Allopurinol and renal impairment; a review on current findings

Sina Bakhshaei[1], Bina Bakhshaei[2], Rastina Mehrani[3], Sina Neshat[4], Zeinab Rezvani[5], Sara Dehghan[6], Hossein Mardanparvar[6], Mahnaz Momenzadeh[5]*

Abstract
Hyperuricemia is described as a serum uric acid level more than 6.0 mg/dL. It is demonstrated by basic research and clinical studies, which the elevation of uric acid level may change the renal histology and function by developing acute and chronic kidney diseases (CKDs), diabetic nephropathy and end-stage renal disease (ESRD). There is no doubt about a significant relationship between uric acid and renal impairment. However, the details of this correlation, especially; between uric acid and renal failure, are discussable. Renal vasoconstriction, antiangiogenic properties, endothelial dysfunction, proinflammatory properties, renal fibrosis, pro-oxidative properties, and alteration of renal autoregulation are the most common mechanisms, which approve the association between uric acid and renal impairment. Allopurinol administration for CKD treatment in patients with gout is one of the most discussable challenges. It should be investigated whether allopurinol can diminish the deterioration of the glomerular filtration rate (GFR) in CKD patients who are at risk of ESRD. Some previous studies reported that allopurinol decreases the CKD incident risk, but others could not confirm this association. The benefit or risks of allopurinol in different stages of CKD, dialysis, and renal transplant are discussed in this study.
Keywords: Hyperuricemia, Uric acid, Renal impairment, Chronic kidney disease, End-stage renal disease, Glomerular filtration rate, Acute kidney injury, Diabetic nephropathy, Hypertension
Citation: Bakhshaei S, Bakhshaei B, Mehrani R, Neshat S, Rezvani Z, Dehghan S, Mardanparvar H, Momenzadeh M. Allopurinol and renal impairment; a review on current findings. J Ren Endocrinol. 2023;9:e25081. doi: 10.34172/jre.2023.25081.

Introduction

Uric acid is synthesized in humans as the byproduct of the purine nucleotide catabolism derived mainly from animal proteins. Hyperuricemia is defined as a serum uric acid level more than 6.0 mg/dL. About 66% of the daily uric acid is cleared by the renal while the residual one-third is by the gastrointestinal tract (1).

Since hyperuricemia is one of the most common renal dysfunctions, scientists need to know the relationship between serum uric acid and kidney function in addition to the impact of allopurinol on renal function and vice versa. It is demonstrated by basic research and clinical studies that the elevation of uric acid level may change the fundamental architecture through developing acute (2) and chronic kidney diseases (CKDs) (3), diabetic nephropathy (4) and end-stage renal disease (ESRD) (5). CKDs are characterized as renal injury or glomerular filtration rate (GFR) < 60 mL/min/1.73 m² during three months or more, regardless of the cause which may exist due to reduced excretion, augmented production, or a combination of both mechanisms. More than 90% of all

cases of hyperuricemia are the consequence of the reduced renal excretion of uric acid. It has been demonstrated that the incidence of hyperuricemia increases in proportion with the GFR decline and vice versa. Around 70% patients with hyperuricemia have a GFR < 60 mL/min per 1.73 m² and 20% have a GFR under 30 mL/min per 1.73 m² (6). These data support the need to adopt more effective treatment strategies for CKD in the background of hyperuricemia (7).

In disease patients, hyperuricemia may be conducted as a disease marker as well as risk factor to predict risk of progression of renal impairment toward ESRD (8). For example, higher serum uric acid was independently accompanied by a larger probability of a decline more than 10 mL/min/1.73 m² for GFR during 59 months in an observational investigation between 900 normotensive participants (9). In addition, it is demonstrated that uric acid is correlated with more progression of renal impairment in patients with IgA nephropathy (10), patients with type 1 diabetes (11) and type 2 diabetes (12).

There is no doubt about a significant relationship

[1]Internal Medicine Department, UHS SoCal Medical Education Consortium Temecula, Ca, USA. [2]Neurology Department, Median Klinik NRZ, Wiesbaden, Germany. [3]School of Medicine, St George University, Grenada, West Indies. [4]Department of Pulmonology, Mayo Clinic, Jacksonville 32224 FL, USA. [5]Nickan Research Institute, Isfahan, Iran. [6]Department of Nursing, Faculty of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
*Corresponding Author: Mahnaz Momenzadeh, Email: Mahnazmomenzadehf@gmail.com, Mahnaz.momenzadeh@pharm.mui.ac.ir

between uric acid and renal impairment. However, the details of this correlation, especially; between uric acid and renal failure, are discussable (13). Benefit or risk of allopurinol in different stages of CKD, dialysis and renal transplant are discussed in this study.

Search strategy
In this study we searched Web of Science, EBSCO, Scopus, PubMed/Medline, DOAJ (Directory of Open Access Journals), Embase, and Google Scholar, using various keywords including; hyperuricemia, uric acid, renal impairment, CKD, ESRD, acute kidney injury, diabetic nephropathy, endothelial dysfunction, end-stage renal disease, renal fibrosis, allopurinol, chronic kidney disease, hypertension and GFR.

Mechanisms of renal impairment by hyperuricemia
Renal vasoconstriction, antiangiogenic properties, endothelial dysfunction, proinflammatory properties, renal fibrosis, pro-oxidative properties, and alteration of renal autoregulation are the most common mechanisms which approve the association between uric acid and renal impairment (14,15). Some other mechanisms by experimental studies involving systemic and glomerular hypertension and/or tubulointerstitial fibrosis, which might be correlated with the direct pro-inflammatory effects of soluble uric acid (16).

Other effects except from uric acid reducing
Given the impact of allopurinol on renal structure and function in individuals with and without gout, there are many questions about its mechanism. Whether these properties are induced by xanthine oxidase (XO) inhibition or consequences afar XO inhibition remains to be discovered. Although research reported that allopurinol's beneficial effects go beyond the XO inhibition (9). An investigation by Gois et al evaluated the efficacy of allopurinol against rhabdomyolysis-linked acute kidney injury (AKI). This study represented an additional protective effect of allopurinol and a new therapeutic approach in rhabdomyolysis-associated AKI by reducing oxidative stress (systemic, renal and muscular), apoptosis and inflammation and upregulation of p21 and increasing kidney tubular cell proliferation

(17). Circulating XO concentration in rheumatoid arthritis (RA) patients' plasma is elevated against those without it. Allopurinol improved the symptoms of arthritis in vitro models of RA. Since this effect does not involve the urate-lowering property of this drug, however, it is probably correlated with its anti-inflammatory effects (18). Several mechanisms are suggested to confer the anti-oxidant and anti-inflammatory properties of allopurinol including accumulation of adenosine, reducing of reactive oxygen species, production of tumor necrosis factor-a, decrease nuclear factor kappa-light-chain-enhancer of activated B cells, blocking the stimulating effects of thioredoxin-interacting protein and decreasing NLRP3 (nucleotide-binding domain-like receptor protein 3) activation and affecting the main cytokines involved in gout inflammation (19).

Serum uric acid lowering treatment
Drugs used in gout are classified to non-steroid anti-inflammatory agents, colchicine and corticosteroids, uricosuric acids and inhibitors of XO. Non-steroid anti-inflammatory agents, colchicine and corticosteroids are administered for both acute and chronic but uricosuric acid agents (increase uric acid excretion) such as probenecid and benzbromarone and inhibitors of XO (inhibits uric acid synthesis) such as allopurinol and febuxostat are administered for long-term prevention of gout and its complications (20).

Allopurinol is a basic urate-lowering therapy in gout patients. Allopurinol is metabolized by XO to oxypurinol which can act as a XO inhibitor. Since the kidneys excrete allopurinol, its poisoning risk is very high in renal failure patients. The main route of removal of allopurinol is by metabolism to oxypurinol (almost 80%), allopurinol-1-riboside (10%) and as the unchanged allopurinol (10%) by the kidneys. The half-life of allopurinol is short (almost 1–2 hours) but half-life of oxypurinol is almost 18–30 hours for cases with normal renal function and depends to kidney function may extend to a week in those with significant renal failure (21).

Allopurinol and chronic kidney disease
There is growing interest directed toward the role of urate lowering agents specially allopurinol due to relationship between uric acid and renal impairment, to ameliorate health outcomes in these circumstances. Allopurinol administration in CKD patients is one of the most challenging issues in gout management treatment. It should be investigated whether allopurinol can weaken the decline of the GFR in CKD patients who risked ESRD. Some previous studies reported that allopurinol decreases the CKD incident risk (9,22-26); however, others could not confirm this association (27,28). Therefore, larger, randomized placebo-controlled and well-designed randomized controlled trials (RCTs) are required to assess the exact renoprotective effects of the uric acid-lowering

therapy specially allopurinol in patients with CKD (29). Several meta-analyses did not show certain results. Bose et al (30) evaluated allopurinol treatment on 476 participants with or without CKD at baseline by eight trials with range duration of 4–24 months. They found in five trials out of eight trials (on 346 participants), allopurinol treatment did not show GFR difference against controls however in three trials (130 participants) this difference was significant (30).

Another meta-analysis by Kanji et al (31), involved 19 RCTs with small sample sizes, which evaluate the effect of allopurinol on kidney function and showed a statistically significant reduction in uric acid, hypertension, and proteinuria and also demonstrated a significant increase in GFR. Accordingly, Kao et al (32) showed allopurinol is able to attenuate of progression left ventricular hypertrophy in humans and improves endothelial/vascular dysfunction in CKD; however, there was no improvement in hypertension. Therefore, it should be highlighted that the treatment of hyperuricemia by allopurinol may or may not affect blood pressure.

In a prospective RCT by Siu et al (22) on 54 hyperuricemia cases with CKD, allopurinol administration at a dose of 100-300 mg/d to normalize uric acid levels, during 12 months, decreased uric acid levels in patients with stage 3 of CKD safely and showed a trend to improve ESRD without blood pressure change.

A small study by Perez-Ruiz et al on 87 patients with gout had administered non-steroid anti-inflammatory agents for gout prior to starting urate lowering therapies. The improvement of the renal function after proper control of hyperuricemia and non-steroidal anti-inflammatory drugs withdrawal was observed (33). Moreover, the study by Goicoechea et al during about 24 months demonstrated that allopurinol use has a positive correlation with slower renal disease progression, decreased hospitalizations, and reduced cardiac disease (34).

Meanwhile, Peng et al stated that febuxostat is superior to allopurinol on sustained reduction in serum uric acid in CKD patients; however, the difference in GFR was not significant (35).

A previous retrospective epidemiologic cohort investigation is directed over eight years with 12 751 individuals while 2690 patients of them received urate-lowering therapies (97% allopurinol). This investigation showed a 30% improvement in GFR in cases who achieved the target uric acid (42%). Comparison of CKD stages showed a 30% improvement in GFR in stage 2 and stage 3 of CKD but not in stage 4 (36).

Accordingly, Goicoechea et al in an RCT study on 113 patients of allopurinol treatment during a two-year period, showed allopurinol decreased the risk of kidney and cardiac disease by 68% and 57%, respectively (26).

The effect of allopurinol in CKD individuals without gout is unclear. An RCT study by Badve et al to slow kidney disease progression from the inhibition of XO (CKD FIX study) (28), is randomly assigned individuals with stage three or four of CKD without gout who had urinary albumin to creatinine ratio of 265 or higher. Goicoechea et al showed allopurinol therapy did not improve renal function decline as compared with placebo (26). They concluded that, the administration of urate lowering therapy in CKD cases without gout is not recommended until researches is completed.

Concretely, two nationally financed trials evaluated the effects of allopurinol on the progression of IgA nephropathy (37) and diabetic renal disorder in type 1 diabetes patients (38).

Study by Shi et al (37) is unable to observe any benefit of allopurinol on renal function or proteinuria during 6 months consequently more studies with longer duration are necessary to determine renal effects of allopurinol on the treatment of IgA nephropathy.

Preventing Early Renal Loss in Diabetes (PERL) evaluates whether lowering SUA with allopurinol slows glomerular filtration rate (GFR) loss in people with type 1 diabetes (T1D) and mild to moderate DKD (38). Uric acid is a risk predictor of diabetic nephropathy at once after the onset of type 1 diabetes. Thus, declining serum uric acid by allopurinol may be useful even in low-risk subjects for type 1 diabetes patients who have not yet advanced microalbuminuria and/or have normal uric acid levels.

In a 10-year follow-up study on modified Diet CKD people, results showed that allopurinol does not reduce the risk of progression of CKD (27).

A trial contains 6190 patients with maximum duration of 85 months named Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial was led to detect whether febuxostat or allopurinol was better for major cardiovascular events in gout patients. This study showed all-cause and cardiovascular mortalities was higher with febuxostat versus allopurinol (39).

Asymptomatic hyperuricemia

Pasina et al showed the dangers of inappropriately treating asymptomatic hyperuricemia (40). Since urate lowering therapies does not influence the pathway of progression toward ESRD, it looks that hyperuricemia does not reduce GFR directly. Therefore Rincon-Choles et al concluded that several long-term follow-up RCTs need before recommending urate-lowering therapies for asymptomatic hyperuricemia and CKD patients (41).

The previous study by Talaat and El-Sheikh published in 2007 followed 50 patients who had been using allopurinol for asymptomatic hyperuricemia. The patients were followed 12 months after allopurinol withdrawal. Talaat and El-Sheikh in their 12 months-follow-up study on 50 asymptomatic hyperuricemia patients under treatment of allopurinol found a significant acceleration of renal disease progression after allopurinol withdrawal (42).

Only large randomized trials would offer conclusive

results concerning efficacy and safety of a preventive treatment for asymptomatic hyperuricemia in CKD.

Brucato et al systematically assessed 13 RCTs discussing urate-lowering therapy in patients with asymptomatic hyperuricemia . Heterogeneity in terms of study design and population was found among the findings (43). Up to now, after reviewing of RCTs specially CARES trial; it cannot be recommended treating of asymptomatic hyperuricemia especially in patients with CKD (16,43).

Adverse events associated with allopurinol

Allopurinol is infamous for prompting hypersensitivity reactions such as allopurinol hypersensitivity syndrome, while 0.4% develops severe cutaneous adverse reactions and a mild skin rash in about 2% of users. Despite rare, hypersensitivity reactions are life threatening and can lead to multi-organ damages, extended hospitalization and raised the risk of mortality. Thus, clinicians treating patients with allopurinol along with renal insufficiency are recommended (44).

In the largest systematic review between 1950–2012, in 48% cases of all 901 published cases of allopurinol hypersensitivity syndrome, CKD was one of the most well-known morbidities (45). It is performed a disproportionality analysis of reported cases of AKI in a post-marketing study associated with allopurinol and febuxostat between 2008 and 2018. AKI for febuxostat and allopurinol was reported respectively 5.7 and 3.3 times more commonly versus other drugs (46).

Allopurinol doses in chronic kidney disease

Although allopurinol has been used for over forty years, its ideal dosage in CKD patients with gout is challenging. Allopurinol often is optimal treatment for cases with chronic gout assumed its efficiency, even in the setting of a decreased GFR. However, caution should be applied in this condition, with low starting doses and gradually titrate it to an effective dose tailored to the serum urate concentration (13).

The association among oxypurinol concentrations, allopurinol dose, CKD, and adverse events in CKD patients causes the recommendation that allopurinol dosage has been preserved on low-therapeutic doses (<6 mg/dL) to decrease the risk of adverse events (47).

Stamp et al (48) studied the associations among allopurinol and renal function and structure in cases with and without kidney dysfunction and addressed allopurinol dosing in gout individuals with disturbed renal function.

Similarly, Vázquez-Mellado et al, showed an increase in the prevalence of adverse reactions to allopurinol in patients who received higher allopurinol doses than those who received adjusted dose according to creatinine clearance rate (49).

Results of a RCT on 183 people with gout, during 24-month indicated that allopurinol dose escalation monthly until serum uric acid <6 mg/dL is safe in people with severe CKD (participants with creatinine clearance <30 mL/min) (50).

Allopurinol in individuals receiving dialysis

Since hemodialysis diminishes plasma urate concentrations, various patients necessitate additional urate-lowering treatment to reach a satisfactory and persistent decrease in plasma urate to prevent gout progression. There are unexpectedly inadequately studies on the management of gout and administration of urate lowering medication in dialysis cases. Various case presentations of individuals on dialysis show effective urate lowering effect of allopurinol (51-53).

It is commonly suggested that in individuals receiving dialysis, the dosage of allopurinol be decreased to a minimum of 100 mg daily. Plasma oxypurinol levels are diminished by almost 50% by dialysis (53). Along with the dose of allopurinol, attentions should be directed toward the arranging of allopurinol administration in relation to hemodialysis. Therefore, attention should be forwarded to dosing after hemodialysis dialysis. If allopurinol is administered before hemodialysis dialysis, therefore a 50% adding in the dosage may be needed post-dialysis (54).

Renal transplantation

Interestingly, the incidence of gout attacks often declines in patients with ESRD, regardless of continuous hyperuricemia. This observation has been referred to altered monocyte cytokine responses to monosodium urate crystals in patients with CKD (55). Renal transplant recipients who experience gout prior to transplantation are likely to have gout post-transplant; therefore, allopurinol should be continued following post-transplant (56). A single center retrospective case-control study on 108 patients was performed with kidney transplant recipients who were treated with allopurinol against control during three months. It is shown in this study that allopurinol administration is associated with preservation of GFR in kidney transplant recipients (57).

Conclusion

Allopurinol administration in the treatment of CKD patients is one of the most controversial issues in gout management treatment. Some previous studies reported that allopurinol decreases the CKD incident risk, but others could not confirm this association. Currently no data to endorse the administration of allopurinol to sluggish the development of chronic renal failure, therefore larger, randomized placebo-controlled and well-designed RCT are required to assess the exact renoprotective effects of the uric acid-lowering therapy specially allopurinol in patients with CKD.

Validation: MM, HM.
Investigation: HM, MM, SN.
Resources: ZR, MM, SB, BB, SN.
Data curation: MM, ZR.
Writing–original draft preparation: ZR, MM
Writing–review and editing: SN, SB, BB, RM, SD, HM, MM.
Visualization: ZR, MM, HM.
Supervision: MM, ZR.
Project administration: MM.

Conflicts of interest
The authors declare that they have no competing interests.

Ethical issues
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

References
1. Johnson RJ, Nakagawa T, Sanchez-Lozada LG, Shafiu M, Sundaram S, Le M, et al. Sugar, uric acid, and the etiology of diabetes and obesity. Diabetes. 2013;62:3307–15.
2. Xu X, Hu J, Song N, Chen R, Zhang T, Ding X. Hyperuricemia increases the risk of acute kidney injury: a systematic review and meta-analysis. BMC Nephrol. 2017;18:27. doi: 10.1186/s12882-016-0433-1.
3. Liu X, Zhai T, Ma R, Luo C, Wang H, Liu L. Effects of uric acid-lowering therapy on the progression of chronic kidney disease: a systematic review and meta-analysis. Ren Fail. 2018; 40: 289–297. doi: 10.1080/0886022X.2018.1456463
4. Kim SM, Choi YW, Seok HY, Jeong KH, Lee SH, Lee TW, et al. Reducing serum uric acid attenuates TGF-β1-induced profibrogenic progression in type 2 diabetic nephropathy. Nephron Exp Nephrol 2012;121:e109–e121. doi:10.1159/000343567.
5. Hsu C-y, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for End-Stage Renal Disease. Arch Intern Med. 2009; 169:342–350. doi: 10.1001/archinternmed.2008.605.
6. Zhu Y, Pandya B, Choi H. Comorbidities of gout and hyperuricemia in the US General Population: NHANES 2007–2008. Am J Med 2012;125:679–87.
7. Gillespie BW, Morgenstern H, Hedgeman E, Tilea A, Scholz N, Shearon T, et al. Nephrology care prior to end-stage renal disease and outcomes among new ESRD patients in the USA. Clin Kidney J 2015;8:772–80.
8. Giordano C, Karasik O, King-Morris K, Asmar A. Uric acid as a marker of kidney disease: review of the current literature. Dis Markers. 2015;2015:382918. doi: 10.1155/2015/382918.
9. Bellomo G, Venanzi S, Verdura C, Saronio P, Esposito A, Timio M. Association of uric acid with change in kidney function in healthy normotensive individuals. Am J Kid Dis. 2010;56:264–73.
10. Ohno I, Hosoya T, Gomi H, Ichida K, Okabe H, Hikita M. Serum uric acid and renal prognosis in patients with IgA nephropathy. Nephron. 2001;87:333-9. doi: 10.1159/000045939.
11. Ficociello LH, Rosolowsky ET, Niewczas MA, Maselli NJ, Weinberg JM, Aschengrau A, et al. High-normal serum uric acid increases risk of early progressive renal function loss in type 1 diabetes: results of a 6-year follow-up. Diabetes Care. 2010;33:1337-43. doi: 10.2337/dc10-0227.
12. Li GX, Jiao XH, Cheng XB. Correlations between blood uric acid and the incidence and progression of type 2 diabetes nephropathy. Eur Rev Med Pharmacol Sci 2018; 22: 506-511. doi: 10.26355/eurrev_201801_14202.
13. Sah OSP, Qing YX. Associations between hyperuricemia and chronic kidney disease: a review. Nephro Urol Mon. 2015; 7: e27233. doi: 10.5812/numonthly.7(3)2015.27233.
14. Ejaz AA, Mu W, Kang DH, Roncal C, Sautin YY, Henderson G, Could uric acid have a role in acute renal failure? Clin J Am Soc Nephrol 2007;2:16-21; doi: 10.2215/CJN.00350106.
15. Su H-y, Yang C, Liang D, Liu H-f. Research Advances in the mechanisms of hyperuricemia-induced renal injury. Biomed Res. Int. 2020;2020:5817348. doi:10.1155/2020/5817348.
16. Eleftheriadis T, Golphinopoulos S, Pissas G, Stefanidis I. Asymptomatic hyperuricemia and chronic kidney disease: Narrative review of a treatment controversial. J Adv Res. 2017;8:555-560. doi: 10.1016/j.jare.2017.05.001.
17. Gois PHF, Canale D, Volpini RA, Ferreira D, Veras MM, Andrade-Oliveira V. Allopurinol attenuates rhabdomyolysis-associated acute kidney injury: Renal and muscular protection. Free Radic Biol Med. 2016;101:176-89. doi: 10.1016/j.freeradbiomed.2016.10.012.
18. Schlesinger N, Brunetti L. Beyond urate lowering: Analgesic and anti-inflammatory properties of allopurinol. Semin Arthritis Rheum. 2020;50:444-40. doi: 10.1016/j.semarthrit.2019.11.009.
19. Ramirez MEG, Bargman JM. Treatment of asymptomatic hyperuricemia in chronic kidney disease:A new target in an old enemy – A review. J Adv Res. 2017;8:551-4. doi: 10.1016/j.jare.2017.04.006.
20. Fields TR. The challenges of approaching and managing gout. Rheum Dis Clin North Am. 2019;45:145-57. doi: 10.1016/j.rdc.2018.09.009.
21. Hande K, Noone R, Stone W. Severe allopurinol toxicity. Description andguidelines for prevention in patients with renal insufficiency. Am J Med. 1984;76:47-56.
22. 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. 2005;47:51-9.
23. Ficociello L, Rosolowsky E, Niewczas MA, Maselli NJ, Weinberg JM, Aschengrau A, et al. High-normal serum uric acid increases risk of early progressive renal function loss in type 1 diabetes: results of a 6-year follow-up. Diabetes Care 2010;33:1337-43.
24. Zoppini G, Targher G, Chonchol M, Ortalda V, Abaterusso C, Pichiri I, et al. Serum uric acid levels and incident chronic kidney disease in patients with type 2 diabetes and preserved kidney function. Diabetes Care. 2012;35:99-104.
25. Weiner D, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS. Uric acid and incident kidney disease in the community. J Am Soc Nephrol. 2008;19:1204-11.
26. 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;65:543-9.
27. Madero M, Sarnak MJ, Wang X, Greene T, Beck GJ, Kusek JW, et al. Uric acid and long-term outcomes in CKD. Am J Kidney Dis. 2009;53:796-803.
28. Badve SV, Pascoe EM, Biostat M, Tiku A, Boudville N, Brown FG, et al. Effects of Allopurinol on the Progression of Chronic Kidney Disease. N Engl J Med. 2020;382:2504-13. doi: 10.1056/NEJMoa1915833.
29. Uchida S, Kumagai T, Chang WX, Tamura Y, Shibata S. Time to target uric acid to retard chronic kidney disease progression. Contrib Nephrol. 2018;192:56-68. doi: 10.1159/000484279.
30. Bose B, Badve SV, Hiremath SS, Boudville N, Brown FG, Cass A, et al. Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis. Nephrol Dial Transplant. 2014;29:406-13.
31. Kanji T, Gandhi M, Clase CM, Yang R. Urate lowering therapy

to improve renal outcomes in patients with chronic kidney disease: systematic review and meta-analysis. BMC Nephrol. 2015;16:58.

32. 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;22:1382-9.

33. Perez-Ruiz F, Calabozo M, Herrero-Beites AM, García-Erauskin G, Pijoan JI. Improvement of renal function in patients with chronic gout after proper control of hyperuricemia and gouty bouts. Nephron. 2000;86:287-91. doi: 10.1159/000045783.

34. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincon A, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010;5(8):1388–93.

35. Peng YL, Tain YL, Lee CT, Yang YH, Huang YB, Wen YH, Hsu CN. Comparison of uric acid reduction and renal outcomes of febuxostat vs allopurinol in patients with chronic kidney disease. Sci Rep. 2020;10,10734. doi: 10.1038/s41598-020-67026-1.

36. Levy G, Shi JM, Cheetham TC, Rashid N. Urate-lowering therapy in moderate to severe chronic kidney disease. Perm J. 2018;22:17-142. doi: 10.7812/TPP/17-142.

37. Shi Y, Chen W, Jalal D, Li Z, Chen W, Mao H, et al. Clinical outcome of hyperuricemia in IgA nephropathy: a retrospective cohort study and randomized controlled trial. Kidney Blood Press Res. 2012;35:153–60.

38. Maahs DM, Caramori L, Cherney DZ, Galecki AT, Gao C, Jalal D, et al. Uric acid lowering to prevent kidney function loss in diabetes: the preventing early renal function loss (PERL) allopurinol study. Curr Diab Rep. 2013;13:550–9.

39. 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; 378:1200-10. doi: 10.1056/NEJMoa1710895

40. Pasina L, Brucato AL, Djade CD, Di Corato P, Ghidoni S, Tettamanti M, et al. Inappropriate prescription of allopurinol and febuxostat and risk of adverse events in the elderly: results from the REPOSI registry. Eur J Clin Pharmacol. 2014;70:1495–503.

41. Rincon-Choles H, Jolly SE, Arrigain S, Konig V, Schold JD, Nakhoul G. Impact of uric acid levels on kidney disease progression. Am J Nephrol. 2017;46:315-22. doi: 10.1159/000481460.

42. Talaat KM, El-Sheikh AR. The effect of mild hyperuricemia on urinary transforming growth factor beta and the progression of chronic kidney disease. Am J Nephrol. 2007;27:435-40.

43. Brucato A, Cianci F, Carnovale C. Management of hyperuricemia in asymptomatic patients: A critical appraisal. Eur J Intern Med. 2020;74:8-17. doi: 10.1016/j.ejim.2020.01.001.

44. Chung WH, Chang WC, Stocker SL, Juo CG, Graham GG, Lee MHH, et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. Ann Rheum Dis . 2015;74:2157-64. doi: 10.1136/annrheumdis-2014-205577.

45. Ramasamy SN, Korb-Wells CS, Kannangara DR, Smith MW, Wang N, Roberts DM, et al. Allopurinol hypersensitivity: a systematic review of all published cases, 1950-2012. Drug Saf. 2013;36:953-80. doi: 10.1007/s40264-013-0084-0.

46. Rey A, Batteux B, Laville SM, Marienne J, Masmoudi K, Gras-Champel V, et al. Acute kidney injury associated with febuxostat and allopurinol: a postmarketing study. Arthritis Res Ther. 2019;21:229. doi: 10.1186/s13075-019-2011-y.

47. Khanna D, Fitzgerald J, Khanna P, et al. 2012 American College of RheumatologyGuidelines for the Management of Gout. Part 1: systematic nonpharmacologicand pharmacologic therapeutic approaches to hyperuricaemia. Arthritis Care Res. 2012;64:1431-46.

48. Stamp LK, O'Donnell JL, Zhang M, James J, Frampton C, Barclay ML, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheumatol. 2011;63:412-21. doi: 10.1002/art.30119.

49. Vázquez-Mellado J, Morales EM, Pacheco-Tena C, Burgos-Vargas R. Relation between adverse events associated with allopurinol and renal function in patients with gout. Ann Rheum Dis. 2001;60:981-3.doi: 10.1136/ard.60.10.981.

50. Stamp LK, Chapman PT, Barclay M, Horne A, Frampton C, Tan P, et al. The effect of kidney function on the urate lowering effect and safety of increasing allopurinol above doses based on creatinine clearance: a post hoc analysis of a randomized controlled trial. Arthritis Res Ther. 2017;19:283. doi: 10.1186/s13075-017-1491-x.

51. Rundles R. Allopurinol in gouty nephropathy and renal dialysis. Ann Rheum Dis. 1966;25:694-6

52. Hayes CP Jr, Metz EN, Robinson RR, Rundles RW. the use of allopurinol (HPP) to control hyperuricemia in patients on chronic intermittent hemodialysis. Trans Am Soc Artif Intern Organs. 1965;11:247-54. doi: 10.1097/00002480-196504000-00047.

53. Day RO, Kannangara DR, Hayes JM, Furlong TJ. Successful use of allopurinol in a patient on dialysis. BMJ Case Rep. 2012;2012:bcr0220125814. doi: 10.1136/bcr.02.2012.5814.

54. Stamp LK, Chapman PT, Barclay M, Horne A, Frampton C, Tan P, et al. Effects of sevelamer and calcium-based phosphate binders on uric acid concentrations in patients undergoing hemodialysis - A randomized clinical trial. Arthritis Res Ther. 2017;21:19:283. doi: 10.1186/s13075-017-1491-x.

55. Schreiner O, Wandel E, Himmelsbach F, Galle PR, Marker-Hermann E: Reduced secretion of proinflammatory cytokines of monosodium urate crystal-stimulated monocytes in chronic renal failure: an explanation for infrequent gout episodes in chronic renal failure patients? Nephrol Dial Transplant. 2000:15;644–649.

56. Stamp L, Ha L, Searle M, O'Donnell J, Frampton C, Chapman P: Gout in renal transplant recipients. Nephrology (Carlton). 2006:11;367–371.

57. Osadchuk L, Bashir MH, TangiralaB, Marcus RJ, Nashar K, Hussain SM, Sureshkumar KK. Effect of allopurinol on slowing allograft functional decline in kidney transplant recipients. Exp Clin Transplant. 2014;12(3):190-4.