Editorial

Kidney Res Clin Pract 2019;38(3):257-259
pISSN: 2211-9132 • eISSN: 2211-9140
https://doi.org/10.23876/j.krcp.19.074

KIDNEY RESEARCH AND CLINICAL PRACTICE

To treat or not to treat asymptomatic hyperuricemia in chronic kidney disease

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Although there is no universally accepted definition of hyperuricemia, serum urate level of > 7.0 mg/dL, based on the limit of urate solubility in body fluid, is widely accepted as the reference for hyperuricemia [1]. Meanwhile, asymptomatic hyperuricemia is defined as elevated serum urate levels in the absence of signs and symptoms of monosodium urate crystal deposition disease. Asymptomatic hyperuricemia is frequently associated with other disorders such as hypertension, chronic kidney disease (CKD), cardiovascular disease, and insulin resistance [2]. To prevent gouty arthritis, cardiovascular disease, and renal failure, the Japanese guidelines for management of hyperuricemia and gout recommends initiating pharmacologic urate-lowering therapy for asymptomatic hyperuricemia when serum urate levels increase to > 8.0 mg/dL [3]. However, this approach is not recommended in the United States and Europe, because inappropriate administration of such therapy for asymptomatic hyperuricemia has been reported to be associated with considerable risks of life-threatening skin and systemic side effects [2].

The kidneys play an important role in uric acid excretion through a complex process involving filtration, reabsorption, and tubular secretion [4]. Generally, decreased kidney function leads to hyperuricemia due to decreased excretion of uric acid. However, there is accumulating evidence that hyperuricemia has a causal relationship with the deterioration of kidney function [5,6], although this relationship remains a matter of some debate. However, a survey concerning the management of asymptomatic hyperuricemia in patients with CKD by Japanese nephrologists showed that most nephrologists (84–89%) treated asymptomatic hyperuricemia in patients with CKD stage 3 to 5 in order to prevent CKD progression or cardiovascular events [7]. In the current issue of *Kidney Research and Clinical Practice*, Cha et al [8] report the results of a survey of Korean nephrologists' perceptions regarding the diagnosis and management of asymptomatic hyperuricemia in patients with CKD. In this study, most respondents (80.4%) reported that they do treat asymptomatic hyperuricemia in patients with CKD, in line with the results from the Japanese survey. In particular, there were overall fewer respondents in the Korean study compared with those in the Japanese study (12.6% vs. 40%). Based on the results of the former survey, the authors carefully suggest that the definition of hyperuricemia should be serum uric acid levels of > 7.0 mg/dL, irrespective of CKD stage. In addition, they recommend that pharmacologic urate-lowering therapy should be considered for patients with serum uric levels of > 8.0 mg/dL. However, further well-designed and well-conducted studies are required to obtain definitive conclusions on the efficacy of urate-lowering agents for the treatment of asymptomatic hyperuricemia in patients with CKD. As summarized in Table 1 [5,6,9], three recent clinical studies have investigated this issue. First, the febuxostat vs. placebo randomized con-

Received July 11, 2019; **Revised** July 17, 2019;
Accepted July 17, 2019
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Table 1. Summary of clinical studies investing the effects of urate-lowering agents on kidney function

Reference	Study design and duration	Urate-lowering therapy	Inclusion criteria	Number of patients	Renal outcomes
Kimura et al [9]	Placebo-controlled randomized double-blind parallel-group study Duration: 108 weeks	Febuxostat 10 mg to 40 mg vs. placebo	Age ≥ 20 years Serum urate level > 7 mg/dL No history of gout eGFR 30 to 59 mL/min/1.73 m^2	443	No significant slope difference in eGFR between groups
Kojima et al [5]	Randomized open parallel controlled study Duration: 3 years	Febuxostat 10 mg to 40 mg vs. allopurinol 100 mg	Age ≥ 65 years Serum urate level > 7 mg/dL Hypertension and/or type 2 diabetes and/or cerebrocardiovascular disease and/or eGFR 30 to 59 mL/min/1.73 m^2	1,070	Febuxostat prevented renal failure[a]
Levy et al [6]	Retrospective epidemiologic study Duration: > 8 years	Allopurinol, febuxostat, or probenecid vs. no urate-lowering therapy	Age ≥ 18 years Serum urate level > 7 mg/dL eGFR 15 to 89 mL/min/1.73 m^2	12,751	Patients with eGFR 30 to 89 mL/min/1.73 m^2 in receiving urate-lowering therapy had 30% improvement in eGFR

eGFR, estimated glomerular filtration rate.

[a]Renal failure was defined as development of microalbuminuria, progression to overt proteinuria, worsening of overt proteinuria, doubling of serum creatinine level, or progression to end-stage renal disease.

trolled trial (RCT) regarding reduced renal function in patients with hyperuricemia complicated by CKD stage 3 (FEATHER) study—an RCT—aimed to assess the effects of urate-lowering agents on the kidney function and to determine whether febuxostat attenuates the deterioration of the kidney function of patients with CKD and asymptomatic hyperuricemia [9]. The subgroup analysis of the FEATHER study demonstrated a significant benefit in terms of preserved kidney function following febuxostat administration in patients without proteinuria or with serum creatinine levels below the median. However, there was no significant difference in estimated glomerular filtration rate (eGFR) decline between the febuxostat and placebo groups. Second, the febuxostat for cerebral and cardiorenovascluar events prevention study (FREED) also an RCT that evaluated the effects of febuxostat in patients ≥ 65 years of age with hyperuricemia who were at risk of any cerebral or cardiovascular disease [5]. Preliminary results revealed that reduced serum uric acid levels in response to febuxostat have a protective effect on kidney function. In this study, however, kidney failure was defined as a composite outcome, including the occurrence of proteinuria as well as increased serum creatinine levels. Third, a retrospective epidemiologic cohort study conducted over 8 years to determine whether the administration of urate-lowering agents was beneficial for patients with mild-to-moderate CKD. The study, by Levy et al [6], suggested that urate-lowering therapy was not associated with any improvement in eGFR in patients with CKD stage 4. Thus, it cannot be concluded that pharmacologic urate-lowering agents have a protective effect on kidney function in patients with CKD and asymptomatic hyperuricemia.

The choice of xanthine oxidase inhibitor as the first-line urate-lowering agent is another controversial issue. Allopurinol has been commonly used for over 50 years. However, adverse effects including rash, leukopenia or thrombocytopenia, and diarrhea have been reported in 3% to 5% of patients. Furthermore, allopurinol-hypersensitivity syndrome (AHS) is a life-threatening side effect, with a mortality rate of 20% to 25%. In particular, concurrent thiazide use and kidney failure are associated with increase in the risk of AHS. Moreover, the association of human leukocyte antigen-B*5801 with AHS has been demonstrated, and the prevalence of this phenotype is relatively high (12.2%) in the Korean population [10]. On the other hand, febuxostat is well tolerated in patients who are hypersensitive or intolerant to allopurinol [10,11]. Febuxostat is metabolized predominantly in the liver, with only 1% to 6% of the dosage being excreted

through the kidneys [12], enabling safe administration in patients with CKD. However, the cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular comorbidities (CARES) trial revealed that all-cause and cardiovascular mortality rates were higher among patients using febuxostat than among those using allopurinol [13]. Because there were no preclinical cardiovascular studies demonstrating the toxic effects of febuxostat in terms of cardiac rhythm, function, or metabolism, the investigators concluded that clarifying the mechanism underling this risk of death is difficult.

Considering the side effects of urate-lowering agents in patients with CKD and the lack of clinical trials showing protective effect of these drugs on kidney function in patients with CKD and asymptomatic hyperuricemia, it is premature to recommend this therapy for asymptomatic hyperuricemia in patients with CKD. Conclusive evidence that pharmacologic urate-lowering therapy attenuates CKD progression in patients with less kidney damage and asymptomatic hyperuricemia is required before firm clinical guidelines can be decided upon.

Conflicts of interest

The author has no conflicts of interest to declare.

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