International Urology and Nephrology (2019) 51:2227–2233
https://doi.org/10.1007/s11255-019-02256-5

NEPHROLOGY - REVIEW

# Treatment of asymptomatic hyperuricemia complicated by renal damage: a controversial issue

**Chun Hu**[1] · **Xiaoyan Wu**[1]

Received: 16 April 2019 / Accepted: 5 August 2019 / Published online: 28 August 2019


**Abstract**
The prevalence of asymptomatic HUA is increasing year after year. HUA is a risk factor for the occurrence and development of renal diseases. However, the role of urate-lowering therapy in asymptomatic HUA complicated by renal damage is still controversial. In some experiments, the treatment of asymptomatic HUA complicated by renal damage may delay the progression of kidney damage. In addition, there is increasing evidence, suggesting that elevated serum uric acid is an independent risk factor for kidney disease. However, in other studies, uric acid-lowering therapy did not improve renal function, and uric acid levels could not be used as an independent predictor for CKD development. Further experimental studies are needed to determine the starting threshold and target value of asymptomatic HUA complicated by renal damage. At the same time, confirmation of the benefits of urate-lowering therapy for kidneys requires studies with larger samples and high-quality RCTs.

**Keywords** Asymptomatic HUA · Urate-lowering therapy · Renal damage

## Introduction

With the improvement of people's living standards, changes in diet, earlier screening, and an aging population [1, 2], the incidence of hyperuricemia (HUA) has been increasing in the past few decades [3], and the onset age of HUA has become younger. Research of HUA is also one of the current hotspots. HUA promotes the occurrence and development of kidney diseases by causing vascular endothelial cell disorders, interstitial inflammation, and oxidative stress activation. However, attention on asymptomatic HUA and its related kidney damage is lacking, and how to deal with asymptomatic HUA and renal damage is still controversial. This article reviews the relationship between asymptomatic HUA and renal damage as well as its treatment.

✉ Xiaoyan Wu
wuxiaoyan123@126.com

[1] Department of Nephrology, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuhan 430071, Hubei, China

## The synthesis and metabolism of uric acid

Uric acid is the end product of purine metabolism [4]. There are two sources of purines in humans: exogenous from proteins rich in purine and nucleic acids and endogenous from synthesis in vivo and catabolism of nucleic acids. The specific process of nucleic acid hydrolysis involves the production of nucleotides from nucleic acids by nuclease, and nucleosides are produced by nucleotidase. Furthermore, nucleosides are hydrolyzed by nucleosidase to form a purine and pyrimidine base, in which the purine base produces xanthine under the action of xanthine invertase and is then converted into uric acid. Under normal circumstances, approximately 70% of the uric acid synthesized and ingested daily is excreted by the kidneys, and another 30% is excreted through the intestine or decomposed by bacteria in the intestine. The renal excretion of uric acid in the human body is a complex process. Uric acid can be freely filtered at the glomerulus. Once filtered, 98% is reabsorbed by the proximal tubule S1 segment, and then, 50% of the uric acid is secreted by the proximal tubule S2 segment, and 40–44% of the uric acid after secretion is reabsorbed by the proximal tubule S3 segment. Finally, the uric acid excreted in the final urine is approximately 6–10% [5]. The formation and excretion of uric acid maintain a dynamic balance in the human body, and HUA is caused by an increase in the production of uric acid or a decrease in uric acid excretion.

## Definition of asymptomatic HUA

In the normal purine diet condition, the fasting serum uric acid level [male > 420 μmol/L (7 mg/dl), female > 357 μmol/L (6 mg/dl)] is known as HUA [6]. Asymptomatic HUA is where patients have HUA [male > 420 μmol/L, female > 357 μmol/L, no matter healthy individuals and/or patients with chronic kidney disease (CKD)] [7] without gout. Asymptomatic HUA is often overlooked in people due to no gout attacks, urinary calculi, and other related symptoms. In the past, treatment or intervention for asymptomatic HUA was generally considered unnecessary. Although asymptomatic HUA has no clinical symptoms, its potential risk for causing kidney damage is valid. A large number of studies have suggested that high uric acid levels are associated with hypertension, cardiovascular disease, and kidney disease. In addition, in patients with CKD, the levels of uric acid are often increased, because uric acid excretion is reduced because of the decreased glomerular filtration rate (GFR) [8, 9]. Therefore, urate-lowering therapy may become a new strategy to prevent diseases such as cardiovascular and renal diseases.

In addition, ultrasound is increasingly used to diagnose and evaluate joint diseases. The specificity of gout was manifested by double contour sign and gouty tophus. In patients with asymptomatic HUA, double contour signs can also be found in ultrasound examination, and gouty tophus can also be found in synovial tendon and soft tissue [10]. Moreover, when the ultrasound shows bone erosion and gout stones in patients with asymptomatic HUA, uric acid levels should be decreased to delay the occurrence of arthropathy and gouty arthritis. Ultrasound can be used in screening for such patients for early detection of joint abnormalities and early intervention to reduce uric acid therapy. Moreover, in patients with gout, the double contour sign was found by ultrasound and could be eliminated after uric acid-lowering treatment, suggesting that ultrasound could evaluate the effect of uric acid-lowering therapy for gout [11]. Viggiano D et al. suggest that treatment of asymptomatic HUA should consider the presence of urate crystals in the urine sediment analysis and ultrasound-confirmed signs of asymptomatic articular damage due to urates and trends in proteinuria, creatinine, and serum urate levels [12].

## The relationship of asymptomatic HUA and kidney disease

In recent years, increasing evidence has suggested that elevated serum uric acid is an independent risk factor for kidney disease [13]. Much of the research has recognized that HUA is associated with kidney damage in the general population, type 2 diabetes patients, and hypertensive patients [14, 15]. Iseki et al. [16], through a survey of 6403 Japanese people with normal renal function, showed that compared with a serum uric acid < 5 mg/dL, the risk of renal insufficiency in a serum uric acid > 8 mg/dL was increased 10.39 times in women and 2.91 times in men in 2 years, indicating that the levels of serum uric acid were associated with the risk of developing high serum creatinine in this screened subjects. Ryoo et al. [17], through a 4-year follow-up investigation of the relationship between CKD and asymptomatic HUA in Korean men, discovered that asymptomatic HUA increased the incidence of CKD when compared with the normal population. Kawashima et al. [18] also described a relationship between asymptomatic HUA and new-onset CKD in 1285 Japanese male workers, showing that HUA, hypertension, and obesity, as well as low serum high-density lipoprotein cholesterol, were significantly associated with new-onset CKD. Asymptomatic HUA may be a predictor of new-onset CKD in Japanese male workers. HUA can serve as a predictive marker for renal outcome in arterial/arteriolar nephrosclerosis patients [19]. HUA is also a valuable predictor for incident coronary artery disease (CAD) events in elderly patients [20]. Serum uric acid level increases were associated with kidney failure in earlier stages of CKD [21]. The use of sartans for arterial hypertension may reduce the uric acid concentration, and sartans are recommended for the treatment of arterial hypertension coexisting with HUA in patients [22]. The sodium–glucose cotransporter 2 (SGLT2) inhibitors decreased serum uric acid in diabetic patients with hyperuricemia [23]. Asymptomatic HUA has been associated with cardiovascular mortality in patients with CKD who transition to hemodialysis [24]. Taken together, the above findings from various studies suggest that hyperuricemia can damage the kidney and serve as a predictive marker for CKD.

In another study, Kim et al. [25] observed that asymptomatic HUA with CKD stage 3 patients can delay renal disease progression via urate-lowering therapy; at the same time, goal-directed urate-lowering therapy seems to have better kidney benefits than continuing initial urate-lowering therapy. Similarly, Siu et al. [26] investigated the relationship between urate-lowering therapy and renal disease and randomly assigned 54 asymptomatic HUA patients with CKD to the experimental group and control group. The experimental group was treated with allopurinol, whereas the control group continued the usual therapy. After treatment for 12 months, the results showed that the serum uric acid level in the experimental group was significantly lower than that in the control group. In addition, the incidence of deterioration in renal function and dialysis (16%) in the experimental group was significantly decreased compared with the control group (46.1%), and the difference was statistically significant, suggesting that allopurinol treatment has a protective effect in slowing kidney disease progression

by decreasing serum uric acid levels. Liu et al. [27] also observed that in patients with asymptomatic HUA and type 2 diabetes, urate-lowering treatment significantly reduced urinary albumin excretion and serum creatinine levels and increased the GFR. In another 6-month, single-center, randomized, double-blind study [28], a total of 108 patients with asymptomatic HUA and CKD stages 3 and 4 were randomly divided into the treatment group or control group. The treatment group received febuxostat therapy, while the control group received a placebo. The results showed that urate-lowering treatment slowed the decline in the estimated GFR. Recently, Goicoechea et al. [29] reported that urate-lowering therapy can delay the progression of kidney disease and reduce cardiovascular events in patients with asymptomatic HUA and CKD through 2-year follow-up. A meta-analysis of randomized clinical trials suggests that urate-lowering treatment may slow CKD progression [30]. The urate-lowering effects of febuxostat in patients with asymptomatic HUA with CKD stages 3-5 were related to a slower renal function progression [31]. Febuxostat in asymptomatic HUA in CKD improves uric acid levels, blood pressure (BP), and estimated GFR at low dose without any adverse events and no cardiac-related events. The therapeutic use of febuxostat in asymptomatic HUA in patients with stages 3–5 CKD improves uric acid levels, and estimated GFR and BP [32]. All these above studies by various investigators emphasize that urate-lowering therapy for asymptomatic HUA and renal damage can protect the kidney (Table 1).

However, in some studies, urate-lowering therapy was not associated with kidney survival. Similarly, Chini et al. [33] analyzed the relationship between asymptomatic HUA and the risk of CKD in 1094 Brazilian workers and found a negative correlation between HUA and GFR, and female gender and age were related to new-onset CKD but not the levels of serum uric acid levels, suggesting that uric acid levels could not be used as an independent predictor for CKD development. A retrospective analysis of Korean hemodialysis patients with end-stage renal disease (ESRD) showed that there was a significant association between HUA and a lower risk of all-cause mortality [34]. In patients with stage 3 CKD and asymptomatic HUA, febuxostat therapy did not reduce the decline in kidney function [35]. In another study by Tanaka et al. [36], they randomly divided 45 patients with asymptomatic HUA and CKD stage 3 into the febuxostat treatment group and the conventional therapy group. The results showed that there was no significant difference in GFR and serum creatinine level between the two groups, but the febuxostat treatment group decreased the urinary levels of albumin and beta 2 microglobulin (β2MG), whereas the conventional therapy group did not change these markers. Similarly, Kanbay et al. [37] also studied uric acid-lowering therapy in patients with asymptomatic HUA and normal renal function, and evaluated GFR compared with baseline in the allopurinol treatment group, but no significant difference was discovered in the levels of urinary protein excretion rate and GFR in the allopurinol treatment group and the control group. HUA often leads to endothelial dysfunction in patients with CKD. Jalal et al. [38] evaluated whether uric acid-lowering therapy can improve endothelial dysfunction. A total of 80 participants with asymptomatic HUA and stage 3 CKD were randomly divided into the experimental group and control group, respectively, and treated with allopurinol or placebo for 3 months, suggesting that uric acid-lowering therapy did not improve endothelial dysfunction. In addition, Beddhu et al. [39] reported that uric acid-lowering therapy did not improve inflammatory markers, fibrosis index, and urinary protein excretion rate in patients with asymptomatic HUA and diabetic nephropathy. Overall, one can conclude from the above studies that hyperuricemia is not damaging the kidney and urate-lowering therapy for asymptomatic HUA and renal damage is ineffective (Table 1).

Likewise, in animal experiments, Sánchez-Lozada et al. [40] established a HUA rat model and demonstrated that high serum uric acid levels contribute to hypertension, renal arteriosclerosis, proteinuria, and tubulointerstitial fibrosis in normal rats. Kang et al. [41] explored the effect of HUA on renal disease in a 5/6 remnant kidney rat model. Rats were fed 2% oxonic acid (OA) to form chronic HUA and then divided into the OA group, OA + allopurinol group, OA + benzbromarone group and the control group (only nephrectomy). The results supported that the serum creatinine increased in each group after a 6-week intervention. The serum creatinine level was highest in the OA group alone, and the OA + allopurinol group or OA + benzbromarone group can downregulate the increase in serum creatinine. The results in proteinuria are similar to serum creatinine. In addition, glomerulosclerosis and renal interstitial fibrosis were observed in the renal tissues of the four groups, but the changes were most obvious in the OA group, whereas the changes in the OA + allopurinol group and OA + benzbromarone group were mild. These studies indicate that high uric acid levels accelerate the progression of kidney disease and that reduced uric acid concentrations can prevent further changes in renal histological and renal function in a rat model of HUA. On one hand, HUA leads to the development of kidney disease; on the other hand, it can aggravate the existing kidney damage. We can avoid the occurrence of kidney damage by lowering serum uric acid. HUA not only causes kidney damage but also results from the production of high BP, whereas hypertension continues to accelerate kidney damage. Therefore, interventions for HUA may play an important role in the development and progression of kidney disease.

**Table 1** Clinical trials of urate-lowering therapy in asymptomatic HUA and renal damage

| Reference | Study design and duration | Urate-lowering therapy | Inclusion criteria | Number of subjects | Outcomes |
|---|---|---|---|---|---|
| Siu et al. [26] | A prospective RCT 12 months | Allopurinol 100 to 300 mg/days vs. usual therapy | Serum urate > 7.6 mg/dl daily proteinuria > 0.5 g and/or creatinine > 1.35 mg/dl (> 120 mmol/l) and < 4.50 mg/dl (< 400 mmol/l) at baseline | $n = 54$ | Allopurinol resulted in a decrease of dialysis dependence |
| Liu et al. [27] | Randomized open parallel-controlled trail 3 years | Allopurinol 100 mg daily vs. conventional treatments | Serum urate (420 and 476 μmol/l) type 2 diabetes | $n = 176$ | Allopurinol decreased UAER and serum creatinine, increase eGFR |
| Sircar et al. [28] | A prospective RCT 6 months | Febuxostat 40 mg/days vs. placebo | Serum urate ≧ 7 mg/dl CKD stages 3 and 4 | $n = 108$ | Febuxostat slowed the decline in eGFR |
| Goicoechea et al. [29] | Prospective RCT 5-year follow-up of 2010 | Allopurinol 100 mg/days vs. standard treatment | eGFR≦60 ml/min/1.73 $m^2$ | $n = 107$ | Allopurinol slowed the decline in eGFR |
| Zeng et al. [30] | A meta-analysis of RCTs 3 months to 48 months | Febuxostat vs. placebo | 20 ml/min/1.73 $m^2$ ≦ eGFR ≦ 50 ml/min/1.73 $m^2$ | $n = 835$ | Febuxostat treatment improved eGFR |
| Liu et al. [31] | A prospective cohort study 6 months | Febuxostat 40 mg/days vs. allopurinol 100 mg/days | Serum urate ≧ 7 mg/dl CKD stages 3-5 | $n = 208$ | Increase in eGFR and decrease in proteinuria |
| Sarvepalli et al. [32] | A prospective observational study 6 months | Febuxostat 40 mg/days vs. standard treatment | Serum urate >6.0mg/dl in females and >7.0mg/dl in malesCKD stages 3a-5 | $n = 53$ | Allopurinol improved UA levels, BP and eGFR |
| Kimura et al. [35] | RCT 108 weeks | Febuxostat 10–40 mg/days vs. placebo | Serum urate (7.0–10.0 mg/dl) CKD stages 3 | $n = 443$ | Febuxostat did not mitigate the decline in eGFR |
| Tanaka et al. [36] | A prospective, randomized, open-label, parallel-group trial 12 weeks | Febuxostat 10–40 mg daily vs. conventional therapy | Serum urate ≧ 7 mg/dl CKD stages 3 | $n = 40$ | No significant difference in eGFR between febuxostat and control groups |
| Jalal et al. [38] | RCT 12 weeks | Allopurinol 100 mg/days vs. placebo | Serum urate ≥7 mg/dl in men and ≥ 6 mg/dl in women CKD stages 3 | $n = 80$ | Allopurinol did not improve endothelial function |
| Beddhu et al. [39] | RCT 24 weeks | Febuxostat 80 mg/days vs. placebo | Serum urate ≥ 327 μmol/L in men and ≥ 274 μmol/L in women type 2 diabetic nephropathy | $n = 80$ | Febuxostat did not improve urinary protein excretion rate |

## Treatment of asymptomatic HUA and renal damage

Regarding the treatment of asymptomatic HUA, the previous guidelines [42] do not recommend any drug therapy, but suggest that it can be controlled with diet prevention and lifestyle changes. The 2012 American College of Rheumatology (ACR) guidelines for gout management did not address the treatment of asymptomatic HUA [43]. Vargas-Santos et al. [44] suggested that the treatment of asymptomatic HUA requires larger randomized controlled trials (RCTs) to assess the renoprotective effect. At present, due to the lack of large-scale RCTs for the treatment of asymptomatic HUA and CKD, patients with asymptomatic HUA and CKD are not recommended to undergo uric acid-lowering therapy. Stamp et al. [45] also indicated that asymptomatic HUA should not be recommended in the absence of further large-scale clinical trials to confirm that the benefits of asymptomatic HUA treatment outweigh the risks.

However, in 2010, a Chinese expert consensus on the treatment of asymptomatic HUA complicated with cardiovascular disease recommended the target value of HUA treatment: serum uric acid level was less than 357 μmol/L (6 mg/dl). Asymptomatic HUA complicated with cardiovascular risk factors or cardiovascular disease (including renal dysfunction, etc.) should be considered for drug therapy when the serum uric acid reaches 475 μmol/L (8 mg/dl); asymptomatic HUA without cardiovascular risk factors or cardiovascular disease should be considered for uric acid-lowering drug therapy when the serum uric acid reaches 535 μmol/L (9 mg/dl). For all asymptomatic HUA patients, a therapeutic lifestyle change is required. In 2011, Chinese guidelines for the diagnosis and treatment of primary gout suggested that asymptomatic HUA is considered with nonpharmacological treatment. Lowering serum uric acid is not recommended, but when the serum uric acid level is still higher than 9 mg/dl after diet control or when the serum uric acid level is higher than 8 mg/dl and with related diseases or family history of HUA, drug treatment should be used. In 2011, Japanese guidelines for the management of HUA and gout recommended asymptomatic HUA without renal disorder and serum uric acid levels not less than 8 mg/dl. Drug treatment should be considered when lifestyle guidance is ineffective. When asymptomatic HUA with renal disorder or other complications and serum uric acid levels reach 8 mg/dl and when asymptomatic HUA without renal disorder or other complications and serum uric acid levels less than 9 mg/dl and lifestyle guidance are ineffective, the patient should be considered for drug treatment. In addition, asymptomatic HUA without renal disorder or other complications and serum uric acid reaches 9 mg/dl was recommended for drug treatment [46]. In addition, A Japanese epidemiological survey shows that the prevalence of asymptomatic HUA in patients under urate-lowering treatment has increased significantly [47]. In 2017, a Chinese experts' consensus on the diagnosis and treatment of patients with CKD complicated with HUA indicated that for patients with asymptomatic HUA and CKD, it is recommended that uric acid-lowering therapy be used when the serum uric acid level is higher than 420 μmol/L in males or the serum uric acid level is higher than 360 μmol/L in females. In addition, the target value of HUA treatment is not less than 360 μmol/L. Another report revealed that the uric acid level is not as low as possible, and the target value of uric acid-lowering therapy is 5–6 mg/dl [48]. Although a large number of epidemiological data have demonstrated a relationship between kidney damage and asymptomatic HUA, the causal relationship is still uncertain, and a large number of RCTs are still needed to estimate the renal benefits in asymptomatic HUA treatment [49–51].

When treating patients with asymptomatic HUA, we also need to pay attention to drug-related adverse events, especially the risk of serious adverse events. Allopurinol treatment of asymptomatic HUA patients has resulted in serious adverse events, such as fatal hypersensitivity reactions [52]. According to large-scale population research from Taiwan, urate-lowering therapy elevated the risk of allopurinol hypersensitivity syndrome and mortality associated with allopurinol hypersensitivity syndrome in the asymptomatic HUA population. Moreover, the risk of allopurinol hypersensitivity syndrome and related mortality also increased when comorbid kidney disease and cardiovascular disease were present [53].

In addition, urate as an antioxidant has a beneficial effect. Urate is an important free radical scavenger similar to glutamate in the central nervous system, so urate may be good for acute stroke [54]. Furthermore, low levels of uric acid are associated with neurodegenerative diseases such as Parkinson's disease [55]. The relationship between uric acid and neurological diseases has also shown the potential negative effects of uric acid-lowering therapy. Therefore, we should maintain the uric acid level at a reasonable and stable range in the treatment of asymptomatic HUA.

In a nutshell, the above review of various literature reports suggests that urate-lowering therapy in asymptomatic HUA complicated by renal damage is still a matter of serious controversy. Previous studies are interesting but also accompanied with some limitations, including the small sample, the short observation time, different race individuals, and the single-centre design. In addition, some clinical trials provide insufficient information on drug-related adverse events and safety issues need to be addressed. Therefore, before a uric acid-lowering therapy for asymptomatic

HUA and renal damage, there is a need to further investigate its efficacy and safety by larger multicenter RCTs.

## Conclusion

For asymptomatic HUA, we should routinely check serum uric acid during physical examination to aid in the early detection and control of high serum uric acid levels in a timely manner. The initial threshold and target value for uric acid-lowering therapy in asymptomatic HUA patients complicated with renal damage are still controversial and require further research. Moreover, some clinically relevant trials are limited by the small sample size and short observation time, and the conclusions from these may not be accurate. Therefore, the renal benefits of urate-lowering therapy for asymptomatic HUA combined with renal damage need to be confirmed using larger samples and high-quality RCTs.

**Funding** This work was supported by fundamental research funds for central universities (2042018kf0142).

### Compliance with ethical standards

**Conflict of interest** All authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

## References

1. Saag KG, Choi H (2006) Epidemiology, risk factors, and lifestyle modifications for gout. Arthritis Res Ther 8(Suppl. 1):S2
2. Richette P, Bardin T (2010) Gout. Lancet 375(9711):318–328
3. Lin KC, Lin HY, Chou P (2000) Community based epidemiological study on hyperuricemia and gout in Kin-Hu, Kinmen. J Rheumatol 27(4):1045
4. Johnson RJ et al (2003) Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 41(6):1183–1190
5. Esparza Martín N, García Nieto V (2011) Hypouricemia and tubular transport of uric acid. Nefrologia 31(1):44–50. https://doi.org/10.3265/Nefrologia.pre2010.Oct.10588
6. Einollahi B, Einollahi H, Rostami Z (2011) Elderlyrenal transplant recipients and renal dysfunction: a risk factor for hyperuricemia. Exp Clin Transpl 9(6):376-38
7. Johnson RJ et al (2005) Resurrection of uric acid as a causal risk factor in essential hypertension. Hypertension 45(1):28
8. Satirapoj B et al (2011) High levels of uric acid correlate with decline of glomerular filtration rate in chronic kidney disease. J Med Assoc Thai 93(suppl 6):S65–S70
9. Ben-Dov IZ, Kark JD (2011) Serum uric acid is a GFR independent long-term predictor of acute and chronic renal insufficiency: the Jerusalem Lipid Research Clinic cohort study. Nephrol Dial Transplant 26(8):2558–2566
10. De Miguel E et al (2012) Diagnosis of gout in patients with asymptomatic hyperuricaemia: a pilot ultrasound study. Ann Rheum Dis 71(1):157–158
11. Thiele RG, Schlesinger N (2010) Ultrasonography shows disappearance of monosodium urate crystal deposition on hyaline cartilage after sustained normouricemia is achieved. Rheumatol Int 30:495–503
12. Viggiano D et al (2018) Urate-lowering agents in asymptomatic hyperuricemia: role of urine sediment analysis and musculoskeletal ultrasound. Kidney Blood Press Res 43(2):606–615
13. Badve SV et al (2011) Challenges of conducting a trial of uric-acid-lowering therapy in CKD. Nat Rev Nephrol 7(5):295–300
14. Lee JE et al (2006) Serum uric acid is associated with microalbuminuria in prehypertension. Hypertension 47(5):962–967
15. Tseng CH (2005) Correlation of uric acid and urinary albumin excretion rate in patients with type 2 diabetes mellitus in Taiwan. Kidney Int 68(2):796–801
16. Iseki K et al (2001) Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertens Res 24(6):691–697
17. Ryoo JH et al (2013) The association between uric acid and chronic kidney disease in Korean men: a 4-year follow-up study. J Korean Med Sci 28(6):855–860
18. Kawashima M et al (2011) Association between asymptomatic hyperuricemia and new-onset chronic kidney disease in Japanese male workers: a long-term retrospective cohort study. BMC Nephrol 12:31
19. Momoki K et al (2017) Hyperuricemia as a predictive marker for progression of nephrosclerosis: clinical assessment of prognostic factors in biopsy-proven arterial/arteriolar nephrosclerosis. J Atheroscler Thromb 24(6):630–642
20. Wu J et al (2017) Asymptomatic hyperuricemia and coronary artery disease in elderly patients without comorbidities. Oncotarget 8(46):80688–80699
21. Srivastava A et al (2018) Uric acid and the risks of kidney failure and death in individuals with CKD. Am J Kidney Dis 71(3):362–370
22. Nieradko-Iwanicka B (2018) What is the role of angiotensin receptor blockers in treatment of hyperuricemia coexisting with arterial hypertension? Reumatologia 56(2):106–110
23. Zhao Y et al (2018) Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: a meta-analysis of randomized controlled trials. Diabetes Obes Metab 20(2):458–462
24. Petreski T et al (2019) Asymptomatic hyperuricemia and cardiovascular mortality in patients with chronic kidney disease who progress to hemodialysis. Int Urol Nephrol 51(6):1013–1018
25. Kim Y et al (2015) Effect of urate lowering therapy on renal disease progression in hyperuricemic patients with chronic kidney disease. J Rheumatol 42(11):2143–2148
26. Siu YP et al (2006) Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 47(1):51–59
27. Liu P et al (2015) Allopurinol treatment improves renal function in patients with type 2 diabetes and asymptomatic hyperuricemia: 3-year randomized parallel-controlled study. Clin Endocrinol (Oxf) 83:475–482
28. Sircar D et al (2015) 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 66:945–950
29. Goicoechea M et al (2015) Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. Am J Kidney Dis 65(4):543–549
30. Zeng XX et al (2018) Efficacy of febuxostat in hyperuricemic patients with mild-to-moderate chronic kidney disease: a

meta-analysis of randomized clinical trials: a PRISMA-compliant article. Medicine (Baltimore) 97(13):e0161
31. Liu X et al (2019) The urate-lowering efficacy and safety of febuxostat versus allopurinol in Chinese patients with asymptomatic hyperuricemia and with chronic kidney disease stages 3-5. Clin Exp Nephrol 23(3):362–370
32. Sarvepalli PS et al (2018) Study of therapeutic efficacy of febuxostat in chronic kidney disease stage IIIA to stage VD. Saudi J Kidney Dis Transpl 29(5):1050–1056
33. Chini LSN, Assis LIS, Lugon JR (2017) Relationship between uric acid levels and risk of chronic kidney disease in a retrospective cohort of Brazilian workers. Braz J Med Biol Res 50(9):e6048
34. Kim CS et al (2017) Relationship between serum uric acid and mortality among hemodialysis patients: retrospective analysis of Korean end-stage renal disease registry data. Kidney Res Clin Pract 36(4):368–376
35. Kimura K et al (2018) Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. Am J Kidney Dis 72(6):798–810
36. Tanaka K et al (2015) Renoprotective effects of febuxostat in hyperuricemic patients with chronic kidney disease: a parallel-group, randomized, controlled trial. Clin Exp Nephrol 19:1044–1053
37. Kanbay M et al (2011) A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. Clin J Am Soc Nephrol 6:1887–1894
38. Jalal D et al (2017) Vascular function and uric acid-lowering in stage 3 CKD. J Am Soc Nephrol 28(3):943–952
39. Beddhu S et al (2016) A randomized controlled trial of the effects of febuxostat therapy on adipokines and markers of kidney fibrosis in asymptomatic hyperuricemic patients with diabetic nephropathy. Can J Kidney Health Dis 3:2054358116675343
40. Sanchez-Lozada LG et al (2005) Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. Kidney Int 67(1):237–247
41. Kang DH et al (2002) A role for uric acid in the progression of renal disease. J Am Soc Nephrol 13(12):2888–2897
42. Corrado A et al (2006) Pathogenesis, clinical findings and management of acute and chronic gout. Minerva Med 97(6):495–509
43. Khanna D et al (2012) 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res 64:1431–1446
44. Vargas-Santos AB, Neogi T (2017) Management of gout and hyperuricemia in CKD. Am J Kidney Dis 70(3):422–439
45. Stamp L, Dalbeth N (2017) Urate-lowering therapy for asymptomatic hyperuricaemia: a need for caution. Semin Arthritis Rheum 46(4):457–464
46. Yamanaka H (2011) Japanese Society of Gout and Nucleic Acid Metabolism. Japanese guideline for the management of hyperuricemia and gout: second edition. Nucleosides Nucleotides Nucleic Acids 30(12):1018–1029
47. Hakoda M, Kasagi F (2018) Increasing trend of asymptomatic hyperuricemia under treatment with urate-lowering drugs in Japan. Mod Rheumatol 1–5
48. Bellomo G, Selvi A (2018) Uric acid: the lower the better? Contrib Nephrol 192:69–76
49. Ramirez MEG, Bargman JM (2017) Treatment of asymptomatic hyperuricemia in chronic kidney disease: a new target in an old enemy—a review. J Adv Res 8(5):551–554
50. Eleftheriadis T et al (2017) Asymptomatic hyperuricemia and chronic kidney disease: narrative review of a treatment controversial. J Adv Res 8(5):555–560
51. Bardin T, Richette P (2017) Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med 15(1):123
52. Carnovale C, Venegoni M, Clementi E (2014) Allopurinol overuse in asymptomatic hyperuricemia: a teachable moment. JAMA Intern Med 174:1031–1032
53. Gutierrez-Macias A et al (2005) Fatal allopurinol hypersensitivity syndrome after treatment of asymptomatic hyperuricaemia. Br Med J 331:623–624
54. Chamorro A et al (2016) Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. Lancet Neurol 15:869–881
55. Shen C et al (2013) Serum urate and the risk of Parkinson's disease: results from a meta-analysis. Can J Neurol Sci 40:73–79