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

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
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 after 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 benz bromarone 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 12751 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 subsequently 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 (15).

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 dosages 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 arangements 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.

**Authors’ contribution**

Conceptualization: MM, SB, BB, ZR.
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