Urate-lowering agents for asymptomatic hyperuricemia in stage 3 – 4 chronic kidney disease: Controversial role of kidney function

Hee Jung Jeon, Jieun Oh, Dong Ho Shin

Department of Internal Medicine, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea

* isaac9713@gmail.com

Abstract

Because the serum uric acid level increases as the glomerular filtration rate (GFR) decreases, hyperuricemia is associated with chronic kidney disease (CKD). Although hyperuricemia is a risk factor for CKD progression, the causal role of uric acid remains controversial in patients with CKD and asymptomatic hyperuricemia. This study included 588 patients with stage 3–4 CKD and asymptomatic hyperuricemia. Using propensity score matching, 165 pairs treated and untreated with pharmacologic urate-lowering therapy were matched. Kaplan-Meier curves were constructed to determine the effect of urate-lowering agents on kidney survival. The prognostic value for kidney survival was ascertained using Cox regression analysis. The GFR changes over time between the patients treated and untreated with urate-lowering agents were assessed using a linear mixed model analysis. The mean age of the matched patients was 63.2 ± 12.7 years, and 52 (15.8%) patients had diabetic nephropathy. The mean estimated GFR (eGFR) and serum uric acid level were 36.7 mL/min/1.73 m² and 7.8 mg/dL, respectively. During a mean follow-up period of 41.9 months, 87 developed end-stage kidney disease (ESKD). The incidence rates of ESKD were comparable between the patients treated and untreated with urate-lowering agents. The Kaplan-Meier analysis indicated that kidney survival was also comparable between them. In the multivariate analysis, heart failure and low eGFR were the significant prognostic factors for kidney survival. However, pharmacologic urate-lowering therapy was not predictive of kidney survival. The overall GFR decline rate was also comparable between the groups (P = 0.13). The efficacy of pharmacologic urate-lowering therapy in delaying CKD progression remains controversial. Therefore, further randomized controlled trials are needed to confirm its efficacy in attenuating kidney function deterioration in patients with stage 3–4 CKD.

Introduction

Uric acid is the poorly soluble circulating end-product of purine metabolism in humans owing to the loss of uricase activity [1]. It has an excellent antioxidant capacity and is necessary for induction of type 2 immune responses [2]. On the contrary, the pathogenic potential of uric...
Acid is associated with inflammatory arthritis, gout, and progression of metabolic syndrome [2]. The kidney plays an important role in uric acid excretion through a complex process involving filtration, reabsorption, and tubular secretion [3]. Generally, decreased kidney function causes hyperuricemia due to decreased excretion of uric acid. In fact, in patients with advanced-stage chronic kidney disease (CKD), the prevalence rate of hyperuricemia is known to exceed 60% [4, 5]. Recent experimental findings attracted new interest in the pathogenic role of uric acid in endothelial dysfunction, inflammation, and vascular disease [6]. In addition, several studies have reported that uric acid accelerates systemic and glomerular hypertension, leading to kidney failure by worsening glomerulosclerosis and tubulointerstitial disease [7]. Interestingly, epidemiologic studies on the general population and patients with CKD showed that hyperuricemia is a major risk factor for the development and progression of kidney diseases [8–12].

Although hyperuricemia is strongly associated with the development of CKD, whether it plays a role in the deterioration of kidney function or is only a marker reflecting such deterioration remains controversial in patients with CKD. In this context, some epidemiologic studies showed no relationship between hyperuricemia and deterioration of kidney function [5, 13]. On the contrary, several clinical trials showed the efficacy of pharmacologic urate-lowering therapy on attenuation of kidney failure in patients with CKD and hyperuricemia [14–16]. However, these studies were mostly single-center studies, which had only small numbers of patients and limited follow-up period durations. Although several meta-analyses were conducted to overcome these limitations [17, 18], the results were inconclusive because of significant heterogeneity with respect to design, end-point, and follow-up period.

The objective of this long-term observational study is to explore the effect of pharmacologic urate-lowering therapy on the kidney function of patients with CKD and asymptomatic hyperuricemia via propensity score matching.

**Materials and methods**

**Ethics statement**

This study was performed in accordance with the Declaration of Helsinki principles and approved by the Institutional Review Board (IRB) of Kangdong Sacred Heart Hospital (Ref. no. 2019-01-005). This was a retrospective medical record-based study, and the study subjects were de-identified. The IRB waived the need for written consent from the participants.

**Patients**

The inclusion criteria were as follows: 1) age of ≥ 18 years; 2) estimated glomerular filtration rate (eGFR) of 15 to 60 mL/min/1.73 m² (calculated using the four-variable Modification of Diet in Renal Disease study equation [19]) for > 3 months; 3) hyperuricemia (serum uric acid levels of ≥ 7 mg/dL); 4) naivety to pharmacologic urate-lowering therapy at least 1 year before study enrollment; and 5) follow-up period of over 12 months. Seven hundred seventy-nine patients were recruited from Kangdong Sacred Heart Hospital for the study from January 2006 to December 2018. However, subjects were excluded if there were any of the following criteria: 1) history of gout or nephrolithiasis (n = 164); 2) rapid decrease in the eGFR of at least 50% within 3 months before eligibility confirmation (n = 11); 3) previous kidney transplantation (n = 4); 4) patients with cancer undergoing chemotherapy (n = 5); and 5) conditions related to hyperuricemia not associated with decreased kidney function (e.g., psoriasis, hemolytic anemia, lymphoproliferative disease, or rhabdomyolysis) (n = 7). Thus, 588 patients were finally included in this study (Fig 1).
Data collection
The date of the first occurrence of a serum uric acid level of > 7 mg/dL was defined as the index date. The inclusion and exclusion criteria were applied on the basis of the index date. To evaluate the effect of long-term hyperuricemia on kidney function, the serum uric acid levels were also investigated during the follow-up period. To capture longitudinal changes in serum uric acid, the area under the serum uric acid level-time curve was calculated and adjusted on the basis of the total follow-up period [20]. In other words, at each visit point in the follow-up period, visit time and serum uric acid level were multiplied, and the sum of the values was divided by the sum of the visit times. This value was defined as the actual serum uric acid level. Urate-lowering agents included xanthine oxidase inhibitors, such as allopurinol and febuxostat. Patients who received urate-lowering agents, renin-angiotensin-aldosterone system blockers, calcium channel blockers, diuretics, salicylates, and warfarin were defined as those treated for > 6 months. Proteinuria was defined as the excretion of > 0.15 of spot urine protein to creatinine ratio [21]. Heart failure was defined as either any diastolic heart failure or a systolic ejection fraction of < 40% as reported on echocardiogram [22, 23].

Description of pharmacologic urate-lowering therapy
Among eligible patients followed-up in nephrology clinic at Kangdong Sacred Heart Hospital, the decision to treat with urate-lowering agents was made by nephrologists. Patients in treated group received urate-lowering agents from the index date. Urate-lowering agents were titrated or switched to other alternative drugs for reaching the target uric acid level (< 6 mg/dL).

Outcome assessment
The initial study endpoint was the development of end-stage kidney disease (ESKD), defined as a condition needing maintenance dialysis or kidney transplantation. Meanwhile, the changes in the eGFR over time were evaluated according to whether the patients were treated with urate-lowering agents. In addition, subgroup analyses of eGFR decline slopes were conducted for sex, age, diabetes, CKD stage, heart failure, proteinuria, and serum uric acid level.
Statistical analysis

Statistical analyses were performed using the SPSS 19.0 (SPSS Inc., Chicago, Illinois, USA) and R version 3.5.1 (http://cran.r-project.org/). The Kolmogorov-Smirnov test was used to analyze the normality of parameter distribution for continuous variables. Continuous variables were expressed as means ± standard deviations or medians (interquartile ranges) and categorical variables as numbers (percentages). Propensity score matching was performed using the MatchIt package in R and variables collected at the index date. Patients with the nearest propensity scores in the two groups (patients treated and untreated with urate-lowering agents) were matched using a 1:1 scheme without replacement using a greedy algorithm. Greedy algorithm is a simple, intuitive algorithm that is used in optimization problems. The algorithm makes the optimal choice at each step as it attempts to find the overall optimal way to solve the entire problem. Propensity score matching allowed the comparison of outcomes between individuals with a similar likelihood. Differences between the two groups were assessed using the t-test, Wilcoxon’s rank sum test, and chi-squared test. Standardized mean differences were also estimated to evaluate the pre-match and post-match imbalance. Kidney survival curves were generated using the Kaplan-Meier method, and between-group survival was compared using the log-rank test. The prognostic values for kidney survival were analyzed by performing Cox regression analysis. The slope of the decline in kidney function over time was calculated using a linear regression analysis of the serial eGFR for each patient. The changes in the eGFR over time were compared between the two groups using a linear mixed model analysis. In this analysis, the patients treated and untreated with urate-lowering agents and follow-up period were treated as fixed effects, and each patient was treated as a random effect such that each subject had a unique intercept and slope. All probabilities were two-tailed, and the level of significance was set at 0.05.

Results

Patient characteristics

The baseline characteristics of the patients treated and untreated with urate-lowering agents are shown in Table 1. A total of 588 patients were included in the study, 165 (28.1%) of whom were treated with urate-lowering agents. The patients treated with urate-lowering agents had a higher proportion of men, higher age, longer follow-up period, and higher serum uric acid level than those untreated with such. After propensity score matching, the two groups were found to have similar characteristics. Of note, standardized mean differences before and after propensity score matching were represented in S1 Fig. Of the 330 patients in the matched analysis, 254 (77.0%) were men, and the average patient age was 58.2 ± 13.6 years. The mean eGFR and serum uric acid level were 36.5 ± 14.9 mL/min/1.73 m² and 7.8 ± 8.2 mg/dL, respectively. In addition, the underlying cause of CKD was diabetes in 52 (15.8%) patients.

Details of pharmacologic urate-lowering therapy after propensity score matching

Ninety patients were prescribed with allopurinol as the urate-lowering agent. The starting dose of allopurinol ranged from 50 mg/day to 100 mg/day, with 100 mg/day being the most common (55/90, 61.1%). The maintenance dose of allopurinol was 100 mg in 65 patients, 200 mg in 23 patients, and 300 mg in two patients. Thirty-four patients switched to febuxostat with a maintenance dose of 40 mg/day. The reason for discontinuation of allopurinol was inefficacy or presence of side effects. Meanwhile, 75 patients were prescribed with febuxostat. The starting dose of febuxostat ranged from 20 mg/day to 40 mg/day, with 20 mg/day being the most...
The maintenance dose of febuxostat was 40 mg in 71 patients and 80 mg in four patients.

Serum uric acid levels after propensity score matching

The baseline serum uric acid levels were comparable between the patients treated and untreated with urate-lowering agents. However, the final serum uric acid level (5.9 ± 1.6 vs. 8.1 ± 1.4, P < 0.001) and actual serum uric acid level (6.1 ± 1.0 vs. 8.0 ± 1.0, P < 0.001) were significantly lower in the patients treated with urate-lowering agents than in those untreated with such. Among the patients treated with urate-lowering agents, the percentage of those whose serum uric acid levels decreased to 6.0 mg/dL during the first 3 months was 98.2%.

Table 1. Characteristics of the study population before and after propensity score matching.

|                                | Before propensity score matching | P value | After propensity score matching | P value |
|--------------------------------|---------------------------------|---------|---------------------------------|---------|
|                                | Patients treated with pharmacologic ULT |        | Patients untreated with pharmacologic ULT |        |
|                                | (n = 423)                       |         | (n = 165)                       |         |
|                                | Patients treated with pharmacologic ULT |        | Patients untreated with pharmacologic ULT |        |
|                                | (n = 165)                       |         | (n = 165)                       |         |
| Men (%)                        | 245 (57.9)                      | <0.001  | 123 (74.5)                      | 0.36    |
| Age (year)                     | 65.6 ± 13.3                     | <0.001  | 58.8 ± 13.2                     | 0.43    |
| Follow-up (month)              | 30.1 ± 23.3                     | <0.001  | 39.8 ± 27.9                     | 0.22    |
| Cause of CKD                   |                                 |         |                                 |         |
| Diabetes (%)                   | 97 (22.9)                       | 0.06    | 26 (15.8)                       | 1.00    |
| Non-diabetes (%)               | 329 (77.1)                      | 0.99    | 139 (84.2)                      | 0.91    |
| Laboratory parameters          |                                 |         |                                 |         |
| eGFR (mL/min/1.73 m²)          | 36.1 ± 14.1                     | 0.51    | 35.9 ± 15.1                     | 0.52    |
| Stage 3 CKD (%)                | 252 (59.6)                      | 0.62    | 93 (56.4)                       | 0.31    |
| Stage 4 CKD (%)                | 171 (40.4)                      | 0.90    | 10 (6.1)                        | 0.65    |
| Urine p/cr                     | 0.57 (0.14–1.95)                | 0.52    | 0.80 (0.17–2.64)                | 0.66    |
| Serum uric acid level (mg/dL)  | 7.6 ± 0.6                       | <0.001  | 7.7 ± 0.7                       | 0.07    |
| Medications                    |                                 |         |                                 |         |
| RAAS blocker (%)               | 282 (66.7)                      | 0.01    | 131 (79.4)                      | 0.89    |
| CCB (%)                        | 159 (37.6)                      | 0.13    | 74 (46.1)                       | 0.91    |
| Diuretics (%)                  | 99 (23.4)                       | 0.02    | 58 (35.2)                       | 0.82    |
| Salicylates (%)                | 73 (17.3)                       | <0.001  | 50 (30.3)                       | 0.91    |
| Warfarin (%)                   | 4 (0.9)                         | 0.65    | 3 (1.8)                         | 1.00    |

Notes: Values are expressed as medians ± standard deviations or numbers (percentages). Stage 3 CKD, eGFR of 60–30 mL/min/1.73 m²; stage 4 CKD, eGFR of 15–30 mL/min/1.73 m²; diuretics, thiazide or furosemide

Abbreviations: CCB, calcium channel blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; ULT, urate-lowering therapy; Urine p/cr, spot urine protein to creatinine ratio

*Spot urine protein to creatinine ratio of > 0.15

https://doi.org/10.1371/journal.pone.0218510.t001

common (49/75, 65.3%). The maintenance dose of febuxostat was 40 mg in 71 patients and 80 mg in four patients.
Incidence rate of ESKD after propensity score matching

During a mean follow-up period of 41.9 ± 30.8 months, 87 patients developed ESKD. The incidence rates of ESKD were comparable between the patients treated and untreated with urate-lowering agents (38; 23.0% vs. 49; 29.7%, $P = 0.21$). The Kaplan-Meier analysis indicated that kidney survival was also comparable between them (Fig 2). The Cox regression analysis was conducted to evaluate the prognostic values for kidney survival. In the univariate analysis, heart failure, diabetes, proteinuria, and low eGFR were the significant prognostic factors for kidney survival. In the multivariate analysis, only heart failure, proteinuria, and low eGFR were the significant prognostic factors. However, pharmacologic urate-lowering therapy was not predictive of kidney survival (Table 2).

Comparison of the eGFR over time

The eGFR during the follow-up period is shown in Fig 3. The linear mixed model analysis revealed that the eGFR over time was comparable between the patients treated and untreated with urate-lowering agents. The mean values of each patient’s eGFR decline slope in the two groups were also comparable (- 2.35 ± 0.39 vs. - 3.45 ± 0.60 mL/min/year/1.73 m$^2$, $P = 0.13$).

The subgroup analysis of the eGFR decline slope was conducted according to sex, age, heart failure, diabetes, proteinuria, CKD stage, and serum uric acid level. It revealed no significant difference between the patients treated and untreated with urate-lowering agents (Table 3).

Discussion

We evaluated the efficacy of urate-lowering agents in attenuating the deterioration of kidney function and effects on the associated clinical factors in patients with stage 3–4 CKD and asymptomatic hyperuricemia. Although clinical factors, such as diabetes, proteinuria, heart failure, and baseline eGFR, affect the deterioration of kidney function, there was no significant difference in kidney survival between the patients treated and untreated with urate-lowering therapy.
agents. In addition, the subgroup analysis of the eGFR decline slope according to sex, age, heart failure, diabetes, proteinuria, CKD stage, and serum uric acid level revealed no significant difference between them.

There is accumulating evidence that hyperuricemia has a causal relationship with the deterioration of kidney function [7–12]; however, such a relationship remains debated upon. In addition, as risks of inappropriate treatment of asymptomatic hyperuricemia have been reported [24, 25], well-designed and well-conducted studies are needed to obtain definitive conclusions on the efficacy of urate-lowering agents in treating asymptomatic hyperuricemia in patients with CKD. The FEbuxostat vs placebo rAndomized controlled Trial regarding reduced renal function in patients with Hyperuricemia complicated by chRonic kidney disease stage 3 (FEATHER) study was conducted as a randomized controlled trial (RCT) to assess the effect of urate-lowering agents on the kidney function of patients with CKD and asymptomatic hyperuricemia [26]. This study was designed to investigate whether febuxostat attenuates the deterioration of the kidney function of patients with CKD and hyperuricemia without any history of gout. However, there were no significant differences in the eGFR decline slope between their febuxostat group and placebo group. In line with this finding, we clearly showed herein that the eGFR decline slopes were comparable between the patients treated and untreated with urate-lowering agents. Although the subgroup analysis in the FEATHER study demonstrated a significant benefit of preserved kidney function from febuxostat administration in patients without proteinuria, the subgroup analysis in our study revealed that there were no benefits regarding kidney function from urate-lowering agent administration. This discrepancy in the results could be explained by the following reasons. First, more patients with stage 4 CKD and proteinuria were included in our study compared with the FEATHER study. Second, different agents (i.e., febuxostat and allopurinol) were prescribed as the urate-lowering agents in our study. The Febuxostat for cerebral and carDiorenovascular Events prEvention stuDy (FREED) was also an RCT that evaluated the effect of febuxostat in patients ≥ 65 years of age with hyperuricemia at a risk for any cerebral or cardiovascular disease [27]. This study showed that lowering the serum uric acid levels using febuxostat had a protective effect on kidney function. However, in this study, kidney failure was defined as a composite outcome, including the

| Variables                          | Univariate Hazard ratio (95% CI) | P value | Multivariate Hazard ratio (95% CI) | P value |
|------------------------------------|----------------------------------|---------|-----------------------------------|---------|
| Men (vs. women)                    | 1.09 (0.67–1.78)                 | 0.74    |                                   |         |
| Age (year)                         | 0.99 (0.97–1.00)                 | 0.07    |                                   |         |
| Diabetes (vs. non-diabetes)        | 2.12 (1.29–3.47)                 | 0.003   | 1.51 (0.90–2.54)                  | 0.12    |
| Heart failure (vs. non-heart failure) | 1.76 (1.15–2.70)               | 0.01    | 1.73 (1.12–2.69)                  | 0.01    |
| Proteinuria* (vs. absent)          | 30.29 (4.22–217.53)             | 0.001   | 13.74 (1.89–100.06)              | 0.01    |
| eGFR (mL/min)                      | 0.93 (0.91–0.95)                | <0.001  | 0.94 (0.92–0.96)                 | <0.001  |
| Serum uric acid level (mg/dL)      | 1.09 (0.84–1.40)                | 0.53    |                                   |         |
| Urate-lowering therapy             | 0.70 (0.46–1.08)                | 0.1     |                                   |         |
| RAAS blocker                       | 2.91 (1.34–6.31)                | 0.01    | 1.96 (0.89–4.28)                 | 0.09    |
| Diuretics (thiazide or furosemide) | 2.25 (1.47–3.45)                | <0.001  | 1.17 (0.75–1.82)                 | 0.50    |

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system

*Spot urine protein to creatinine ratio of > 0.15

https://doi.org/10.1371/journal.pone.0218510.t002
occurrence of proteinuria, as well as increased serum creatinine level. In addition, more patients with stage 3 CKD were also included in this study compared with our study.

It is well known that certain clinical factors, such as diabetes, proteinuria, heart failure, and baseline eGFR, could exacerbate the eGFR decline rate in patients with CKD [28–31]. In our study, although pharmacologic urate-lowering therapy was not related to kidney survival, univariate Cox regression analysis revealed that the above-mentioned clinical factors were also the significant prognostic factors for kidney survival. Especially, in multivariate Cox regression analysis, heart failure and proteinuria were found to be an independent predictor of kidney survival. Experimental findings suggested that uric acid leads to kidney failure primarily by causing systemic and glomerular hypertension [32]. In addition, recent clinical studies showed that urate-lowering therapies in asymptomatic hyperuricemia patients with CKD 2–5 have higher rates of eGFR improvement [33–35]. However, patients with advanced-stage CKD,
including stages 4 and 5, commonly develop severe systemic hypertension mainly due to water and sodium retention. In this situation, the contribution of uric acid in deteriorating kidney function may become less relevant. In fact, the study by Levy G et al. showed patients on urate-lowering therapy have no improvement in the eGFR in CKD stage 4 [34]. In addition, some epidemiologic studies showed that hyperuricemia was not significantly associated with kidney survival [5, 13]. Therefore, large-scale RCTs on the treatment of hyperuricemia for kidney survival in patients with mild-to-moderate CKD, including stages 2 and 3 CKD, according to certain pathologic conditions are needed.

Table 3. Subgroup analysis of the eGFR decline slopes.

| Subgroup | Group                  | N  | Mean  | Between-group difference (95% CI)          | P value |
|----------|------------------------|----|-------|-------------------------------------------|---------|
| Sex      |                        |    |       |                                           |         |
| Male     | No pharmacologic ULT   | 123| - 3.15| - 0.89 (- 2.74–0.97)                      | 0.35    |
|          | Pharmacologic ULT      | 131| - 2.26|                                           |         |
| Female   | No pharmacologic ULT   | 42 | - 2.31| 0.40 (- 1.71–2.52)                       | 0.70    |
|          | Pharmacologic ULT      | 34 | - 2.71|                                           |         |
| Age      |                        |    |       |                                           |         |
| < 58 years| No pharmacologic ULT   | 75 | - 3.33| - 0.08 (- 2.82–2.66)                      | 0.96    |
|          | Pharmacologic ULT      | 85 | - 3.25|                                           |         |
| ≥ 58 years| No pharmacologic ULT   | 90 | - 2.61| - 1.20 (- 2.67–0.26)                      | 0.11    |
|          | Pharmacologic ULT      | 80 | - 1.41|                                           |         |
| Diabetes |                        |    |       |                                           |         |
| Absent   | No pharmacologic ULT   | 139| - 2.23| - 0.01 (- 1.59–1.57)                      | 0.99    |
|          | Pharmacologic ULT      | 139| - 2.22|                                           |         |
| Present  | No pharmacologic ULT   | 26 | - 6.72| - 3.62 (- 7.61–0.37)                      | 0.07    |
|          | Pharmacologic ULT      | 26 | - 3.1 |                                           |         |
| Heart failure |                        |    |       |                                           |         |
| Absent   | No pharmacologic ULT   | 110| - 2.93| - 0.48 (- 1.94–0.98)                      | 0.52    |
|          | Pharmacologic ULT      | 112| - 2.45|                                           |         |
| Present  | No pharmacologic ULT   | 55 | - 4.49| - 2.33 (- 5.48–0.81)                      | 0.15    |
|          | Pharmacologic ULT      | 53 | - 2.16|                                           |         |
| CKD stage|                        |    |       |                                           |         |
| 3        | No pharmacologic ULT   | 93 | - 2.50| - 0.90 (- 2.98–1.17)                      | 0.39    |
|          | Pharmacologic ULT      | 102| - 1.60|                                           |         |
| 4        | No pharmacologic ULT   | 72 | - 4.7 | - 1.10 (- 2.78–0.59)                      | 0.20    |
|          | Pharmacologic ULT      | 63 | - 3.6 |                                           |         |
| Proteinuria |                        |    |       |                                           |         |
| Absent   | No pharmacologic ULT   | 38 | 0.15  | 0.06 (- 1.84–1.97)                        | 0.95    |
|          | Pharmacologic ULT      | 37 | 0.09  |                                           |         |
| Presenta | No pharmacologic ULT   | 127| - 4.53| - 1.47 (- 3.15–0.22)                      | 0.89    |
|          | Pharmacologic ULT      | 128| - 3.06|                                           |         |
| Serum uric acid level |                        |    |       |                                           |         |
| < 7.8 mg/dL | No pharmacologic ULT   | 107| - 3.74| - 1.47 (- 3.26–0.31)                      | 0.14    |
|          | Pharmacologic ULT      | 114| - 2.27|                                           |         |
| ≥ 7.8 mg/dL | No pharmacologic ULT   | 58 | - 2.90| - 0.36 (- 2.70–1.98)                      | 0.19    |
|          | Pharmacologic ULT      | 51 | - 2.54|                                           |         |

*aSpot urine protein to creatinine ratio of > 0.15

Abbreviations: eGFR, estimated glomerular filtration rate; ULT, urate-lowering therapy

https://doi.org/10.1371/journal.pone.0218510.t003
Xanthine oxidase inhibitors with either allopurinol or febuxostat are recommended as the first-line pharmacologic urate-lowering agents [36]. Allopurinol has been commonly used for > 50 years [37]. However, mild side effects, such as rash, leukopenia or thrombocytopenia, and diarrhea, occur in 3% - 5% of patients taking such [37]. In addition, although allopurinol hypersensitivity syndrome (AHS) is infrequent, it is a life-threatening side effect, with a mortality rate of 20% - 25%. Further, concurrent thiazide use and kidney failure increase the risk for AHS. Moreover, in the Korean population, the prevalence rate of human leukocyte antigen-B' 5801 findings related to AHS is relatively high (12.2%) [36]. Meanwhile, febuxostat is well tolerated in patients experiencing hypersensitivity/intolerance to allopurinol [38]. In addition, it is metabolized predominantly in the liver, with only 1% - 6% of the dose being excreted through the kidney [39]. Therefore, the process of eliminating febuxostat from the body allows its safe administration in patients with CKD. However, the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Comorbidities trial showed that the all-cause and cardiovascular mortality rates were higher in the febuxostat group than in the allopurinol group in patients with gout and cardiovascular disease [40]. Taken together, pharmacologic urate-lowering agents must be carefully administered to patients with CKD.

Our study has certain limitations. First, the study was an uncontrolled retrospective study. However, propensity score matching was used to reduce any bias owing to confounding variables commonly found in uncontrolled data. In addition, in most patients treated with urate-lowering agents, the uric acid levels were consistently maintained at < 6.0 mg/dL for a long period. Second, only a small number of patients were enrolled in this study. Therefore, the interpretation of the subgroup analysis findings may be limited. Third, different agents (i.e., febuxostat and allopurinol) were prescribed as the urate-lowering agents in our study.

In conclusion, considering the side effects of urate-lowering agents in patients with CKD, there is a need to establish their efficacy according to certain pathologic conditions in patients with stage 2–3 CKD. Therefore, a large-scale prospective trial is needed to confirm such.

Supporting information

S1 Fig. Standardized differences before and after propensity score matching comparing covariate values for patients treated with pharmacologic ULT or untreated with pharmacologic ULT. ULT, urate-lowering therapy.

(TIF)

Author Contributions

Conceptualization: Hee Jung Jeon, Jieun Oh, Dong Ho Shin.
Data curation: Hee Jung Jeon, Jieun Oh, Dong Ho Shin.
Formal analysis: Hee Jung Jeon, Dong Ho Shin.
Funding acquisition: Dong Ho Shin.
Investigation: Hee Jung Jeon, Jieun Oh, Dong Ho Shin.
Methodology: Hee Jung Jeon, Dong Ho Shin.
Project administration: Jieun Oh, Dong Ho Shin.
Resources: Hee Jung Jeon, Jieun Oh, Dong Ho Shin.
Software: Dong Ho Shin.
Supervision: Jieun Oh.
Validation: Hee Jung Jeon, Jieun Oh.
Visualization: Hee Jung Jeon, Dong Ho Shin.
Writing – original draft: Hee Jung Jeon, Dong Ho Shin.
Writing – review & editing: Hee Jung Jeon, Jieun Oh, Dong Ho Shin.

References

1. Wu XW, Muzny DM, Lee CC, Caskey CT. Two independent mutational events in the loss of urate oxidase during hominoi d evolution. J Mol Evol. 1992; 34:78–84. PMID: 1556746.

2. El Ridi R, Tallima H. Physiological functions and pathogenic potential of uric acid: A review. J Adv Res. 2017; 8:487–493. https://doi.org/10.1016/j.jare.2017.03.003 PMID: 28748115.

3. Bobulescu IA, Moe OW. Renal transport of uric acid: evolving concepts and uncertainties. Adv Chronic Kidney Dis. 2012; 19:358–371. https://doi.org/10.1053/j.ackd.2012.07.009 PMID: 23089270.

4. Richette P, Bardin T. Gout. Lancet. 2010; 375:318–328. https://doi.org/10.1016/S0140-6736(09)60683-7 PMID: 19962116.

5. 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. https://doi.org/10.1053/j.akd.2008.12.021 PMID: 19303683.

6. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. Semin Nephrol; 2005; 25:39–42. PMID: 15660333.

7. Johnson RJ, Nakagawa T, Jalal D, Sanchez-Lozada LG, Kang DH, Ritze E. Uric acid and chronic kidney disease: which is chasing which? Nephrol Dial Transplant. 2013; 28:2221–2228. https://doi.org/10.1093/ndt/gft029 PMID: 23543594.

8. Li L, Yang C, Zhao Y, Zeng X, Liu F, Fu P. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease?: A systematic review and meta-analysis based on observational cohort studies. BMC Nephrol. 2014; 15:122. https://doi.org/10.1186/1471-2369-15-122 PMID: 25064611.

9. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS. Uric acid and incident kidney disease in the community. J Am Soc Nephrol. 2008; 19:1204–1211. https://doi.org/10.1681/ASN.2007101075 PMID: 1837481.

10. 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 Kidney Dis. 2010; 56:264–272. https://doi.org/10.1053/j.akd.2010.01.019 PMID: 2038436.

11. Bakan A, Oral A, Elicioglu OC, Takir M, Kostek O, Ozkok A, et al. Hyperuricemia is associated with progression of IgA nephropathy. Int Urol Nephrol. 2015; 47:673–678. https://doi.org/10.1007/s11255-015-0939-7 PMID: 25767142.

12. Obermayr RP, Temml C, Gutjahr G, Knechtlisdorfer M, Oberbauer R, Klausera-Braun R. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol. 2008; 19:2407–2413. https://doi.org/10.1681/ASN.2008010080 PMID: 18799720.

13. Sturm G, Kollerits B, Neyer U, Ritze E, Kronenberg F, Group MS. Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? The Mild to Moderate Kidney Disease (MMKD) Study. Exp Gerontol. 2008; 43:347–352. https://doi.org/10.1016/j.exger.2008.01.006 PMID: 18294794.

14. 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; 65:543–549. https://doi.org/10.1053/j.ajkd.2014.11.016 PMID: 2559565.

15. Gibson T, Rodgers V, Potter C, Simmonds HA. Allopurinol treatment and its effect on renal function in gout: a controlled study. Ann Rheum Dis. 1982; 41:59–65. https://doi.org/10.1136/ard.41.1.59 PMID: 7039523.

16. Kanbay M, Huddam B, Azak A, Solak Y, Kadioglu GK, Kirbas I, et al. 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. 2011; 6:1887–1894. https://doi.org/10.2215/CJN.11451210 PMID: 21786336.

17. 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; 29:406–413. https://doi.org/10.1093/ndt/gft378 PMID: 24402021.

18. 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. https://doi.org/10.1186/s12882-015-0047-2 PMID: 2592856.
19. National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39:51–266. PMID: 11904577.

20. Kim Y, Shin S, Kim K, Choi S, Lee K. Effect of Urate Lowering Therapy on Renal Disease Progression in Hyperuricemic Patients with Chronic Kidney Disease. J Rheumatol. 2015; 42:2143–2148. https://doi.org/10.3899/jrheum.150067 PMID: 26428209.

21. Chapter 1: Definition and classification of CKD. Kidney Int Suppl (2011). 2013; 3:19–62. https://doi.org/10.1038/kisup.2012.64 PMID: 23741058.

22. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37:2129–2200. https://doi.org/10.1093/eurheartj/ehw128 PMID: 27208619.

23. Writing Committee M, Yancy CW, Jessup M, Bozkurt B, Butler J, Case DE Jr., et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013; 128:e240–327. https://doi.org/10.1161/CIR.0b013e31829e8776 PMID: 23741058.

24. 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; 13:550–559. https://doi.org/10.1007/s11892-013-0381-0 PMID: 23649945.

25. Pasinella L, Brucato AL, Giacalone CD, D’Amato P, Ghidoni S, Tettamanti M, et al. Inappropriate prescription of allopurinol and febuxostat and risk of adverse events in the elderly: results from the REPSo registry. Eur J Clin Pharmacol. 2014; 70:1503–1507. https://doi.org/10.1007/s00228-014-1752-4 PMID: 25228251.

26. Kimura K, Hosoya T, Uchida S, Inaba M, Makino H, Maruyama S, et al. Febuxostat Therapy for Patients With Stage 3 CKD and Asymptomatic Hyperuricemia: A Randomized Trial. Am J Kidney Dis. 2018; 72:798–810. https://doi.org/10.1053/j.ajkd.2018.06.028 PMID: 30177485.

27. Alexander W. European Society of Cardiology Congress 2018. P T. 2018; 43:622–626. PMID: 30271107.

28. Sarnak MJ. A patient with heart failure and worsening kidney function. Clin J Am Soc Nephrol. 2014; 9:1790–1798. https://doi.org/10.2215/CJN.11601113 PMID: 24783684.

29. Hunsicker LG, Adler S, Caggiula A, England BK, Greene T, Kusek JW, et al. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. Kidney Int. 1997; 51:1908–1919. PMID: 9186882.

30. Chapter 2: Definition, identification, and prediction of CKD progression. Kidney Int Suppl (2011). 2013; 3:63–72. https://doi.org/10.1038/kisup.2012.65 PMID: 23018976.

31. Halbesma N, Kuiken DS, Brantsma AH, Bakker SJ, Wetzels JF, De Zeeuw D, et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. J Am Soc Nephrol. 2006; 17:2582–2590. https://doi.org/10.1681/ASN.2005121352 PMID: 16899519.

32. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzari M, et al. A role for uric acid in the progression of renal disease. J Am Soc Nephrol. 2002; 13:2888–2897. https://doi.org/10.1097/01.asn.0000034910.58454.fd PMID: 12444207.

33. Liu X, Wang H, Ma R, Shao L, Zhang W, Jiang W, et al. 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. 2019; 23:362–370. https://doi.org/10.1007/s10157-018-1652-5 PMID: 30521473.

34. Levy G, Shi JM, Cheetham TC, Rashid N. Urate-Lowering Therapy in Moderate to Severe Chronic Kidney Disease. Pernn J. 2018; 22:17–142. https://doi.org/10.7812/TPP/17-142 PMID: 30201087.

35. Tsuji T, Ohishi K, Takeda A, Goto D, Sato T, Ohashi N, et al. The impact of serum uric acid reduction on renal function and blood pressure in chronic kidney disease patients with hyperuricemia. Clin Exp Nephrol. 2018; 22:1300–1308. https://doi.org/10.1007/s10157-018-1580-4 PMID: 29700702.

36. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012; 64:1431–1446. https://doi.org/10.1002acr.21772 PMID: 23024028.

37. Wallace SL, Singer JZ. Therapy in gout. Rheum Dis Clin North Am. 1988; 14:441–457. PMID: 3051159.

38. Hu M, Tomlinson B. Febuxostat in the management of hyperuricemia and chronic gout: a review. Ther Clin Risk Manag. 2008; 4:1209–1220. https://doi.org/10.2147/tcrm.s3310 PMID: 19337428.
39. Khosravan R, Grabowski BA, Wu JT, Joseph-Ridge N, Vernillet L. Pharmacokinetics, pharmacodynamics and safety of febuxostat, a non-purine selective inhibitor of xanthine oxidase, in a dose escalation study in healthy subjects. Clin Pharmacokinet. 2006; 45:821–841. https://doi.org/10.2165/00003088-200645080-00005 PMID: 16884320.

40. 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; 378:1200–1210. https://doi.org/10.1056/NEJMoa1710895 PMID: 29527974.