So, it is reasonable to assume that the results of this trial can be appropriately extrapolated to the CKD population.

Uric Acid Reabsorption Inhibitors

Benzbromarone is commonly used in hyperuricemia patients because it can suppress the tubular reabsorption by inhibiting the URAT1. It is indicated for use in patients presenting with mild to moderate renal dysfunction or renal transplantation. Benzbromarone is contraindicated in patients with an eGFR<20 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. Urine alkalization is indispensable to patients who are taking benzbromarone.

Probenecid can not only inhibit the tubular reabsorption of UA but also accelerate the dissolution of UA crystal. A study by Kim et al. [124] reveals that probenecid significantly reduces the risk of cardiovascular diseases. For now, the clinical use of probenecid in

hyperuricemia is gradually decreasing. The cardiovascular effect of probenecid may provide the possibility to revitalize this traditional drug.

Besides the traditional medicine, there are some novel selective UA reabsorption inhibitors called RDEA594 (lesinurad). This new drug could inhibit both URAT1 and the organic anion transporter 4 (OAT4). Lesinurad can be used to treat hyperuricemia in patients who fail to achieve the target serum UA level with XOIs. However, lesinurad monotherapy is not recommended due to the higher occurrence of renal adverse events [125]. Until now, finding safe and effective UA-lowering drugs for patients with kidney disease is still an urgent problem to be solved.

Except for benzbromarone and lesinurad, many highly selective URAT1 inhibitors are being developed, such as RDEA-3170 (RDEA684), SHR4640, verinurad, URC-102, and SAP-001. Among them, SHR4640 has made the fastest progress. The present study indicated a superior serum UA-lowering effect and a well-tolerated safety profile after 5-week treatment with once-daily 5 mg/10 mg of SHR4640 as compared with placebo in Chinese subjects with hyperuricemia [126]. The occurrence of renal adverse events caused by SHR4640 is dose-dependent, like many other URAT1 inhibitors. Combination with high doses of XOIs can significantly reduce the renal safety risk by reducing UA excretion by the kidneys [127]. Hyperuricemia patients were grouped into 3 groups by various medication regimens, with allopurinol, benzbromarone, or both drugs. Over the data of 8,047 gout patients, 3 groups all had a linear dose-response relationship between the numbers of defined daily doses and the risk of AS [128]. Little clinical research has been done on the relationship of other URAT1 inhibitors with AS.

Uricase

Uricases include rasburicase and pegloticase, which decompose the UA into smaller soluble molecules. They are indicated for patients with refractory gout for whom other drugs are ineffective or contraindicated. None of them are currently available in China, and they are not recommended as first-line agents. Main adverse reactions of pegloticase include serious cardiovascular events and infusion and immunogenic reactions [129]. There are no data on the use of uricase in patients with renal dysfunction.

Urine Alkalization

Maintaining urine pH within 6.2–6.9 is recommended to patients receiving UA-lowering drugs, especially the UA reabsorption inhibitor, to increase the solubility of UA in urine. In CKD patients with hyperuricemia, sodium bicarbonate will be more suitable and safer than citrate preparations [130].

Others

Losartan is often used to protect renal function by antagonizing Ang II receptor. Studies find that losartan can also lower the serum UA level by inhibiting URAT1 [131]. Many studies have confirmed the role of losartan in delaying the progression of kidney disease. In hemodialysis patients, long-term blockade of the RAS by trandolapril and losartan may prevent the acceleration of AS and have a beneficial effect on uremic dyslipidemia [132]. However, losartan's UA-lowering effect is weak when used alone, which should be used in combination with other UA-lowering drugs. Losartan therapy may assist in lowering blood UA in peritoneal dialysis patients with hyperuricemia combined with hypertension. Lipid-lowering drugs, including fenofibrate and statins, can significantly improve renal function in patients with coronary artery disease [133] and decrease the serum UA level by regulating the endothelial NO pathway [134] and promoting UA excretion through kidney. Like losartan, these drugs are weak in lowering serum UA level by using monotherapy.

Sodium-dependent glucose transporter 2 (SGLT-2) inhibitors offer the possibility of kidney protection by reducing intraglomerular pressure, systemic blood pressure, and serum UA concentration [135]. An interesting study found that empagliflozin restores the beneficial effect of cardiac microvascular endothelial cells by reducing mitochondrial oxidative damage, leading to reduced ROS accumulation and increased endothelial NO bioavailability [136]. A randomized controlled trial found that SGLT-2 inhibitors are safe (do not increase) and may reduce the occurrence of AS [137], suggesting that SGLT-2 inhibitors can be used as the UA-lowering treatment.

## Prospect and Long-Term Management of UA and Atherosclerosis in CKD Patients

The classical mechanisms of AS and UA in CKD patients, including oxidative stress, endothelial dysfunction, and inflammation, have been studied during various pathways. Considering the complexity of the internal environment in CKD patients, these findings may have been due to chance. The interactions between them also bring unpredictability to the cascade response. The studies focused on inflammasome are more deficient at present. In addition, mechanism of endothelial

function relies too heavily on NO cross talk, limiting more direct observation of this mechanism from other perspectives. The booming immune-related research in recent years, on the other hand, suggests innate immunity and inflammation as a new cross-research direction.

The association between UA-lowering therapy and kidney outcomes varies by different populations [138]. However, there is no reliable evidence to suggest that UA-lowering therapy should be excluded from CKD treatment guidelines. Given the known benefits of UA-lowering therapy, such as reducing the residual risk of AS [44, 71], having a beneficial effect in ischemia-reperfusion lesion after coronary angioplasty [55], and improving blood pressure control that slowed the progression of AS and CKD [139], the use of UA-lowering drugs remains an important part of the treatment of patients with CKD. Indeed, UA-lowering therapy should be carried out in a cautious way, given that no universally appropriate serum UA concentration has been identified for each CKD patient, regardless of stage or underlying physical condition.

There is a J-shaped correlation [140] showed between serum UA levels and all-cause mortality in CKD patients. It remains unclear whether the therapeutic effect of UA-lowering drugs on AS is due to the reduction of serum UA levels or the inhibition of oxidative stress. Nevertheless, the benefits of UA-lowering therapy cannot be overlooked. In conclusion, there is still a lot of room for exploration on the optimal application dose, time to start medication, suitable crowd, and mode of administration in CKD patients.

Many traditional drugs discovered in the study of new mechanisms, such as losartan, SGLT-2 inhibitors, and statins. In response to the previously mentioned oxidative stress mechanism, losartan was found to reduce UA-induced COX-2 elevation [68]. SGLT-2 inhibitors and statins also reduce cardiovascular risk through more than one pathway. As commonly used drugs in CKD, these drugs have a wide range of use, indicating that further research could be conducted into the potential mechanisms of action of inexpensive and readily available pharmaceuticals.

The achievements suggest that AS may be caused and mitigated of serum UA levels by different pathways. Therefore, a variety of pharmacological options are available from different prospects for the prevention and treatment. Now researchers [141] think they have found a new link between gut microbiota and variation in the AS burden by using mice. Gut microbes control the AS burden through catabolizing purine, which suggests that serum UA levels are an important pathway for gut microbes to regulate AS. Ordered intestinal microbiome plays an important role in the clearance of uremic toxins like p-cresol, IS, and p-cresyl sulfate, some of which work with UA to promote the formation and development of AS [142]. The results demonstrate that subclinical AS in CKD patients may be prevented and treated by modifying the homeostasis of the gut microbiome.

At the same time, there are many new drugs discovered in the study of classical mechanisms, such as lesinurad, SHR4640, and uricase. They function in a more powerful way, which encourages us to explore a new generation of more efficient drugs. Despite the emergence of these new drugs targeting on classical or new mechanisms, research on their safety and efficacy remains inadequate. This indicates a necessity for further multicenter, long-term, large-scale clinical studies in patients with or without CKD.

As a predictor, UA can act a role in recognizing early AS in CKD patients [143]. Serum UA levels can be used to predict the progression of subclinical AS and identify the population that is at the highest risk of AS even if CKD is not clinically diagnosed [144], which is of great significance for early prevention, screening, and long-term management. Meanwhile, some scholars have turned their attention to genetics. A genetic marker of serum UA levels called the rs734553 polymorphism in the GLUT9 gene was a strong modifier of the relationship between age, IMT, and carotid internal diameter [145]. This genetic study has limited clinical significance, but it points us to new research directions. And beyond that, the level of serum UA can unite with some novel risk factors such as serum total bilirubin concentration to predict the prevalence and incidence of CKD in the general population or AS progression in CKD patients [146].

UA is closely related to oxidative stress, especially in patients with CKD who are vulnerable to oxidative stress. Accordingly, several antioxidants have been proposed to apply to further decrease oxidative stress and serum UA level. Health management has become increasingly integrated into modern life. Antioxidants have become star foods for preventing and delaying disease. Therefore, daily diets [147] containing curcumin, L-arginine, and vitamin C that are antioxidants will have potentials in preventing AS.

Most studies concluding that UA is an independent risk factor for AS have been based on non-CKD populations. Evidence of UA directly influencing AS in CKD patients from randomized controlled trials are still lack of reliable data [148]. The time to start UA-lowering therapy, the dosage of different populations at different modes of stages of CKD, different administration and

dosage forms, and the optimal target level are not clear. Additionally, there are still a lack of clinical studies on the association between serum UA level and AS progression in the CKD population. Moreover, it is difficult to study the serum UA level independently because it is related to many factors. How to study independent UA factors and how to manage them in a clinically complex pathophysiological environment remain to be discovered. At last, common UA-lowering drugs have respective advantages and disadvantages, and there are not enough clinical studies on the efficacy and safety of various newly discovered drugs with related effects.

There are still some limitations. Thus, there are many reasons to believe that there could be some relationships between serum UA and AS, but further causation in CKD patients is still not clear. The specific connection may be hidden in the mechanisms just waiting for further investigations.

## Conclusion

People with CKD face the risk of premature death, mainly due to cardiovascular diseases. Among many risk factors, serum UA levels are discovered to play an essential role in this process. Although many relevant studies have been conducted, they are still limited by insufficient causal relationship, small sample size, and unclear elaboration. The above research results show that serum UA levels are extensively involved in numerous aspects of the AS process in CKD patients, including oxidative stress, inflammation, endothelial dysfunction, immune response, and many other mechanisms. Appropriate UA concentrations in different internal environments are critical for patients with CKD.


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## Conflict of Interest Statement

The authors declare no conflict of interest.


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## Author Contributions

Yuchu Liu is mainly responsible for collecting literature and drafting the review. Zeyu Li and Yuanwen Xu helped to modify the figures and revise the manuscript. Haiping Mao and Naya Huang provided supervision and revised the manuscript. All authors read and approved the final manuscript.

## References


1 Orowan E. The origin of man. Nature. 1955; 175(4459):683–4. https://doi.org/10.1038/175683a0

2 Kuwabara M, Niwa K, Hisatome I, Nakagawa T, Roncal-Jimenez CA, Andres-Hernando A, et al. Asymptomatic hyperuricemia without comorbidities predicts cardiometabolic diseases: five-year Japanese cohort study. Hypertension. 2017;69(6): 1036–44. https://doi.org/10.1161/HYPERTENSIONAHA.116.08998

3 Gracia M, Betriu À, Martínez-Alonso M, Arroyo D, Abajo M, Fernández E, et al. Predictors of subclinical atheromatosis progression over 2 Years in patients with different stages of CKD. Clin J Am Soc Nephrol. 2016;11(2):287–96. https://doi.org/10.2215/cjn.01240215

4 Pérez Fontán M, Borràs Sans M, Bajo Rubio MA, Rodriguez-Carmona A, Betriu A, Valdivielso JM, et al. Low serum levels of Vitamin D are associated with progression of subclinical atherosclerotic vascular disease in peritoneal dialysis patients: a prospective, multicenter study. Nephron. 2017;136(2): 111–20. https://doi.org/10.1159/000458418

5 Xia X, He F, Wu X, Peng F, Huang F, Yu X. Relationship between serum uric acid and all-cause and cardiovascular mortality in patients treated with peritoneal dialysis. Am J Kidney Dis. 2014;64(2):257–64. https://doi.org/10.1053/j.ajkd.2013.08.027

6 Goicoechea M, De Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincón A, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010;5(8):1388–93. https://doi.org/10.2215/CJN.01580210

7 Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet. 2017;389(10075):1238–52. https://doi.org/10.1016/S0140-6736(16)32064-5

8 Richette P, Bardin T. Gout. Lancet. 2010; 375(9711):318–28. https://doi.org/10.1016/S0140-6736(09)60883-7

9 Terkeltaub R, Bushinsky DA, Becker MA. Recent developments in our understanding of the renal basis of hyperuricemia and the development of novel antihyperuricemic therapeutics. Arthritis Res Ther. 2006; 8(Suppl 1):S4. https://doi.org/10.1186/ar1909

10 Terkeltaub RA. Clinical practice. Gout. N Engl J Med. 2003;349(17):1647–55. https://doi.org/10.1056/NEJMcp030733

11 Jalal DI. Hyperuricemia, the kidneys, and the spectrum of associated diseases: a narrative review. Curr Med Res Opin. 2016; 32(11):1863–9. https://doi.org/10.1080/03007995.2016.1218840

12 Ichida K, Matsuo H, Takada T, Nakayama A, Murakami K, Shimizu T, et al. Decreased extra-renal urate excretion is a common cause of hyperuricemia. Nat Commun. 2012;3(1):764. https://doi.org/10.1038/ncomms1756
13 Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin–angiotensin system. J Hypertens. 2008;26(2):269–75. https://doi.org/10.1097/HJH.0b013e3282f240bf
14 Yu MA, Sánchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. J Hypertens. 2010;28(6):1234–42. https://doi.org/10.1097/hjh.0b013e328337da1d
15 Zhang J, Zhang Y, Wu Q, Chen B. Uric acid induces oxidative stress via an activation of the renin–angiotensin system in 3T3-L1 adipocytes. Endocrine. 2015;48(1):135–42. https://doi.org/10.1007/s12020-014-0239-5
16 Zhang J, Diao B, Lin X, Xu J, Tang F. TLR2 and TLR4 mediate an activation of adipose tissue renin-angiotensin system induced by uric acid. Biochimie. 2019;162:125–33. https://doi.org/10.1016/j.biochi.2019.04.013
17 Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, et al. Hyperuricemia induces endothelial dysfunction. Kidney Int. 2005;67(5):1739–42. https://doi.org/10.1111/j.1523-1755.2005.00273.x
18 Bjornstad P, Laffel L, Lynch J, El Ghormli L, Weinstock RS, Tollefsen SE, et al. Elevated serum uric acid is associated with greater risk for hypertension and diabetic kidney diseases in obese adolescents with type 2 diabetes: an observational analysis from the treatment options for type 2 diabetes in adolescents and youth (TODAY) study. Diabetes Care. 2019;42(6):1120–8. https://doi.org/10.2337/dc18-2147
19 Tseng CH. Correlation of uric acid and urinary albumin excretion rate in patients with type 2 diabetes mellitus in Taiwan. Kidney Int. 2005;68(2):796–801. https://doi.org/10.1111/j.1523-1755.2005.00459.x
20 Ejaz AA, Nakagawa T, Kanbay M, Kuwabara M, Kumar A, Garcia Arroyo FE, et al. Hyperuricemia in kidney disease: a major risk factor for cardiovascular events, vascular calcification, and renal damage. Semin Nephrol. 2020;40(6):574–85. https://doi.org/10.1016/j.semnephrol.2020.12.004
21 Wanner C, Krane V, März W, Olschewski M, Mann JFE, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238–48. https://doi.org/10.1056/NEJMoa043545
22 Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360(14):1395–407. https://doi.org/10.1056/NEJMoa0810177
23 Badve SV, Brown F, Hawley CM, Johnson DW, Kanellis J, Rangan GK, et al. Challenges of conducting a trial of uric-acid-lowering therapy in CKD. Nat Rev Nephrol. 2011;7(5):295–300. https://doi.org/10.1038/nrneph.2010.186
24 Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation. 2002;105(22):2619–24. https://doi.org/10.1161/01.cir.0000017502.58595.ed
25 Guthikonda S, Sinkey C, Barenz T, Haynes WG. Xanthine oxidase inhibition reverses endothelial dysfunction in heavy smokers. Circulation. 2003;107(3):416–21. https://doi.org/10.1161/01.cir.0000046448.26751.58
26 Katsiki N, Mikhailidis DP. Hyperuricaemia in cardiovascular diseases: a passive or an active player? Med Princ Pract. 2015;24(3):269–70. https://doi.org/10.1159/000381398
27 Feng L, Hua C, Sun H, Qin LY, Niu PP, Guo ZN, et al. Association between serum uric acid level and carotid atherosclerosis in Chinese individuals aged 75 Years or older: a hospital-based case-control study. J Nutr Health Aging. 2018;22(4):508–12. https://doi.org/10.1007/s12603-017-0984-2
28 Sugiura T, Dohi Y, Takagi Y, Yokochi T, Yoshikane N, Suzuki K, et al. Increased impact of serum uric acid on arterial stiffness and atherosclerosis in females. J Atheroscler Thromb. 2022;29(11):1672–91. https://doi.org/10.5551/jat.63368
29 Song M, Li N, Yao Y, Wang K, Yang J, Cui Q, et al. Longitudinal association between serum uric acid levels and multiterritorial atherosclerosis. J Cel Mol Med. 2019;23(8):4970–9. https://doi.org/10.1111/jcmm.14337
30 So A, Thorens B. Uric acid transport and disease. J Clin Investig. 2010;120(6):1791–9. https://doi.org/10.1172/JCI42344
31 Mazidi M, Katsiki N, Mikhailidis DP, Banach M. Association of ideal cardiovascular health metrics with serum uric acid, inflammation and atherogenic index of plasma: a population-based survey. Atherosclerosis. 2019;284:44–9. https://doi.org/10.1016/j.atherosclerosis.2018.09.016
32 Tanaka A, Taguchi I, Teragawa H, Ishizaka N, Kanzaki Y, Tomiyama H, et al. Febuxostat does not delay progression of carotid atherosclerosis in patients with asymptomatic hyperuricemia: a randomized, controlled trial. In: Borghi C, editor; 2020. Vol. 17. https://doi.org/10.1371/journal.pmed.1003095
33 Tanaka A, Toyoda S, Kato T, Yoshida H, Hamasaki S, Watarai M, et al. Association between serum urate level and carotid atherosclerosis: an insight from a post hoc analysis of the PRIZE randomised clinical trial. RMD Open. 2022;8(1):e002226. https://doi.org/10.1136/rmdopen-2022-002226
34 Kao MP, Ang DS, Gandy SJ, Nadir MA, Houston JG, Lang CC, et al. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. J Am Soc Nephrol. 2011;22(7):1382–9. https://doi.org/10.1681/ASN.2010111185
35 Goicoechea M, Garcia De Vinuesa S, Verdalles U, Verde E, Macias N, Santos A, et al. Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. Am J Kidney Dis. 2015;65(4):543–9. https://doi.org/10.1053/j.ajkd.2014.11.016
36 Sircar D, Chatterjee S, Waikhom R, Golay V, Raychaudhury A, Chatterjee S, et al. Efficacy of febuxostat for slowing the GFR decline in patients with CKD and asymptomatic hyperuricemia: a 6-month, double-blind, randomized, placebo-controlled trial. Am J Kidney Dis. 2015;66(6):945–50. https://doi.org/10.1053/j.ajkd.2015.05.017
37 Su X, Xu B, Yan B, Qiao X, Wang L. Effects of uric acid-lowering therapy in patients with chronic kidney disease: a meta-analysis. In: Seguro AC, editor. PLoS One; 2017. Vol. 12. https://doi.org/10.1371/journal.pone.0187550
38 Li N, Cui L, Shu R, Song H, Wang J, Chen S, et al. Associations of uric acid with the risk of cardiovascular disease and all-cause mortality among individuals with chronic kidney disease: the Kailuan Study. Eur J Prev Cardiol. 2024(online July 1):zwae222.
39 Bakris GL, Mikami H, Hirata M, Nakajima A, Cressman MD. A non-purine xanthine oxidoreductase inhibitor reduces albuminuria in patients with dkd: a randomized controlled trial. Kidney360. 2021;2(8):1240–50. https://doi.org/10.34067/KID.0001672021
40 Siu YP, Leung KT, Tong MKH, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis. 2006;47(1):51–9. https://doi.org/10.1053/j.ajkd.2005.10.006
41 Doria A, Galecki AT, Spino C, Pop-Busui R, Cherney DZ, Lingvay I, et al. Serum urate lowering with allopurinol and kidney function in type 1 diabetes. N Engl J Med. 2020;382(26):2493–503. https://doi.org/10.1056/NEJMoa1916624
42 Badve SV, Pascoe EM, Tiku A, Boudville N, Brown FG, Cass A, et al. Effects of allopurinol on the progression of chronic kidney disease. N Engl J Med. 2020;382(26):2504–13. https://doi.org/10.1056/NEJMoa1915833
43 Hisatome I, Li P, Miake J, Taufiq F, Mahati E, Maharani N, et al. Uric acid as a risk factor for chronic kidney disease and cardiovascular disease — Japanese guideline on the management of asymptomatic hyperuricemia. Circ J. 2021;85(2):130–8. https://doi.org/10.1253/circj.CJ-20-0406

44 Lee SB, Lee HJ, Ryu HE, Park B, Jung DH. Elevated uric acid levels with early chronic kidney disease as an indicator of new-onset ischemic heart disease: a cohort of Koreans without diabetes. Biomedicines. 2023;11(8):2212. https://doi.org/10.3390/biomedicines11082212
45 Junyent M, Martínez M, Borràs M, Coll B, Valdivielso JM, Vidal T, et al. Predicting cardiovascular disease morbidity and mortality in chronic kidney disease in Spain. The rationale and design of NEFRONA: a prospective, multicenter, observational cohort study. BMC Nephrol. 2010;11:14. https://doi.org/10.1186/1471-2369-11-14
46 Junyent M, Martínez M, Borrás M, Bertriu A, Coll B, Craver L, et al. [Usefulness of imaging techniques and novel biomarkers in the prediction of cardiovascular risk in patients with chronic kidney disease in Spain: the NEFRONA project]. Nefrologia. 2010;30(1):119–26. https://doi.org/10.3265/Nefrologia.pre2010.Jan.10216
47 Betriu A, Martinez-Alonso M, Arcidiacono MV, Cannata-Andia J, Pascual J, Valdivielso JM, et al. Prevalence of subclinical atherosclerosis and associated risk factors in chronic kidney disease: the NEFRONA study. Nephrol Dial Transpl. 2014;29(7):1415–22. https://doi.org/10.1093/ndt/gfu038
48 Valdivielso JM, Rodríguez-Puyol D, Pascual J, Barrios C, Bermúdez-López M, Sánchez-Niño MD, et al. Atherosclerosis in chronic kidney disease: more, less, or just different? Arterioscler Thromb Vasc Biol. 2019;39(10):1938–66. https://doi.org/10.1161/ATVBAHA.119.312705
49 Ishizaka N, Ishizaka Y, Toda EI, Nagai R, Yamakado M. Association between serum uric acid, metabolic syndrome, and carotid atherosclerosis in Japanese individuals. Arterioscler Thromb Vasc Biol. 2005;25(5):1038–44. https://doi.org/10.1161/01.ATV.0000161274.87407.26
50 Jin M, Yang F, Yang I, Yin Y, Luo JJ, Wang H, et al. Uric acid, hyperuricemia and vascular diseases. Front Biosci. 2012;17(2):656–69. https://doi.org/10.2741/3950
51 Chao H, Liu J, Lin J, Chen C, Wu C, Cheng T. Uric acid stimulates endothelin-1 gene expression associated with NADPH oxidase in human aortic smooth muscle cells. Acta Pharmacol Sin. 2008;29(11):1301–12. https://doi.org/10.1111/j.1745-7254.2008.00877.x
52 Kon V, Linton MF, Fazio S. Atherosclerosis in chronic kidney disease: the role of macrophages. Nat Rev Nephrol. 2011;7(1):45–54. https://doi.org/10.1038/nrneph.2010.157
53 Yang X, Gu J, Lv H, Li H, Cheng Y, Liu Y, et al. Uric acid induced inflammatory responses in endothelial cells via up-regulating(pro)renin receptor. Biomed Pharmacother. 2019;109:1163–70. https://doi.org/10.1016/j.biopha.2018.10.129
54 Komori H, Yamada K, Tamai I. Hyperuricemia enhances intracellular urate accumulation via down-regulation of cell-surface BCRP/ABCG2 expression in vascular endothelial cells. Biochim Biophys Acta Biomembr. 2018;1860(5):973–80. https://doi.org/10.1016/j.bbamem.2018.01.006
55 Okafor ON, Farrington K, Gorog DA. Allopurinol as a therapeutic option in cardiovascular disease. Pharmacol Ther. 2017;172:139–50. https://doi.org/10.1016/j.pharmthera.2016.12.004
56 Burgoyne JR, Oka S, Ale-Agha N, Eaton P. Hydrogen peroxide sensing and signaling by protein kinases in the cardiovascular system. Antioxid Redox Signal. 2013;18(9):1042–52. https://doi.org/10.1089/ars.2012.4817
57 Knock GA. NADPH oxidase in the vasculature: expression, regulation and signalling pathways; role in normal cardiovascular physiology and its dysregulation in hypertension. Free Radic Biol Med. 2019;145:385–427. https://doi.org/10.1016/j.freeradbiomed.2019.09.029
58 Ruggiero C, Cherubini A, Ble A, Bos AJG, Maggio M, Dixit VD, et al. Uric acid and inflammatory markers. Eur Heart J. 2006;27(10):1174–81. https://doi.org/10.1093/eurheartj/ehi879
59 Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid–induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol. 2005;16(12):3553–62. https://doi.org/10.1681/ASN.2005050572
60 Suliman ME, Johnson RJ, García-López E, Qureshi AR, Molinaei H, Carrero JJ, et al. J-shaped mortality relationship for uric acid in CKD. Am J Kidney Dis. 2006;48(5):761–71. https://doi.org/10.1053/j.ajkd.2006.08.019
61 Hoyer FF, Nahrendorf M. Uremic toxins activate macrophages: implications for atherosclerosis in chronic kidney disease. Circulation. 2019;139(1):97–100. https://doi.org/10.1161/CIRCULATIONAHA.118.037308
62 Nakano T, Katsuki S, Chen M, Decano JL, Halu A, Lee LH, et al. Uremic toxin indoxyl sulfate promotes proinflammatory macrophage activation via the interplay of OATP2B1 and dll4-notch signaling: potential mechanism for accelerated atherogenesis in chronic kidney disease. Circulation. 2019;139(1):78–96. https://doi.org/10.1161/CIRCULATIONAHA.118.034588
63 Zhu D, Wang Y, Zou C, SheZheng XZ, Zheng Z. The role of uric acid in the pathogenesis of diabetic retinopathy based on Notch pathway. Biochem Biophys Res Commun. 2018;503(2):921–9. https://doi.org/10.1016/j.bbrc.2018.06.097
64 Liang WY, Zhu XY, Zhang JW, Feng XR, Wang YC, Liu ML. Uric acid promotes chemokine and adhesion molecule production in vascular endothelium via nuclear factor-kappa B signaling. Nutr Metab Cardiovasc Dis. 2015;25(2):187–94. https://doi.org/10.1016/j.numecd.2014.08.006
65 Rabadi MM, Kuo MC, Ghaly T, Rabadi SM, Weber M, Goligorsky MS, et al. Interaction between uric acid and HMGB1 translocation and release from endothelial cells. Am J Physiol Ren Physiol. 2012;302(6):F730–F741. https://doi.org/10.1152/ajprenal.00520.2011
66 Lu C, Wu L, Tang MY, Liu YF, Liu L, Liu XY, et al. Indoxyl sulfate in atherosclerosis. Toxicol Lett. 2023;383:204–12. https://doi.org/10.1016/j.toxlet.2023.07.001
67 Price KL, Sautin YY, Long DA, Zhang L, Miyazaki H, Mu W, et al. Human vascular smooth muscle cells express a urate transporter. J Am Soc Nephrol. 2006;17(7):1791–5. https://doi.org/10.1681/ASN.2006030264
68 Oğuz N, Kırça M, Çetin A, Yeşilkaya A. Effect of uric acid on inflammatory COX-2 and ROS pathways in vascular smooth muscle cells. J Recept Signal Transduct Res. 2017;37(5):500–5. https://doi.org/10.1080/10799893.2017.1360350
69 Yin W, Zhou QL, OuYang SX, Chen Y, Gong YT, Liang YM. Uric acid regulates NLRP3/IL-1β signaling pathway and further induces vascular endothelial cells injury in early CKD through ROS activation and K+ efflux. BMC Nephrol. 2019;20(1):319. https://doi.org/10.1186/s12882-019-1506-8
70 Li H, Qian F, Liu H, Zhang Z. Elevated uric acid levels promote vascular smooth muscle cells (VSMC) proliferation via an nod-like receptor protein 3 (NLRP3)-Inflammasome-Dependent mechanism. Med Sci Monit. 2019;25:8457–64. https://doi.org/10.12659/MSM.916667
71 Kimura Y, Yanagida T, Onda A, Tsukui D, Hosoyamada M, Kono H. Soluble uric acid promotes atherosclerosis via AMPK (AMP-Activated protein kinase)-mediated inflammation. Arterioscler Thromb Vasc Biol. 2020;40(3):570–82. https://doi.org/10.1161/ATVBAHA.119.313224
72 Speer T, Dimmeler S, Schunk SJ, Fliser D, Ridker PM. Targeting innate immunity-driven inflammation in CKD and cardiovascular disease. Nat Rev Nephrol. 2022;18(12):762–78. https://doi.org/10.1038/s41581-022-00621-9
73 Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med Overseas Ed. 2017;377(12):1119–31. https://doi.org/10.1056/nejmoa1707914
74 Ridker PM, Tuttle KR, Perkovic V, Libby P, MacFadyen JG. Inflammation drives residual risk in chronic kidney disease: a CANTOS substudy. Eur Heart J. 2022;43(46):4832–44. https://doi.org/10.1093/eurheartj/ehac444
75 Baylis C. Nitric oxide deficiency in chronic kidney disease. Am J Physiol Ren Physiol. 2008;294(1):F1–F9. https://doi.org/10.1152/ajprenal.00424.2007

76 Higashi Y, Noma K, Yoshizumi M, Kihara Y. Endothelial function and oxidative stress in cardiovascular diseases. Circ J. 2009; 73(3):411–8. https://doi.org/10.1253/circj.cj-08-1102

77 Huang PL. eNOS, metabolic syndrome and cardiovascular disease. Trends Endocrinol Metab. 2009;20(6):295–302. https://doi.org/10.1016/j.tem.2009.03.005

78 Jayachandran M, Qu S. Harnessing hyperuricemia to atherosclerosis and understanding its mechanistic dependence. Med Res Rev. 2021;41(1):616–29. https://doi.org/10.1002/med.21742

79 Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation. 2007; 115(10):1285–95. https://doi.org/10.1161/CIRCULATIONAHA.106.652859

80 Gersch C, Palii SP, Kim KM, Angerhofer A, Johnson RJ, Henderson GN. Inactivation of nitric oxide by uric acid. Nucleosides Nucleotides Nucleic Acids. 2008;27(8):967–78. https://doi.org/10.1080/15257770802257952

81 Maruhashi T, Hisatome I, Kihara Y, Higashi Y. Hyperuricemia and endothelial function: from molecular background to clinical perspectives. Atherosclerosis. 2018;278: 226–31. https://doi.org/10.1016/j.atherosclerosis.2018.10.007

82 Li P, Zhang L, Zhang M, Zhou C, Lin N. Uric acid enhances PKC-dependent eNOS phosphorylation and mediates cellular ER stress: a mechanism for uric acid-induced endothelial dysfunction. Int J Mol Med. 2016;37(4):989–97. https://doi.org/10.3892/ijmm.2016.2491

83 Choi Y, Yoon Y, Lee K, Hien TT, Kang KW, Kim K, et al. Uric acid induces endothelial dysfunction by vascular insulin resistance associated with the impairment of nitric oxide synthesis. FASEB J. 2014;28(7): 3197–204. https://doi.org/10.1096/fj.13-247148

84 Zhen H, Gui F. The role of hyperuricemia on vascular endothelium dysfunction. Biomed Rep. 2017;7(4):325–30. https://doi.org/10.3892/br.2017.966

85 Wu G, Morris SM. Arginine metabolism: nitric oxide and beyond. Biochem J. 1998; 336(Pt 1):1–17. https://doi.org/10.1042/bj3360001

86 Zharikov S, Krotova K, Hu H, Baylis C, Johnson RJ, Block ER, et al. Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells. Am J Physiol Cel Physiol. 2008;295(5):C1183–C1190. https://doi.org/10.1152/ajpcell.00075.2008

87 Sánchez-Lozada LG, Lanaspa MA, Cristóbal-García M, García-Arroyo F, Soto V, Cruz-Robles D, et al. Uric acid-induced endothelial dysfunction is associated with mitochondrial alterations and decreased intracellular ATP concentrations. Nephron Exp Nephrol. 2012;121(3–4):e71–e78. https://doi.org/10.1159/000345509

88 Hong Q, Qi K, Feng Z, Huang Z, Cui S, Wang L, et al. Hyperuricemia induces endothelial dysfunction via mitochondrial Na+/Ca2+ exchanger-mediated mitochondrial calcium overload. Cell Calcium. 2012; 51(5):402–10. https://doi.org/10.1016/j.ceca.2012.01.003

89 Schroeder JC, DiNatale BC, Murray IA, Flaveny CA, Liu Q, Laurenzana EM, et al. The uremic toxin 3-indoxyl sulfate is a potent endogenous agonist for the human aryl hydrocarbon receptor. Biochemistry. 2010;49(2):393–400. https://doi.org/10.1021/bi901786x

90 Ito S, Osaka M, Edamatsu T, Itoh Y, Yoshida M. Crucial role of the aryl hydrocarbon receptor (AhR) in indoxyl sulfate-induced vascular inflammation. J Atheroscler Thromb. 2016;23(8):960–75. https://doi.org/10.5551/jat.34462

91 Lee JS, Cella M, McDonald KG, Garlanda C, Kennedy GD, Nukaya M, et al. AHR drives the development of gut ILC22 cells and postnatal lymphoid tissues via pathways dependent on and independent of Notch. Nat Immunol. 2011;13(2):144–51. https://doi.org/10.1038/ni.2187

92 Dou L, Poitevin S, Sallée M, Addi T, Gondouin B, McKay N, et al. Aryl hydrocarbon receptor is activated in patients and mice with chronic kidney disease. Kidney Int. 2018;93(4):986–99. https://doi.org/10.1016/j.kint.2017.11.010

93 Atala A. Re:uric acid stones in the urinary bladder of aryl hydrocarbon receptor (AhR) knockout mice. J Urol. 2012;188(3):1042. https://doi.org/10.1016/j.juro.2012.05.040

94 Speer T, Owala FO, Holy EW, Zewinger S, Frenzel FL, Stähli BE, et al. Carbamylated low-density lipoprotein induces endothelial dysfunction. Eur Heart J. 2014;35(43): 3021–32. https://doi.org/10.1093/eurheartj/ehu111

95 Netea MG, Quintin J, van der Meer JWM. Trained immunity: a memory for innate host defense. Cell Host Microbe. 2011;9(5): 355–61. https://doi.org/10.1016/j.chom.2011.04.006

96 Ponticelli C, Podestà MA, Moroni G. Hyperuricemia as a trigger of immune response in hypertension and chronic kidney disease. Kidney Int. 2020;98(5):1149–59. https://doi.org/10.1016/j.kint.2020.05.056

97 Milanesi S, Verzola D, Cappadona F, Bonino B, Murugavel A, Pontremoli R, et al. Uric acid and angiotensin II additively promote inflammation and oxidative stress in human proximal tubule cells by activation of toll-like receptor 4. J Cel Physiol. 2019; 234(7):10868–76. https://doi.org/10.1002/jcp.27929

98 Yoshifuji A, Wakino S, Irie J, Tajima T, Hasegawa K, Kanda T, et al. Gut *Lactobacillus* protects against the progression of renal damage by modulating the gut environment in rats. Nephrol Dial Transpl. 2016;31(3):401–12. https://doi.org/10.1093/ndt/gfv353

99 Andrade-Oliveira V, Amano MT, Correa-Costa M, Castoldi A, Felizardo RJF, De Almeida DC, et al. Gut bacteria products prevent AKI induced by ischemia-reperfusion. J Am Soc Nephrol. 2015; 26(8):1877–88. https://doi.org/10.1681/ASN.2014030288

100 Rossi M, Johnson DW, Morrison M, Pascoe EM, Coombes JS, Forbes JM, et al. Synbiotics easing renal failure by improving gut microbiology (SYNERGY): a randomized trial. Clin J Am Soc Nephrol. 2016;11(2): 223–31. https://doi.org/10.2215/CJN.05240515

101 Crişan TO, Cleophas MCP, Oosting M, Lemmers H, Toenhake-Dijkstra H, Netea MG, et al. Soluble uric acid primes TLR-induced proinflammatory cytokine production by human primary cells via inhibition of IL-1Ra. Ann Rheum Dis. 2016; 75(4):755–62. https://doi.org/10.1136/annrheumdis-2014-206564

102 Joosten LAB, Crişan TO, Bjornstad P, Johnson RJ. Asymptomatic hyperuricaemia: a silent activator of the innate immune system. Nat Rev Rheumatol. 2020;16(2): 75–86. https://doi.org/10.1038/s41584-019-0334-3

103 Borghi C, Agabiti-Rosei E, Johnson RJ, Kielstein JT, Lurbe E, Mancia G, et al. Hyperuricaemia and gout in cardiovascular, metabolic and kidney disease. Eur J Intern Med. 2020;80:1–11. https://doi.org/10.1016/j.ejim.2020.07.006

104 Reiss AB, Miyawaki N, Moon J, Kasselman LJ, Voloshyna I, D'Avino R, et al. CKD, arterial calcification, atherosclerosis and bone health: inter-relationships and controversies. Atherosclerosis. 2018;278:49–59. https://doi.org/10.1016/j.atherosclerosis.2018.08.046

105 Ueda N, Takasawa K. Impact of inflammation on ferritin, hepcidin and the management of iron deficiency anemia in chronic kidney disease. Nutrients. 2018; 10(9):1173. https://doi.org/10.3390/nu10091173

106 Malyszko J, Malyszko JS, Matuszkiewicz-Rowinska J. Hepcidin as a therapeutic target for anemia and inflammation associated with chronic kidney disease. Expert Opin Ther Targets. 2019;23(5):407–21. https://doi.org/10.1080/14728222.2019.1599358

107 Kumagai T, Matsukawa N, Kaneko Y, Kusumi Y, Mitsumata M, Uchida K. A lipid peroxidation-derived inflammatory mediator: identification of 4-hydroxy-2-nonenal as a potential inducer of cyclooxygenase-2 in macrophages. J Biol Chem. 2004;279(46): 48389–96. https://doi.org/10.1074/jbc.M409935200

108 Liu X, Wang H, Huang C, Meng Z, Zhang W, Li Y, et al. Association between platelet distribution width and serum uric acid in Chinese population. Biofactors. 2019;45(3):326–34. https://doi.org/10.1002/biof.1491

109 Yun BH, Chon SJ, Lee YJ, Han EJ, Cho S, Choi YS, et al. Association of metabolic syndrome with coronary atherosclerosis in non-diabetic postmenopausal women. Climacteric. 2015;18(2):284–9. https://doi.org/10.3109/13697137.2014.960384

110 McGovern AP, de Lusignan S, Van Vlymen J, Liyanage H, Tomson CR, Gallagher H, et al. Serum phosphate as a risk factor for cardiovascular events in people with and without chronic kidney disease: a large community based cohort study. In: Kronenberg F, editor; 2013. Vol. 8. https://doi.org/10.1371/journal.pone.0074996

111 Ellam T, Wilkie M, Chamberlain J, Crossman D, Eastell R, Francis S, et al. Dietary phosphate modulates atherogenesis and insulin resistance in apolipoprotein E knockout mice—brief report. Arterioscler Thromb Vasc Biol. 2011;31(9):1988–90. https://doi.org/10.1161/ATVBAHA.111.231001

112 Feng X, Zheng Y, Guan H, Zhou X, Xu Y, Zhang X, et al. The association between urinary glucose and renal uric acid excretion in non-diabetic patients with stage 1-2 chronic kidney disease. Endocr Res. 2021;46(1):28–36. https://doi.org/10.1080/07435800.2020.1850760

113 Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med. 2004;350(11):1093–103. https://doi.org/10.1056/NEJMoa035700

114 Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Alcohol intake and risk of incident gout in men: a prospective study. Lancet. 2004;363(9417):1277–81. https://doi.org/10.1016/S0140-6736(04)16000-5

115 Wang M, Jiang X, Wu W, Zhang D. A meta-analysis of alcohol consumption and the risk of gout. Clin Rheumatol. 2013;32(11):1641–8. https://doi.org/10.1007/s10067-013-2319-y

116 Chen JH, Wen CP, Wu SB, Lan JL, Tsai MK, Tai YP, et al. Attenuating the mortality risk of high serum uric acid: the role of physical activity underused. Ann Rheum Dis. 2015;74(11):2034–42. https://doi.org/10.1136/annrheumdis-2014-205312

117 Aune D, Norat T, Vatten LJ. Body mass index and the risk of gout: a systematic review and dose–response meta-analysis of prospective studies. Eur J Nutr. 2014;53(8):1591–601. https://doi.org/10.1007/s00394-014-0766-0

118 Williams PT. Effects of diet, physical activity and performance, and body weight on incident gout in ostensibly healthy, vigorously active men. Am J Clin Nutr. 2008;87(5):1480–7. https://doi.org/10.1093/ajcn/87.5.1480

119 Richette P, Poitou C, Manivet P, Denis J, Bouillot J, Clément K, et al. Weight loss, xanthine oxidase, and serum urate levels: a prospective longitudinal study of obese patients. Arthritis Care Res. 2016;68(7):1036–42. https://doi.org/10.1002/acr.22798

120 George J, Carr E, Davies J, Belch JJF, Struthers A. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. Circulation. 2006;114(23):2508–16. https://doi.org/10.1161/CIRCULATIONAHA.106.651117

121 Jalal DI, Decker E, Perrenoud L, Nowak KL, Bispham N, Mehta T, et al. Vascular function and uric acid-lowering in stage 3 CKD. J Am Soc Nephrol. 2017;28(3):943–52. https://doi.org/10.1681/ASN.2016050521

122 Desideri G, Rajzer M, Gerritsen M, Nurmohamed MT, Giannattasio C, Tausche AK, et al. Effects of intensive urate lowering therapy with febuxostat in comparison with allopurinol on pulse wave velocity in patients with gout and increased cardiovascular risk: the FORWARD study. Eur Heart J Cardiovasc Pharmacother. 2022;8(3):236–42. https://doi.org/10.1093/ehjcvp/pvaa144

123 White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med. 2018;378(13):1200–10. https://doi.org/10.1056/NEJMoa1710895

124 Kim SC, Neogi T, Kang EH, Liu J, Desai RJ, Zhang M, et al. Cardiovascular risks of probenecid versus allopurinol in older patients with gout. J Am Coll Cardiol. 2018;71(9):994–1004. https://doi.org/10.1016/j.jacc.2017.12.052

125 Tausche AK, Alten R, Dalbeth N, Kopicko J, Fung M, Adler S, et al. Lesinurad monotherapy in gout patients intolerant to a xanthine oxidase inhibitor: a 6 month phase 3 clinical trial and extension study. Rheumatology. 2017;56(12):2170–8. https://doi.org/10.1093/rheumatology/kex350

126 Lin Y, Chen X, Ding H, Ye P, Gu J, Wang X, et al. Efficacy and safety of a selective URAT1 inhibitor SHR4640 in Chinese subjects with hyperuricaemia: a randomized controlled phase II study. Rheumatology. 2021;60(11):5089–97. https://doi.org/10.1093/rheumatology/keab198

127 Qu Y, Yu Y, Pan J, Li H, Cui C, Liu D. Systematic review and model-based analysis to identify whether renal safety risks of URAT1 inhibitors are fully determined by uric acid-lowering efficacies. Semin Arthritis Rheum. 2023;63:152279. https://doi.org/10.1016/j.semarthrit.2023.152279

128 Lin HC, Daimon M, Wang CH, Ho Y, Uang YS, Chiang SJ, et al. Allopurinol, benzbromarone and risk of coronary heart disease in gout patients: a population-based study. Int J Cardiol. 2017;233:85–90. https://doi.org/10.1016/j.ijcard.2017.02.013

129 Becker MA, Baraf HSB, Yood RA, Dillon A, Vázquez-Mellado J, Ottery FD, et al. Long-term safety of pegloticase in chronic gout refractory to conventional treatment. Ann Rheum Dis. 2013;72(9):1469–74. https://doi.org/10.1136/annrheumdis-2012-201795

130 Multidisciplinary Expert Task Force on Hyperuricemia and Related Diseases. Chinese multidisciplinary expert consensus on the diagnosis and treatment of hyperuricemia and related diseases. Chin Med J. 2017;130(20):2473–88. https://doi.org/10.4103/0366-6999.216416

131 Kim EJ, Song WH, Lee JU, Shin MS, Lee S, Kim BO, et al. Efficacy of losartan and carvedilol on central hemodynamics in hypertensives: a prospective, randomized, open, blinded end point, multicenter study. Hypertens Res. 2014;37(1):50–6. https://doi.org/10.1038/hr.2013.112

132 Ichihara A, Hayashi M, Kaneshiro Y, Takemitsu T, Homma K, Kanno Y, et al. Low doses of losartan and trandolapril improve arterial stiffness in hemodialysis patients. Am J Kidney Dis. 2005;45(5):866–74. https://doi.org/10.1053/j.ajkd.2005.02.022

133 Athyros VG, Mikhailidis DP, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, et al. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. J Clin Pathol. 2004;57(7):728–34. https://doi.org/10.1136/jcp.2003.012989

134 Xilifu D, Abudula A, Rehemu N, Zhao L, Zhou X, Zhang X. Effect of rosuvastatin on hyperuricemic rats and the protective effect on endothelial dysfunction. Exp Ther Med. 2014;8(6):1683–8. https://doi.org/10.3892/etm.2014.2027

135 Gilbert RE. SGLT-2 inhibition in patients with kidney disease. Diabetes Metab. 2014;40(6 Suppl 1):S23–S27. https://doi.org/10.1016/S1262-3636(14)72692-8

136 Juni RP, Al-Shama R, Kuster DWD, Van Der Velden J, Hamer HM, Vervloet MG, et al. Empagliflozin restores chronic kidney disease–induced impairment of endothelial regulation of cardiomyocyte relaxation and contraction. Kidney Int. 2021;99(5):1088–101. https://doi.org/10.1016/j.kint.2020.12.013

137 Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. The design and rationale for the dapagliflozin effect on cardiovascular events (DECLARE)–TIMI 58 trial. Am Heart J. 2018;200:83–9. https://doi.org/10.1016/j.ahj.2018.01.012

138 Hassan W, Shrestha P, Sumida K, Thomas F, Sweeney PL, Potukuchi PK, et al. Association of uric acid–lowering therapy with incident chronic kidney disease. JAMA Netw Open. 2022;5(6):e2215878. https://doi.org/10.1001/jamanetworkopen.2022.15878

139 Buzas R, Tautu OF, Dorobantu M, Ivan V, Lighezan D. Serum uric acid and arterial hypertension—data from Sephar III survey. In: Shimosawa T, editor; 2018. Vol. 13. https://doi.org/10.1371/journal.pone.0199865
140 Hsu SP, Pai MF, Peng YS, Chiang CK, Ho TI, Hung KY. Serum uric acid levels show a "J-shaped" association with all-cause mortality in haemodialysis patients. Nephrol Dial Transpl. 2004;19(2):457–62. https://doi.org/10.1093/ndt/gfg563
141 Kasahara K, Kerby RL, Zhang Q, Pradhan M, Mehrabian M, Lusis AJ, et al. Gut bacterial metabolism contributes to host global purine homeostasis. Cell Host Microbe. 2023;31(6):1038–53.e10. https://doi.org/10.1016/j.chom.2023.05.011
142 Młynarska E, Budny E, Saar M, Wojtanowska E, Jankowska J, Marciszuk S, et al. Does the composition of gut microbiota affect chronic kidney disease? Molecular mechanisms contributed to decreasing glomerular filtration rate. Int J Mol Sci. 2024;25(19):10429. https://doi.org/10.3390/ijms251910429
143 Mutluay R, Konca C, Erten Y, Paşaoğlu H, Değer SM, Ağirgün C, et al. Predictive markers of asymptomatic atherosclerosis in end-stage renal disease patients. Ren Fail. 2010;32(4):448–54. https://doi.org/10.3109/08860221003658258
144 Rodrigues TC, Maahs DM, Johnson RJ, Jalal DI, Kinney GL, Rivard C, et al. Serum uric acid predicts progression of subclinical coronary atherosclerosis in individuals without renal disease. Diabetes Care. 2010;33(11):2471–3. https://doi.org/10.2337/dc10-1007
145 Mallamaci F, Testa A, Leonardis D, Tripepi R, Pisano A, Spoto B, et al. A genetic marker of uric acid level, carotid atherosclerosis, and arterial stiffness: a family-based study. Am J Kidney Dis. 2015;65(2):294–302. https://doi.org/10.1053/j.ajkd.2014.07.021
146 Erdogan D, Gullu H, Yildirim E, Tok D, Kirbas I, Ciftci O, et al. Low serum bilirubin levels are independently and inversely related to impaired flow-mediated vasodilation and increased carotid intima-media thickness in both men and women. Atherosclerosis. 2006;184(2):431–7. https://doi.org/10.1016/j.atherosclerosis.2005.05.011
147 Roumeliotis S, Roumeliotis A, Dounousi E, Eleftheriadis T, Liakopoulos V. Dietary antioxidant supplements and uric acid in chronic kidney disease: a review. Nutrients. 2019;11(8):1911. https://doi.org/10.3390/nu11081911
148 Navaneethan SD, Beddhu S. Associations of serum uric acid with cardiovascular events and mortality in moderate chronic kidney disease. Nephrol Dial Transpl. 2009;24(4):1260–6. https://doi.org/10.1093/ndt/gfn621