Insights into renal damage in hyperuricemia: Focus on renal protection (Review)

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Abstract. The incidence of hyperuricemia has increased recently, posing a serious threat to public health. Hyperuricemia is associated with an increased risk of gout, chronic kidney disease (CKD), obesity, metabolic syndrome, type 2 diabetes mellitus, hypertension, hypertriglyceridaemia, metabolic dysfunction-associated steatotic liver disease, acute kidney injury, coronary heart disease and cardiovascular disease (CVD). These diseases are commonly accompanied by varying degrees of kidney damage. A number of randomized controlled clinical trials have investigated the effectiveness of UA-lowering therapies in preventing kidney disease progression. The present review provided fundamental insights into the pathogenesis, principles and therapeutic approaches for managing hyperuricemia in patients with aforementioned diseases and assesses the effect of uric acid-lowering therapy on diabetic nephropathy, systemic lupus erythematosus, CKD, CVD and obesity progression.

Contents

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1. Introduction

Uric acid (UA), the final product of both exogenous purines obtained from the diet and endogenous purines released from damaged, dying and dead cells, is mainly synthesized in the liver, intestine and vascular endothelium (1,2). Of the total UA produced daily, ~70% is excreted through the kidneys and the remaining 30% is excreted from the intestine (3). Hyperuricemia, a condition when the amount of UA produced exceeds the amount of UA excreted, can occur due to multiple factors, including acquired factors and rare genetic factors, such as myeloproliferative diseases, high-purine diet, alcohol intake, fructose intake, hypoxanthine guanine phosphoribosyltransferase deficiency and excessive phosphoribosylpyrophosphate synthase (Fig. 1) (4).

UA has been recognized as a mediator in a number of pathological processes, including inflammation, apoptosis, oxidative stress, vascular smooth muscle cell proliferation and endothelial dysfunction, involved in the development of various conditions, such as type 2 diabetes mellitus (T2DM), metabolic syndrome (MS), obesity, hypertension, cardiovascular disease (CVD), hypertriglyceridemia, metabolic dysfunction-associated steatotic liver disease (MASLD), acute kidney injury and chronic kidney disease (CKD; Fig. 2) (5,6). The incidence and prevalence of hyperuricemia continues to rise, contributing to increased overall morbidity and mortality rates as well as a greater economic burden on healthcare. Consequently, it is now considered a major public health concern.

Increased serum UA levels are closely associated with kidney disease. Kidney disease, particularly when associated with a decrease in glomerular filtration rate, can lead to increased serum UA levels due to insufficient UA excretion

resulting from renal failure. Therefore, hyperuricemia may be a secondary phenomenon in patients with kidney disease (7). However, renal damage may be associated with increased oxidative stress induced by intracellular UA (Fig. 1) (8-11). Hence, studying the interaction between blood UA and the kidneys is of great significance.

Epidemiological and empirical studies have revealed an association between hyperuricemia and an increased risk of CKD, new-onset hypertension, stroke, CVD and coronary heart disease (CHD) (4,12). These diseases are commonly accompanied by varying degrees of kidney damage. The present review summarized the complex correlation between hyperuricemia and renal injury as well as the pathophysiological factors associated with UA management. Furthermore, it also assessed the correlation between UA, CKD, gout, diabetes, obesity, systemic lupus erythematosus (SLE) and CVD and discussed several existing management strategies for hyperuricemia.

2. Source and metabolic characteristics of UA

The regulation of UA levels is complex and involves multiple factors, including the regulation of UA production in the liver and its excretion through the kidneys and intestine (13). Of UA, ~80% and 20% is produced from the endogenous and exogenous purines, respectively. UA from exogenous sources, primarily from foods rich in purine compounds, nucleic acids and nucleoproteins such as beans, seafood, animal viscera, mushrooms, alcohol and meat, endogenous UA is formed by the conversion, decomposition and metabolism of amino acids, nucleic acids and phosphoribosyl groups (Fig. 1) (2,14).

Xanthine oxidase, a vital rate-limiting enzyme in purine metabolism, converts hypoxanthine to xanthine and xanthine to UA, which are the two essential steps in the UA production from purines (14). Xanthine oxidase also converts guanine nucleotides to xanthine, which is further oxidized to UA by xanthine oxidase (15,16). Hyperuricemia is primarily caused by excessive intake and decreased excretion of UA (17). UA excretion disorders may be caused by various factors originally involving abnormal expression of urate transporters in the proximal tubules, such as glucose transporter 9 (GLUT9), uric acid transporter 1 (URAT1), organic anion transporter 1 (OAT1), OAT3 and ATP-binding cassette subfamily G member 2 (ABCG2) (18,19). Notably, regulating the expression of these urate transporters can improve UA excretion (19,20).

3. UA in CKD

Urate is primarily excreted through three pathways: glomerular filtration, tubular reabsorption and tubular secretion (21). Decreased glomerular filtration, decreased tubular secretion and enhanced tubular reabsorption can increase UA levels, ultimately causing hyperuricemia over time. Hyperuricemia is generally associated with CKD. A recent meta-analysis reported an occurrence of hyperuricemia in patients with advanced CKD, with a prevalence of 64 and 50% in patients with stage 3 and 4 or 5 CKD, respectively (22). Therefore, hyperuricemia is a risk factor for CKD progression (23).

Studies have shown that renal fibrosis, vascular damage and endothelial dysfunction are the main characteristics of UA-induced renal injury (4,8,9,24,25). As a potential mechanism underlying CKD progression due to hyperuricemia, sodium urate crystals can induce epithelial-mesenchymal transition (EMT) in renal epithelial cells. This process is characterized by enhanced α-smooth muscle actin production, excessive extracellular matrix (ECM) deposition, activation of NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasomes and oxidative stress due to NADPH oxidase-dependent reactive oxygen species (ROS) and XO-dependent ROS (8-11,26). Furthermore, renal interstitial fibrosis is also associated with the activation of the TGF-β/Smad3 pathway in hyperuricemia nephropathy (HN) mice (27).

The regulation of the transporters involved in urate excretion and reabsorption as well as the signaling pathways involved in urate-induced kidney damage may alleviate hyperuricemia-induced kidney damage. For example, Fang *et al* (18) report that *Eucommia ulmoides* cortex ethanol extract significantly reduces serum uric acid (SUA) levels, which are associated with increased mRNA expression of *OAT1* and *OAT3* and significantly decrease the mRNA levels of *GLUT9* and *URAT1* in the kidney.

A clinical trial involving 269,651 patients demonstrates that UA-lowering therapy is not associated with beneficial kidney outcomes in patients with kidney function at least 60 ml/min/1.73 m^2 and no albuminuria (28). Moreover, this trial reports a higher risk of developing CKD and proteinuria in patients with less severely elevated serum UA concentrations receiving UA-lowering treatment (28). The 2024 Clinical Practice Guideline for Chronic Kidney Disease recommends urate-lowering interventions for symptomatic hyperuricemia, but not for asymptomatic hyperuricemia, in patients with CKD. The evidence supporting the use of urate-lowering therapy to delay CKD progression in patients with asymptomatic hyperuricemia remains insufficient (29). Consequently, UA-lowering treatments are not recommended to patients with asymptomatic hyperuricemia for slowing the progression of kidney disease. By contrast, a meta-analysis of 17 studies demonstrates the importance of considering UA-lowering therapy in clinical strategies for patients with CKD with asymptomatic hyperuricemia (30). Some studies suggest that UA lowering is beneficial in preventing CKD development (31,32). However, the results of these trails may not be conclusive, considering their quality. Therefore, more clinical trials are necessary to establish the baseline blood UA concentration requiring UA-lowering treatment to timely prevent or alleviate kidney damage associated with elevated UA levels.

4. UA and kidney damage in gout

Hyperuricemia can induce renal arteriopathy, reduce renal blood flow, increase urinary albumin excretion and cause gout nephropathy, also known as HN. It is characterized by renal interstitial and tubular damage (33). Increased and accumulated UA readily forms monosodium urate crystals in the kidney following hyperuricemia. These crystals further damage tubular epithelial cells by inducing endoplasmic reticulum stress, mitochondrial disorders, autophagy dysfunction and ultimately apoptosis. Hyperuricemia leads to both crystal and crystal-independent kidney injuries (Fig. 2) (34), involving oxidative stress, renal cell apoptosis, angiotensin

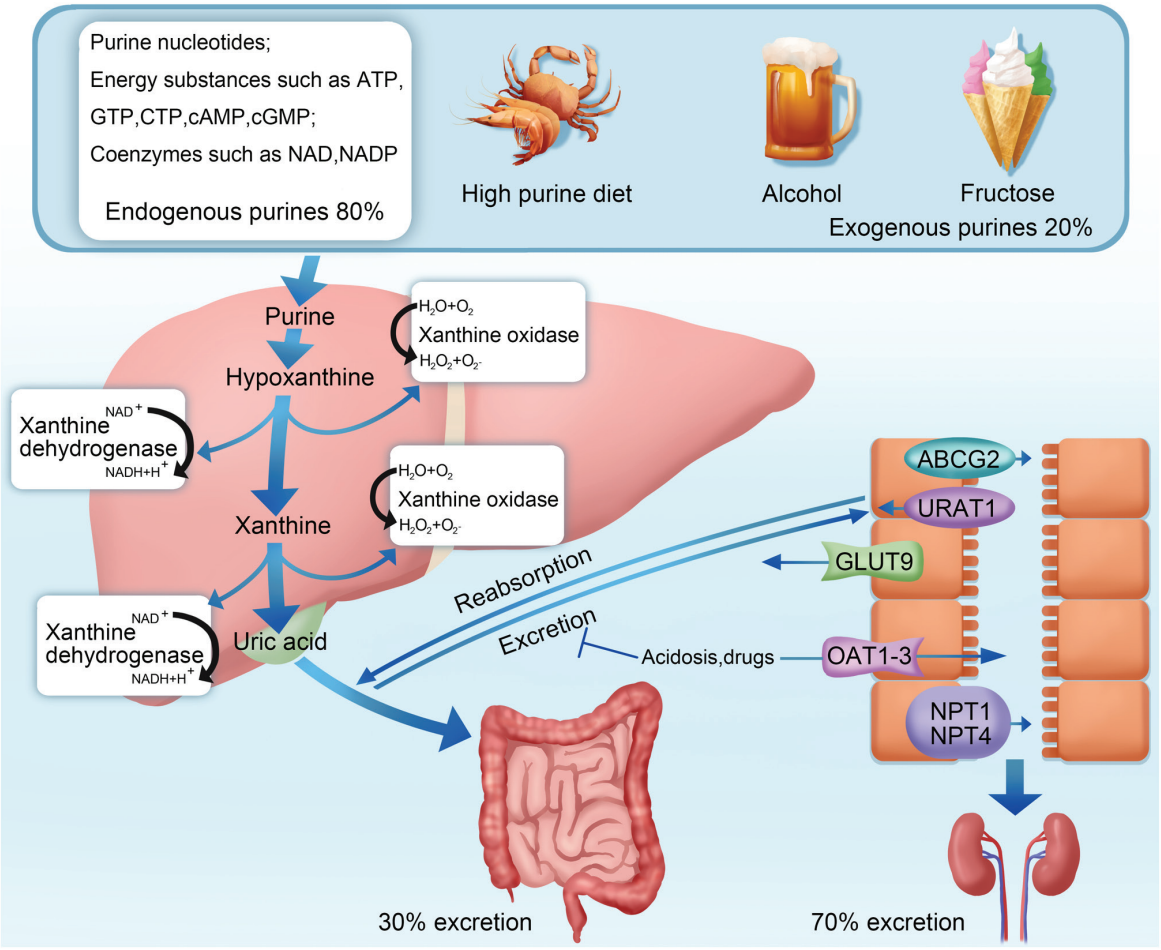

Figure 1. UA is the final product of purine, with ~80 and 20% derived from the endogenous purine metabolism and exogenous purine sources (such as high purine diet, alcohol intake and fructose intake), respectively. The conversion, decomposition and metabolism of amino acids, nucleic acids and phosphate ribose groups in the body generates endogenous UA. XOR enzyme catalyzes the terminal two reactions of purine catabolism in humans. In particular, XOR catalyzes the oxidation from hypoxanthine to xanthine and from xanthine to UA, with the simultaneous reduction of NAD+ or O_2. Notably, 70 and 30% UA is excreted through the kidneys and intestine, respectively. UA, uric acid; XOR, xanthine oxidoreductase.

system activation and inflammatory responses (35). The inflammatory response and the ROS released by injured mitochondria play essential roles in HN pathogenesis (36,37) and increased levels of NLRP3 inflammasome, NF-κB and inflammatory mediators, including IL-1β, IL-6, TNF-α, MCP-1 and ICAM-1, further accelerate HN progression (19,26,35,37,38). Furthermore, autophagy is also involved in the development of renal fibrosis, which is associated with the activation of renal fibroblasts, EMT, mitochondrial fission, cell pyroptosis and apoptosis (38,39). In a hyperuricemia rat model, the autophagy inhibitor 3-MA, when administered as a delayed treatment, effectively reduces the deposition of ECM proteins by blocking EMT, as well as the phosphorylation of STAT3 and NF-κB. Furthermore, it inhibits the release of various profibrotic cytokines/chemokines in damaged kidneys (39). Notably, the inhibition of NLRP3 inflammasome-mediated pyroptosis due to autophagy blockade prevents HN progression (38).

Multiple compounds and traditional Chinese medicines can improve HN by inhibiting inflammation, modulating the expression of UA transporters and reducing cell apoptosis. A recent study demonstrates that the SGLT2 inhibitor dapagliflozin ameliorates UA-induced tubular dysfunction and fibrotic activation in HN by activating the ERRα-OAT1 axis to enhance UA excretion (40). The naturally occurring flavonol fisetin exhibits anti-inflammatory, antioxidant and antiangiogenic properties (35). Ren *et al* (35) demonstrate that UA levels can be lowered by regulating the expression of kidney urate transporters, including OAT1, OAT3, URAT1 and ABCG2. Based on traditional Chinese medicine theory and clinical practice in kidney disease treatment, a self-designed renal herb formula protects against HN by inhibiting the apoptosis of resident kidney cells and inflammatory response by targeting the NF-κB and p53 signaling pathways (34). Furthermore, an ethanol extract of the bark of *Liriodendron chinense* (Hemsl.) Sarg (EELC) can increase urine UA excretion in HN mice by upregulating OAT1, OAT3 and ABCG2 (41). Additionally, inhibition of JAK2/STAT3 signaling attenuates HN progression by alleviating renal inflammation (35,41).

5. UA and kidney damage in diabetes

Diabetes, a multisystemic disorder caused by absolute or relative insulin deficiency or peripheral tissue resistance to insulin, is one of the most important comorbidities of MS (42-44). Hyperuricemia is a common complication of T2DM and serum UA levels are an important risk factor for T2DM

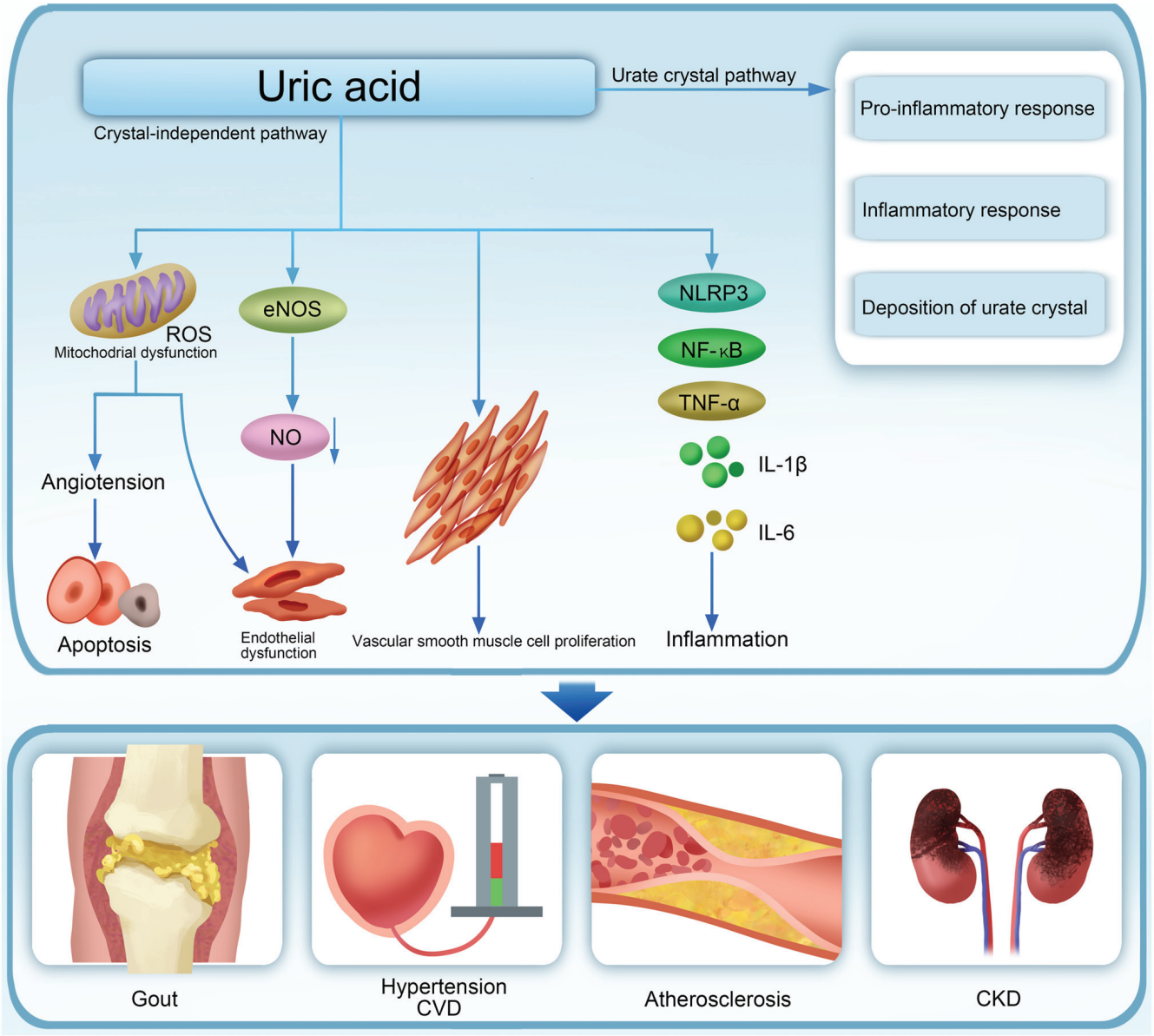

Figure 2. Uric acid is considered a mediator in the pathological process, including inflammation, cell apoptosis, oxidative stress, vascular smooth muscle cell proliferation and endothelial dysfunction, involving the development of various diseases, including gout, hypertension, cardiovascular disease, atherosclerosis and chronic kidney disease. ROS, reactive oxygen species; eNOS, endothelial nitric oxide synthase; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; CVD, cardiovascular disease; CKD, chronic kidney disease.

occurrence and development, as well as its associated complications (Table I) (45). The magnitudes of insulin resistance and serum UA concentration are significantly correlated and insulin resistance, a risk factor for hyperuricemia, contributes to decreased UA excretion by the kidneys, resulting in hyperuricemia (46,47). In a previous study, decreased urinary urate excretion following insulin administration in rats is associated with increased and decreased expressions of URAT1 (a major urate reabsorption transporter) and ABCG2 (a major urate secretory transporter), respectively (48). A study involving patients with hyperuricemia and T2DM reports reduced albuminuria and serum urate concentration following intensive urate-lowering therapy with verinurad combined with the XOI febuxostat (49).

A number of epidemiological studies report a correlation between serum UA levels and the risk of diabetic kidney disease (DKD). Jalal *et al* (50) conducted a prospective observational study analyzing data from a coronary artery calcification study of patients with type 1 diabetes (T1D) involving a stepwise logistic regression model to predict the development of microalbuminuria or macroalbuminuria after a 6-year follow-up in 324 participants without evidence of trace or macroalbuminuria at baseline. Baseline serum UA levels, HbA1c and prealbuminuria are predictive factors for microalbuminuria or macroalbuminuria. The study revealed that every 1 mg/dl increase in serum UA baseline levels increased the risk of developing trace or large amounts of albuminuria at 6 years by 80% (50). Similarly, a cross-sectional study involving 20,464 adult patients with T1D from Italy, with available SUA measurements for 11,162 patients, reported an association between elevated serum UA levels and low estimated glomerular filtration rate (eGFR) (51). Previous research

Table I. Evidence on the association between serum uric acid levels and diabetic kidney disease.

First author/s, year	Study population	Sample size	Age, year	Sex	Group	Results	(Refs.)
Zhou, 2023	Patient	3,162	≥65	Female, male	Four groups based on SUA quartile as follows: Q1 (≤259.5 μmol/l), Q2 (259.5-313.3 μmol/l) Q3 (313.3-373.0 μmol/l) Q4 (>373 μmol/l)	The optimal cutoff value of serum UA for the risk of new-onset CKD in older patients with diabetes is 347.4 μmol/l. Hyperuricemia is an independent predictor of incident CKD.	(111)
Aktas, 2023	Patient	287	29-92	Female, male	Patients with diabetes with DKI Patients with diabetes without DKI	UA to HDL ratio has an independent predictive role in DKI.	(112)
Ji, 2022	Patient (meta-analysis)	25,741	>18	Female, male	Highest category of SUA Lowest category of SUA Per 1 mg/dl increase of SUA	Serum UA is associated with an increased risk of diabetic kidney disease in patients with T2DM.	(54)
Pilemann-Lyberg, 2018	Patient	54		Female, male	Highest quartile Lower quartiles	UA is weakly associated with a decline in GFR in patients with type 1 diabetes with overt nephropathy.	(113)
Doria, 2020	Patient	530	51.1 (mean age)	Female, male	Placebo group Allopurinol group	No evidence of clinically meaningful benefits of serum urate reduction with allopurinol on kidney outcomes among patients with T1D and early-to-moderate DKD. During the intervention period, the mean serum urate level decreased from 6.1 to 3.9 mg/dl with allopurinol and remained at 6.1 mg/dl in the placebo group.	(56)
D'Elia, 2024	Patient	2,230	18-95	Female, male	Group 1: participants with evidence of overt kidney dysfunction (KD[+], with eGFR ≤60 ml/min per 1.73 m^2) Group 2: participants without evidence of overt kidney dysfunction (KD[-], with eGFR >60 ml/min per 1.73 m^2)	SUA/sCr ratio >5.35 units was associated with a significantly higher mortality rate in patients with normal kidney function, whereas SUA/sCr ratio >7.50 units was associated with higher CV mortality in patients with overt kidney dysfunction.	(114)
Ahola, 2017	Patient	3,895	27-52	Female, male	Group 1: Normal AER Group 2: Microalbuminuria Group 3: Macroalbuminuria Group 4: End-stage renal disease	Serum UA concentration is not causally related to diabetic nephropathy but is a downstream marker of kidney damage.	(115)

SUA, serum uric acid; UA, uric acid; CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus; DKI, diabetic kidney injury; sCr, serum creatinine; AER, albumin excretion rate; T1D, type 1 diabetes; DKD, diabetic kidney disease; GFR, glomerular filtration rate; CV, cardiovascular; HDL, high-density lipoproteins.

also establishes an association between SUA levels and DKD risk in patients with T2D (52,53). Additionally, a meta-analysis involving 25,741 patients with T2DM demonstrates an association between serum UA levels and an increased risk of DKD in these patients (54).

Two large randomized clinical trials examining UA reduction in patients with T1D found that treatment of hyperuricemia did not improve the progression of preexisting kidney disease (55,56). In the Preventing Early Renal Function Loss in T1D study, the reduction of SUA levels with allopurinol did not provide any benefits for reducing GFR rate or to other renal outcomes in patients with T1D, early to moderate diabetic nephropathy, or high normal SUA levels (56). Overall, these results failed to demonstrate a statistically significant effect of allopurinol on kidney outcomes in these patients. However, some studies have demonstrated that febuxostat plus verinurad can improve albuminuria in patients with T2DM by reducing serum UA levels (49). Therefore, UA-lowering therapy may exert different effects on kidney damage caused by different types of diabetes. Nevertheless, more clinical studies are warranted in the future.

6. UA and kidney damage in obesity

A close relationship has been reported between obesity and the development of end-stage renal disease in later years (57,58). Obesity is also associated with CKD progression (58) and obesity-related glomerular diseases include proteinuria, glomerular enlargement, progressive glomerulosclerosis and CKD. UA is an important risk factor for renal injury in metabolically unhealthy patients with obesity (59). Furthermore, obesity is a risk factor for hyperuricemia (60). A retrospective analysis of 8,522 participants showed a positive correlation between SUA levels and obesity or being overweight (61). Weight loss effectively lowers UA levels (62,63). Moreover, bariatric surgery significantly reduced serum UA levels within 12 and 24 months in patients with and without diabetes (60).

UA accumulation is an important and deleterious step in obesity (64). The resistin/UA index assesses the risk of MS and is a prognostic factor for young individuals with obesity (65). This index correlates with glucose, insulin and insulin resistance (65). Importantly, individuals with obesity exhibit an increased risk of kidney damage. Moreover, insulin resistance, UA levels and blood pressure are the main risk factors for kidney injury. Therefore, stringent monitoring by physicians is essential to assess the potentially harmful interactions between obesity and its metabolic phenotypes. Various measures such as weight loss, exercises, improved insulin sensitivity and serum UA monitoring may be crucial in further offsetting the increased risk of kidney injury in individuals with obesity.

Bariatric surgery can significantly lower serum UA levels in patients with severe obesity (66-68). Furthermore, a meta-analysis by Yeo *et al* (69) indicates that weight loss achieved through bariatric surgery reduces serum UA levels and decreases the frequency of gout attacks (70). These results suggest a close relationship between obesity and hyperuricemia. However, further research is needed to determine whether UA-lowering therapy can improve renal function in patients with obesity.

7. UA and kidney damage in SLE

A strong inflammatory response in the kidneys can damage the glomeruli and tubulointerstitium. As UA is produced by damaged cells and promotes immune inflammatory responses, it is considered a key molecule in the pathogenesis of diseases such as hypertension, kidney disease and SLE (71,72). SLE is an autoimmune disease that affects several organs. Lupus nephritis (LN) is a serious complication of SLE. LN is closely associated with hyperuricemia and UA is considered a risk factor for renal injury in SLE (Table II) (72,73). Multivariate analysis in a previous study confirms high UA levels as an independent variable associated with LN (73). Serum UA levels are generally considered markers of renal dysfunction. Particularly, UA is associated with the severity of kidney disease in patients with LN and is an indicator of poor prognosis in SLE (74,75). Higher UA levels contribute to the development of new kidney damage in patients with SLE independent of other known risk factors (74). A study involving 45 patients reported age, hemoglobin, blood UA, urine protein, IL-17 and IL-34 as independent risk factors for poor prognosis in LN (76). Serum UA levels of <6.05 mg/dl at 12 months of follow-up indicate good long-term renal outcomes in LN (75).

UA is constitutively expressed in cells and an increase in its concentration following cell damage stimulates dendritic cell maturation, recruiting other immune cells and leading to the release of inflammatory mediators. UA is considered a key mediator produced by damaged cells, acting as a danger signal and promoting inflammatory responses (72). Hyperuricemia may serve as an adjuvant for the development and progression of renal injury in SLE (77). UA-lowering therapy may slow down the deterioration in LN and can effectively delay the progression of CKD. Notably, analysis of GFR and serum creatinine levels revealed significant benefits of UA-lowering treatment in hospitalized patients compared with the patients in the control group. Additionally, UA-lowering treatment may improve kidney outcomes. In a previous study, the control group had a higher number of patients with significantly worse renal function than the treatment group (78). Therefore, treating hyperuricemia may reduce kidney damage and slow the SLE-induced renal function loss.

8. UA and kidney damage in CVD

CVD is the most common cause of death worldwide (79) and hyperuricemia is a risk factor for CVD. Soluble UA promotes atherosclerosis by activating the NLRP3 inflammasome, whereas decreased UA levels attenuate atherosclerotic plaque development (80). In a study involving 441,771 person-years of follow-up, 1,288 deaths from CVD were associated with high serum UA levels (81). Furthermore, a 5-year cohort study shows that asymptomatic hyperuricemia without comorbidities could predict CVD (82). UA exhibits a sex-related effect, with an optimal threshold for predicting cardiovascular outcomes and all-cause mortality, reflecting potential sex differences in disease pathophysiology (83).

Hypertension is a major cardiovascular risk factor owing to its high prevalence, correlation with other risk factors and effect on major cardiovascular events (84). Several clinical trials and animal studies demonstrate that UA can cause hypertension,

Table II. Evidence on the association between serum uric acid and SLE in patients with LN.

First author/s, year	Study population	Sample number	Age, year	Sex	Group	Results	(Refs.)
Hafez, 2021	Patient	60	>18	Female, male	Group 1: 30 patients with LN (females: 22, males: 8) Group 2: 30 patients without LN (female: 28, males: 2)	The serum UA levels were significantly higher in group 1 compared with group 2. Group 1 had significantly higher SLEDAI and SLEDAI-R scores than group 2. The serum UA level was a significant predictor of nephritis in patients with SLE, with the best cut-off value being >4.9 mg/dl.	(72)
Oh, 2020	Patient and control	578	35.7 (±12.3)	Female, male	81 males (51 control and 30 with hyperuricemia) 497 females (311 controls and 186 with hyperuricemia)	The serum UA was an independent risk factor for LN progression. The serum UA level was associated with female sex, not male sex. During the follow-up period, a total of 51 (8.8%) patients experienced progression of LN, with 24 (6.6%) patients with LN progressions in the control group and 27 (12.5%) in the hyperuricemia group.	(116)
Elnady, 2021	Patient and control	89	18-50	Female	Group 1: 25 patients with LN Group 2: 26 patients without LN Group 3: 38 healthy controls	All patients with LN with baseline serum UA ≥0.52 mmol/l exhibited new-onset renal damage within 43 months. High serum UA levels had a significant association with LN onset and new onset of renal damage.	(117)
Calich, 2018	Patient	46	18-45	Female	Group 1: LN+ (n=18) Group 2: LN- (n=28)	The LN+ group had higher serum UA levels (5.54±1.67 mg/dl) than both LN- (3.65±1.09 mg/dl; P<0.001) and control (3.65±1.09 mg/dl; P<0.001) groups. LN was associated with higher UA levels.	(73)
Han, 2023	Patient	123	39.48 (±13.54)	Female, male	Control group (LN+, n=51) Hyperuricemia group (LN + HUA, n=72)	The laboratory tests at renal biopsy revealed hyperuricemia in 72 (58.5%) of the 123 patients. Higher serum UA levels in females with LN were associated with increased risk of renal progression.	(77)
Wang, 2024	Patient	194			Control group Hyperuricemia group	For each 100 μmol/l increase in serum UA levels, the risk of ESRD or death increased by 10%. SUA levels are directly associated with renal arteriolar damage and poor prognosis in patients with LN.	(118)
Ugolini-Lopes, 2019	Patient	80				Serum UA level of <6.05 mg/dl at 12 months of follow-up is a predictor of good long-term renal outcome in LN.	(75)

Table II. Continued.

First author/s, year	Study population	Sample number	Age, year	Sex	Group	Results	(Refs.)
Wen, 2022	Patient	1,297	≥14	Female, male	HUA group Non-HUA group	The 5- and 10-year mortality rates did not differ significantly between the HUA and non-HUA groups, respectively. During the 52-month follow-up, the 5- and 10-year incidence rates of renal endpoint events were 11.1 and 19.5% in the HUA group and 8.3 and 13.8% in the non-HUA group, respectively.	(119)

LN, lupus nephritis; UA, uric acid; SLEDAI, SLE disease activity index; SLEDAI-R, renal SLEDAI score; ESRD, end-stage renal disease; HUA, hyperuricemia.

kidney disease and CVD. Hyperuricemia is associated with an increased risk of CVD but not with stroke or CHD alone in patients with hypertension (12). Hyperuricemia occurs in 25-40% of individuals with untreated hypertension (85). Mild hyperuricemia is linked with early signs of renal injury regardless of the eGFR in primary hypertension (86). Randomized controlled trials report a substantial decrease in blood pressure following an uricosuric agent- or XOR inhibitor-induced reduction in serum UA levels (87-89). Increased oxidative stress associated with the biochemical processes involved in UA production could explain the interactions between elevated SUA levels and hypertension (90). UA may contribute to hypertension via endothelial dysfunction induced by both crystal-dependent (extracellular UA) and crystal-independent (intracellular UA) pathways (87).

Elevated circulating serum UA levels are strongly associated with the development of hypertension and renal disease (91) and previous research demonstrates an increase in the incidence of kidney disease and hypertension in patients with gout. Furthermore, a correlation is reported among elevated UA levels, renal artery disease and hypertension. Moreover, some randomized intervention studies demonstrate benefits of the treatment of asymptomatic hyperuricemia in improving blood pressure regulation and renal function (92).

UA induces hypertension through its effect on endothelial function and impairment of nitric oxide production (91,93). Hypertension may be the primary cause of subclinical kidney injury (94,95). Therefore, UA, urate crystals and XOR (especially XO, which produces oxidative stress) may contribute to the development of renal disease, hypertension and CVD through tubular interstitial disorder, endothelial dysfunction, stimulation of the renin-angiotensin system and vascular smooth muscle cell proliferation (90,91,93). A clinical trial involving 30 adolescents with newly diagnosed stage 1 essential hypertension and serum UA levels of ≥6.0 mg/dl shows that treatment with allopurinol markedly decreases UA levels and significantly reduces casual and ambulatory systolic and diastolic blood pressure (89). However, this effect of allopurinol may not be due to UA reduction but rather by regulating endothelial dysfunction by decreasing UA and xanthine oxidase-induced oxidants. Nevertheless, more clinical trials are needed to validate these results and assess their general applicability to a larger hypertensive population.

9. Urate-lowering therapy

Lifestyle management, as the overall principle of non-pharmacological treatment for hyperuricemia, includes limiting alcohol consumption, diet control, exercise and weight loss in individuals with obesity, followed by the management of related comorbidities and risk factors such as hypertension, hyperlipidemia, hyperglycemia and smoking. In terms of diet, animal foods with high purine content (e.g., animal viscera, seafood) should be restricted. In addition, sweet fruits and soft drinks containing fructose should be consumed in moderate amounts, as they can increase blood UA levels.

Individualized therapeutic approaches should be adopted while selecting UA-lowering drugs. UA-lowering therapy drugs are categorized based on their mechanisms of action as follows: i) Inhibitors of UA synthesis, including XOIs such

Table III. Effect of urate-lowering therapy in preventing kidney damage.

First author/s, year	Drug	Mechanism	Dose, mg	Sample size	Criterion	Results	(Refs.)
Goicoechea, 2010	Allopurinol	Xanthine oxidase inhibitor	100	113	Patients with eGFR <60 ml/min	Allopurinol treatment slowed renal disease progression and reduced the risk of cardiovascular events in compared with standard therapy. After 24 months of allopurinol treatment, serum UA levels were significantly decreased in patients treated with allopurinol, from 7.8±2.1 to 6.0±1.2 mg/dl, whereas serum UA levels of individuals in the control group remain unchanged throughout the study period.	(120)
Kwak, 2018	Febuxostat		20-80	111	Patients with allopurinol-refractory hyperuricemia CKD	Febuxostat effectively lowered serum UA levels and was well tolerated in patients with CKD and allopurinol-refractory hyperuricemia. Febuxostat treatment significantly lowered serum UA levels, with response rates of >70% at all the time points for 1 year.	(121)
Kao, 2011	Allopurinol	Xanthine oxidase inhibitor	300	53	Patients with stage 3 CKD and LVH	Allopurinol could regress LVH and improve endothelial/vascular dysfunction in patients with CKD. Allopurinol at 300 mg once daily also reduced baseline urate levels by 41% from 0.44±0.09 to 0.26±0.85 mmol/l after 9 months.	(122)
Badve, 2020	Allopurinol	Xanthine oxidase inhibitor	100-300	363	Patients with stage 3 or 4 CKD and no history of gout	Allopurinol did not slow the decline in eGFR in patients with CKD. Allopurinol continuously reduced serum UA levels by an average of 35%.	(55)
Smink, 2012	Losartan	Angiotensin receptor blocker		2,387	Patients with T2DM and nephropathy	Losartan significantly reduced serum UA in patients with T2DM and nephropathy and the effect of losartan on serum UA levels contributed to its ultimate cardiovascular-protective effect.	(123)
Castilla-Ojo, 2023	Losartan	Angiotensin receptor blocker	50	55	Patients with SBP <180 mm Hg and DBP 90-109 mm Hg	Losartan significantly reduced serum urate, especially among younger adults with hypertension.	(124)

Table III. Continued.

First author/s, year	Drug	Mechanism	Dose, mg	Sample size	Criterion	Results	(Refs.)
Heerspink, 2024	Verinurad/ Allopurinol	Allopurinol: xanthine oxidase inhibitor Verinurad: urate transporter 1 inhibitor	300	861	Patients with serum urate concentrations ≥6.0 mg/dl, eGFR ≥25 ml/min per 1.73 m^2	Verinurad in combination with allopurinol did not decrease UACR or eGFR decline but further reduced serum urate compared with allopurinol alone or placebo.	(125)
Nagaraju, 2023	Febuxostat/ Allopurinol	Xanthine oxidase inhibitor	43.70±14.5 108.51±40	101	Patients with Stage 3 or 4 CKD and hyperuricemia (>7 mg/dl)	Febuxostat was superior at reducing hyperuricemia than allopurinol, but no significant difference was observed for CKD progression.	(23)
Xin, 2016	Allopurinol	Xanthine oxidase inhibitor	300-900	594	Patients at risk of cardiovascular risks	Allopurinol therapy is associated with significantly improved endothelial function in patients at risk of CVD risks. Compared with the control group, treatment using allopurinol reduced serum UA and the ΔUA between allopurinol and control groups ranged from -59.4 to -12.1%.	(126)
Konishi, 2022	Febuxostat	Xanthine oxidase inhibitor	10-40	1,070	Patients with asymptomatic hyperuricemia without gout.	Febuxostat reduces the risk of the composite of cerebral, cardiovascular and renal events and mortality in the secondary prevention setting.	(127)

eGFR, estimated glomerular filtration rate; UA, uric acid; CKD, chronic kidney disease; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; DBP, diastolic blood pressure; T2DM, type 2 diabetes; UACR, urinary albumin-creatinine ratio

as allopurinol and febuxostat; ii) enhancers of UA excretion, including probenecid, benzbromarone and selective UA reabsorption transporter inhibitors; and iii) promoters of UA dissolution, such as uricase (96).

Allopurinol acts as a precursor of oxypurinol by targeting the active site of xanthine oxidase and inhibiting the final step of purine metabolism, thereby reducing UA production without disrupting purine nucleoside synthesis. As selective inhibitors of xanthine oxidase, allopurinol and other XOIs effectively lower UA levels with an acceptable safety profile, making them commonly prescribed treatments for hyperuricemia (97-99). Febuxostat is a non-purine XOI that exhibits an efficacy similar to that of allopurinol in patients with hypersensitivity to allopurinol. This medication, similar to oxypurinol, is well-tolerated in individuals with CKD owing to its tight binding to the active site of xanthine oxidase, thereby inhibiting the conversion of purines into UA. Xanthine oxidase is predominantly localized in the liver, where it exhibits the highest activity (46,97). Uricosurics, including drugs such as probenecid, benzbromarone and sulfinpyrazone, can lower UA levels by increasing renal clearance of urate. The American College of Rheumatology recommends probenecid as the preferred uricosuric drug because it prevents urate reabsorption in the proximal tubule, thereby decreasing serum urate levels (96,100).

Urate-lowering therapies can effectively prevent kidney damage during the progression of CKD, CVD, gout and obesity (Table III) (101). Notably, a 2-year clinical trial demonstrates that allopurinol treatment improves the eGFR and reduces CV risk (101). Furthermore, benzbromarone exhibits improved efficacy in rapidly reducing SUA levels and inhibiting inflammation in patients with hyperuricemia and gout compared with febuxostat (102). According to the 2020 American College of Rheumatology Guidelines for the Management of Gout, urate-lowering therapy is recommended in patients with gout and CKD (103). Sodium-glucose cotransporter type 2 inhibitors (SGLT2i) are revolutionary treatments for patients with T2DM with cardiovascular, kidney and serum urate-lowering benefits (104). SGLT2i significantly lowers UA levels and cardiovascular kidney metabolic risk in patients with gout (105). Furthermore, SGLT2i dapagliflozin ameliorates UA-induced tubular dysfunction and fibrotic activation in patients with HN by enhancing UA excretion (40). Losartan is currently the only angiotensin II receptor blocker that significantly reduces UA levels. Clinical guidelines recommend the addition or switching to losartan as an antihypertensive drug for patients with gout, as it lowers both blood pressure and UA levels (106). Losartan can ameliorate renal interstitial fibrosis through different molecular mechanisms in both clinical and animal experiments (107-110).

A clinical controlled trial involving patients with stage 3 or 4 CKD, with most patients having hyperuricemia (despite hyperuricemia not being an inclusion criterion), receiving allopurinol or placebo treatment for 2 years reports that allopurinol treatment did not significantly affect the rate of GFR decline (55). Another clinical trial involving 530 patients with T1D and early-to-moderate diabetic nephropathy reports no clinical benefit of reducing serum urate using allopurinol for renal prognosis (56). These inconsistent results indicate that response to treatment aimed at reducing UA levels may vary due to the highly complex clinical features of patients, including factors such as age, weight, sex and complications. Accordingly, the selection of appropriate patients and careful clinical trial design are crucial for determining the efficacy of such treatments. Furthermore, clinical trials results may guide intervention strategies and must be seriously analyzed and summarized. Importantly, high-quality randomized controlled trials are essential for accurately identifying the indications of UA-lowering therapy.

10. Conclusion

UA, urate crystals and XOR-mediated oxidative stress probably participate in the progression of CKD, hypertension and CVD through pathological mechanisms such as vascular smooth muscle cell proliferation, endothelial dysfunction and renal tubulointerstitial disorders. However, whether urate-lowering therapy effectively prevents the progression of diabetic nephropathy, LN, CKD, CVD and obesity in asymptomatic patients with hyperuricemia remains controversial. Prior to reaching a definitive conclusion on initiating treatment for hyperuricemia, personalized treatment for patients with hyperuricemia combined with other diseases should be considered to effectively reduce SUA levels. Moreover, high-quality and comprehensive clinical and basic scientific research on hyperuricemia and purine metabolism, as well as a definitive assessment of the effects of urate-lowering therapy on kidney function preservation, is required through larger clinical studies in the future.

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Availability of data and materials

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Authors' contributions

JJ and XM were responsible for project administration, conceptualisation and also designed the method for writing the review. HY and JY wrote and edited the manuscript. TZ reviewed and made significant revisions to the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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