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Comparative assessment of the effects of dotinurad and febuxostat on the renal function in chronic kidney disease patients with hyperuricemia

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Although hyperuricemia is associated with chronic kidney disease (CKD), the impact of uric acid (UA)-lowering drugs on CKD has been controversial. Previous investigations have primarily included xanthine oxidase inhibitors; therefore, research of dotinurad, a recently developed selective urate reabsorption inhibitor, is necessary. This retrospective study included 58 patients with CKD; of these, 29 newly initiated dotinurad and 29 initiated febuxostat. The effects of dotinurad and febuxostat on the serum UA, urinary UA-to-creatinine ratio (UUCR), and estimated glomerular filtration rate (eGFR) during 3 months were analyzed to compare their impacts on renal function. Dotinurad and febuxostat decreased serum UA (8.40 ± 1.11 to 6.50 ± 0.80 mg/dL [p < 0.001] and 8.91 ± 1.21 to 6.05 ± 1.28 mg/dL [p = < 0.001], respectively). The UUCR increased after dotinurad (0.35 ± 0.15 to 0.40 ± 0.21 g/gCr [p = 0.024]); however, it decreased after febuxostat (0.33 ± 0.12 to 0.21 ± 0.06 g/gCr [p = 0.002]). The eGFR improved after dotinurad (33.9 ± 15.2 to 36.2 ± 15.9 mL/min/1.73 m^2 [p < 0.001]). No change was observed after febuxostat treatment (33.4 ± 19.6 to 34.1 ± 21.6 mL/min/1.73 m^2). Renal function improved only with dotinurad, thus highlighting its renoprotective effects beyond the reduction of serum UA.

Keywords Chronic kidney disease, Dotinurad, Hyperuricemia, Selective urate reabsorption inhibitor, Urate transporter-1, Urinary uric acid

Chronic kidney disease (CKD) is a public health burden with an increasing prevalence[1,2]. In addition to metabolic abnormalities such as diabetes, hypertension, and dyslipidemia, hyperuricemia is strongly associated with kidney injury[3–8]. Hyperuricemia is associated with a higher incidence of CKD and the progression of preexisting CKD[9–13]; however, the association between hyperuricemia and CKD is not consistent[14,15]. Additionally, a reduction in the glomerular filtration rate can result in hyperuricemia. Therefore, whether hyperuricemia aggravates CKD or is merely a marker that reflects kidney dysfunction requires elucidation. One retrospective cohort study suggested an association between CKD and urinary uric acid (UA) excretion rather than serum uric acid levels[16].

Hyperuricemia can be classified as the overproduction type, extrarenal underexcretion type, or renal underexcretion type[17]. Currently, two types of drugs that target either UA production or urinary excretion can be used to treat hyperuricemia. Xanthine oxidase inhibitors (XOIs) target the rate-limiting enzyme involved in purine catabolism, thus leading to reduced UA production associated with hypoxanthine and xanthine[18]. Several studies with small cohorts have shown that XOIs effectively reduce serum UA levels and are preferable for preventing CKD progression[19–23]. However, large-scale randomized controlled trials failed to reveal the beneficial effects of XOIs, such as allopurinol and febuxostat, on renal outcomes[24–26]. Some clinical trials showed

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that benzbromarone, a uricosuric drug, may be more beneficial than XOIs[27,28], suggesting that uricosuric agents may be preferable for preventing CKD progression.

Recently, dotinurad, which is a new class of uricosuric drugs, has been developed. Dotinurad increases urinary urate excretion by selectively inhibiting urate transporter 1 (URAT1) expressed in the renal proximal tubule. Some observational studies have shown that dotinurad effectively reduces UA levels in patients with CKD[29–31]. Similar to conventional uricosuric drugs, such as benzbromarone, dotinurad is expected to exert renoprotective effects. However, its effects on patients with CKD require further clarification. Therefore, this study investigated the efficacy of dotinurad to reduce serum UA levels and its effects on renal function and compared those effects with those of XOIs on the renal function of patients with CKD.

Results

Patient characteristics

Among 83 recruited patients who newly initiated UA-lowering drug treatment, 25 were excluded because they were lost to follow-up (n = 7), switched from another UA-lowering drug (n = 7), underwent dialysis (n = 4), discontinued drug treatment (n = 3), experienced acute kidney injury (n = 3), or underwent renal transplantation (n = 1). As a result, a total of 58 patients were included in the analysis (Fig. 1). The patient characteristics are summarized in Table 1, Supplementary Table S1, and Supplementary Fig. 1. None of the patients had a history of gout. The major cause of CKD was nephrosclerosis (32.8%), followed by chronic glomerulonephritis (25.9%). Renin–angiotensin–aldosterone system inhibitors (RAS-i) and sodium-glucose cotoransporter-2 inhibitors (SGLT2-i) were used in 34 (58.6%) and in 11 (19.0%) patients. Among them, one patient in the febuxostat group started SGLT2-i during the observational period. Serum UA was not associated with the estimated glomerular filtration rate (eGFR) ($r = -0.059$; $p = 0.66$). The UUCR was significantly associated with the eGFR ($r = 0.504$; $p = 0.003$) and fractional excretion of UA (FEUA) ($r = 0.438$; $p = 0.011$). A multivariate linear regression analysis adjusted for sex, age, BMI, and UA revealed that both the eGFR and FEUA were independently associated with the UUCR (eGFR: standardized beta coefficient [stdβ] = 0.901 and $p < 0.001$; FEUA: stdβ = 0.761 and $p < 0.001$). In this cohort, 85% of patients had a UUCR < 0.5 g/gCr, indicating that the renal underexcretion type was dominant. Among 58 patients, 29 initiated dotinurad treatment and 29 initiated febuxostat treatment. Significant differences in age (68.1 ± 15.9 vs. 62.7 ± 16.5 years; $p = 0.21$), UA (8.40 ± 1.11 vs. 8.91 ± 1.21 mg/dL; $p = 0.098$), eGFR (33.9 ± 15.2 vs. 33.4 ± 19.6 mL/min/1.73 m^2; $p = 0.92$), and other laboratory parameters except for urinary *N*-acetyl-β-D-glucosaminidase (7.41 ± 4.87 vs. 12.25 ± 10.00 g/dL; $p = 0.029$) were not observed between the dotinurad and febuxostat groups (Table 1).

Effects of UA-lowering drugs

Changes in serum UA levels are summarized in Table 2 and Fig. 2. All patients in the dotinurad group initiated treatment at 0.5 mg daily. The daily dosages of dotinurad and febuxostat at 3 months were 0.71 ± 0.41 mg and

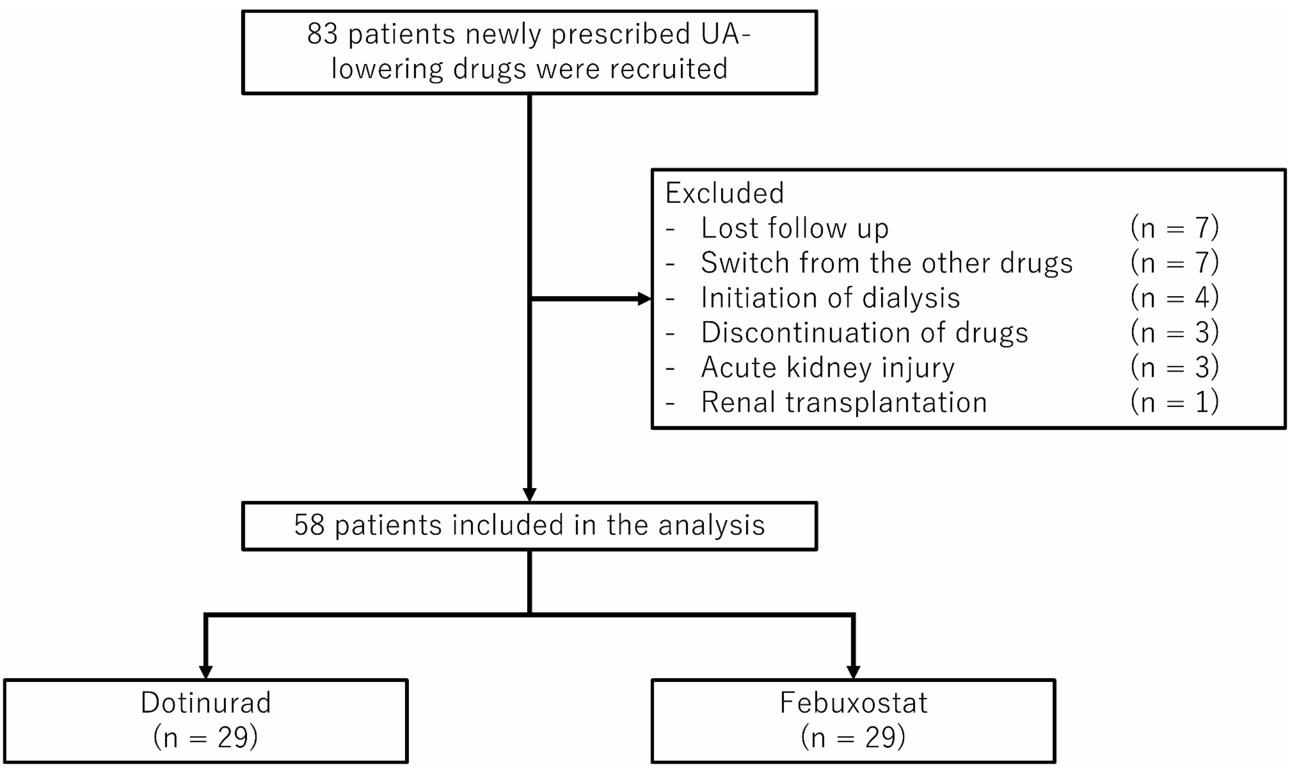

Fig. 1. Study participants. Of the 83 patients recruited, 58 were included in the analysis.

	All	Dotinurad	Febuxostat	*P* value
Number	58	29	29	
Age (years)	65.4 ± 16.3	68.1 ± 15.9	62.7 ± 16.5	0.21
Sex (male/female)	40/18	21/8	19/10	0.57
Body mass index (kg/m^2)	23.4 ± 3.8	23.2 ± 2.7	23.7 ± 4.7	0.61
SBP (mmHg)	137 ± 18	138 ± 18	137 ± 19	0.83
DBP (mmHg)	81 ± 14	79 ± 13	82 ± 16	0.41
Etiology of CKD				0.31
Nephrosclerosis	18 (32.8)	12 (41.4)	7 (24.1)	
Glomerulonephritis	15 (25.9)	5 (17.2)	10 (34.5)	
Diabetic kidney disease	8 (13.8)	4 (13.8)	4 (13.8)	
Polycystic kidney disease	6 (10.3)	4 (13.8)	2 (6.9)	
Other	10 (17.2)	4 (13.8)	6 (20.7)	
RAS inhibitors (+/-)	34/24	16/13	18/11	0.42
SGLT2 inhibitors (+/-)	11/47	5/24	6/23	0.74
Uric acid (mg/dL)	8.65 ± 1.18	8.40 ± 1.11	8.91 ± 1.21	0.098
Creatinine (mg/dL)	1.63 (0.52–5.61)	1.56 (0.70–4.06)	1.69 (0.52–5.61)	0.46
eGFR (mL/min/1.73m^2)	33.6 ± 17.4	33.9 ± 15.2	33.4 ± 19.6	0.92
Sodium (mmol/L)	140.7 ± 3.0	141.0 ± 2.8	140.4 ± 3.2	0.49
Potassium (mmol/L)	4.5 ± 0.6	4.5 ± 0.5	4.4 ± 0.6	0.56
Chloride (mmol/L)	105.4 ± 3.7	105.8 ± 3.2	105.1 ± 4.2	0.51
Triglyceride (mg/dL)	171 ± 118	163 ± 117	181 ± 120	0.61
HDL-C (mg/dL)	60 ± 24	57 ± 22	65 ± 28	0.24
LDL-C (mg/dL)	108 ± 33	109 ± 33	107 ± 33	0.83
HbA1c (%)	6.3 ± 0.7	6.4 ± 0.8	6.3 ± 0.6	0.83
Urinary pH	6.0 (5.0–7.5)	5.75 (5.0–7.5)	6.0 (5.0–7.0)	0.36
UUCR (g/gCr)	0.35 ± 0.14	0.35 ± 0.15	0.33 ± 0.12	0.61
FEUA (%)	7.05 ± 2.62	7.21 ± 2.73	6.57 ± 2.36	0.56
UPCR (g/gCr)	0.47 (0.01–15.87)	0.26 (0.01–4.91)	1.08 (0.01–15.87)	0.060
Urinary NAG (g/dL)	9.38 ± 7.70	7.41 ± 4.87	12.25 ± 10.00	0.029

Table 1. Patient characteristics. eGFR, estimated glomerular filtration rate; Systolic blood pressure, SBP; Diastolic blood pressure, DBP; High-density lipoprotein cholesterol, CKD, chronic kidney disease; HDL-C; Low-density lipoprotein cholesterol, LDL-C; Urinary uric acid-to-creatinine ratio, Fractional excretion of uric acid, FEUA; UUCR, Urinary uric acid-to-creatinine ratio; UPCR, Urinary protein-to-creatinine ratio; NAG, *N*-acetyl-β-D-glucosaminidase

	Baseline	After 3 months	*P*
Uric acid (mg/dL)			
Dotinurad	8.40 ± 1.11	6.50 ± 0.80	< 0.001
Febuxostat	8.91 ± 1.21	6.05 ± 1.28	< 0.001
UUCR (g/gCr)			
Dotinurad	0.35 ± 0.15	0.40 ± 0.21	0.024
Febuxostat	0.33 ± 0.12	0.21 ± 0.06	0.002
FEUA (%)			
Dotinurad	7.21 ± 2.73	9.71 ± 3.76	< 0.001
Febuxostat	6.57 ± 2.36	4.84 ± 2.73	0.019
Daily dosage (mg)			
Dotinurad	0.5 ± 0	0.71 ± 0.41	
Febuxostat	11.6 ± 4.0	13.1 ± 6.8	

Table 2. Accelerated UA excretion and improvement in serum UA after dotinurad. FEUA, fractional excretion of uric acid; UUCR, urinary uric acid-to-creatinine ratio.

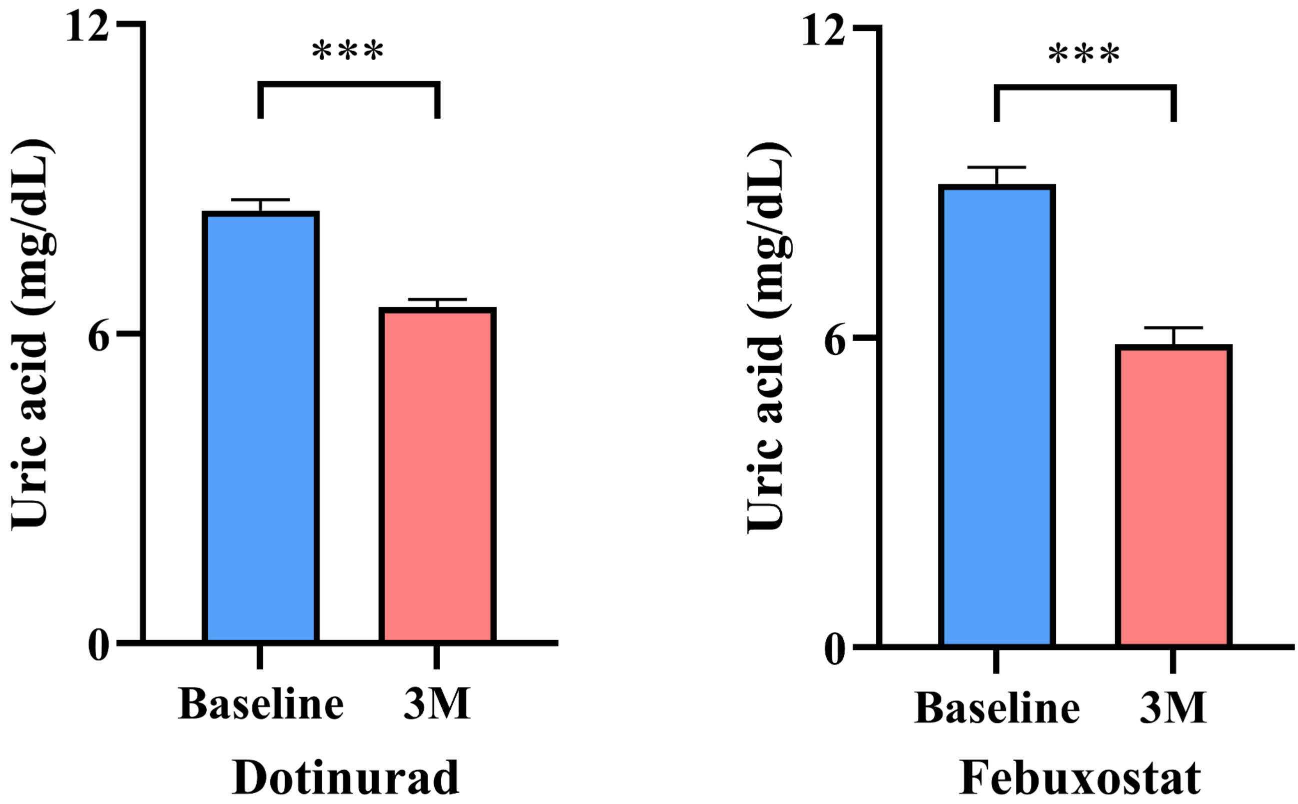

Fig. 2. Reduction in serum uric acid after treatment. Serum uric acid levels of the dotinurad and febuxostat groups at baseline and 3 months after treatment are shown. ***$p < 0.001$ (paired t test).

13.1 ± 6.8 mg, respectively. At 3 months, dotinurad significantly increased the UUCR (0.35 ± 0.15 to 0.40 ± 0.21 g/gCr; $p = 0.024$) and FEUA (7.21% ± 2.73% to 9.71% ± 3.76%; $p < 0.001$) and lowered serum UA (8.40 ± 1.11 to 6.50 ± 0.80 mg/dL; $p < 0.001$). Similarly, the serum UA significantly decreased in the febuxostat group (8.91 ± 1.21 to 6.05 ± 1.28 mg/dL; $p < 0.001$); however, febuxostat significantly decreased the UUCR (0.33 ± 0.12 to 0.21 ± 0.06 g/gCr; $p = 0.002$) and FEUA (6.57% ± 2.36% to 4.84% ± 2.73%; $p = 0.019$). The decrease in UA levels of the febuxostat group during 3 months of treatment was significantly larger than that of the dotinurad group (1.90 ± 1.25 mg/dL in the dotinurad group; 2.87 ± 1.53 mg/dL in the febuxostat group; $p = 0.019$). In the dotinurad group, there were no significant changes in metabolic parameters including triglyceride (TG) (163 ± 117 to 177 to 118 mg/dL, $p = 0.36$), HDL-C (57 ± 22 to 55 ± 22 mg/dL, $p = 0.75$), LDL-C (109 ± 33 to 111 ± 29 mg/dL, $p = 0.47$), HbA1c (6.4 ± 0.8 to 6.6 ± 1.2%, $p = 0.14$), systolic blood pressure (138 ± 18 to 137 ± 17 mmHg, $p = 0.78$), and diastolic blood pressure (79 ± 13 to 81 ± 13 mmHg, $p = 0.17$). We further investigated the association between the decrease in UA and patient characteristics. Serum UA at baseline was significantly associated with the UA improvement during 3 months of treatment (r = 0.774 and $p < 0.001$ in the dotinurad group; r = 0.587 and $p = 0.001$ in the febuxostat group). The TG level (r = − 0.530; $p = 0.020$) was negatively correlated with UA improvement in the febuxostat group. Other factors such as renal function at baseline were not associated with UA improvement (Table 3).

Renal function changes

To assess changes in renal function after treatment, eGFR levels before treatment, at baseline, and after 3 months of treatment were compared. The eGFR of all 58 patients was 36.6 ± 18.2 mL/min/1.73 m^2 before 3 months of treatment, and it decreased to 33.6 ± 17.4 mL/min/1.73 m^2 ($p < 0.001$) upon initiation of UA-lowering drug treatment, indicating that renal injury was progressive in this cohort. The rate of decline in eGFR during the observation period did not differ among the dotinurad and the febuxostat group ($p = 0.10$). In the dotinurad group, renal dysfunction progressed significantly before treatment; however, it improved significantly after 3 months of treatment (before treatment: 35.2 ± 14.7; baseline: 33.9 ± 15.2; after 3 months of treatment: 36.2 ± 15.9 mL/min/1.73 m^2; $p < 0.001$). Similarly, the eGFR of the febuxostat group before treatment decreased significantly; however, 3 months of febuxostat treatment did not change the eGFR (before treatment: 37.9 ± 21.3; baseline: 33.4 ± 19.6; after 3 months of treatment: 34.1 ± 21.6 mL/min/1.73 m^2; $p = 0.002$) (Table 4 and Fig. 3). Changes in the eGFR before and after treatment were significant in the dotinurad group (− 5.50% ± 8.81% to 7.45% ± 8.97%; $p < 0.001$), but not in the febuxostat group (− 10.74% ± 13.56% to − 0.42% ± 22.61%; $p = 0.067$). Because this study included CKD patients with wide range eGFR, we compared the percent changes in the eGFR for each group to minimize the variability. The percentage changes in eGFR from baseline were significantly higher in the dotinurad group than those in the febuxostat group (7.45 ± 8.97% vs − 0.42 ± 22.61%, $p = 0.042$).

	Dotinurad		Febuxostat	
	r	*P*	r	*P*
Age (years)	− 0.280	0.14	0.332	0.085
Body mass index (kg/m^2)	0.186	0.34	− 0.318	0.099
Uric acid (mg/dL)	0.774	< 0.001	0.587	0.001
Creatinine (mg/dL)	− 0.258	0.18	0.042	0.83
eGFR (mL/min/1.73 m^2)	0.157	0.42	0.024	0.90
Triglyceride (mg/dL)	0.177	0.37	− 0.530	0.020
HDL-C (mg/dL)	− 0.213	0.27	0.268	0.30
LDL-C (mg/dL)	− 0.201	0.31	0.160	0.54
Urinary pH	0.310	0.11	− 0.136	0.51
UUCR (g/gCr)	0.347	0.097	− 0.006	0.99
UPCR (g/gCr)	− 0.224	0.24	− 0.043	0.84

Table 3. Correlations with decreased uric acid. eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UPCR, urinary protein-to-creatinine ratio; UUCR, urinary uric acid-to-creatinine ratio.

eGFR (mL/min/1.73 m^2)	Before treatment	Baseline	After 3 months	P^a
Dotinurad	35.2 ± 14.7*	33.9 ± 15.2	36.2 ± 15.9 ***	< 0.001
Febuxostat	37.9 ± 21.3**	33.4 ± 19.6	34.1 ± 21.6	0.002

ΔeGFR (%)	Before	After	P^b
Dotinurad	− 5.50 ± 8.81	7.45 ± 8.97	< 0.001
Febuxostat	− 10.74 ± 13.56	− 0.42 ± 22.61	0.067

Table 4. Improvement in glomerular filtration rate after treatment. eGFR, estimated glomerular filtration rate; UA, uric acid. [a]Two-way analysis of variance (ANOVA). [b]Paired t-test. *$p < 0.05$ compared to baseline, **$p < 0.01$ compared to baseline, and ***$p < 0.001$ compared to baseline (post hoc Tukey test).

Furthermore, we conducted a multivariate analysis that include baseline eGFR and the rate of decline in eGFR before treatment. The multivariate regression analysis that included baseline eGFR, rate of decline in eGFR before treatment, and treatment drug showed that dotinurad treatment was significantly associated with an increase in the percentage change in eGFR (stdβ = 0.281, $p = 0.044$).

We also assessed urinary protein and tubular injury markers during treatment. The urinary protein-to-creatinine ratio (UPCR) of the dotinurad group did not significantly change (from 0.26 [0.01–4.91] to 0.35 [0.01–3.35] g/gCr; $p = 0.26$) (Table 5). Additionally the UPCR of the febuxostat group did not significantly change (from 1.08 [0.01–15.87] to 1.18 [0.03–5.97] g/gCr; $p = 0.44$). Urinary *N*-acetyl-β-D-glucosaminidase did not significantly change in the dotinurad (7.41 ± 4.87 to 9.02 ± 9.04 g/dL; $p = 0.28$) and febuxostat (12.25 ± 10.00 to 9.51 ± 7.48 g/dL; $p = 0.32$) groups. Urinary pH in the dotinurad group did not show significant change (from 6.0 [5.0–7.5] to 5.5 [5.0–7.0]; $p = 0.064$). No patient in the dotinurad group developed nephrolithiasis; 4 cases were prescribed alkali supplementation to prevent stone formation.

Because renal proximal tubular epithelial cells, which are the target of dotinurad, secrete certain amounts of creatinine, they may influence the calculated eGFR. Although we could not assess whether dotinurad improved the eGFR through accelerated renal tubular creatinine secretion, we confirmed changes in the glomerular filtration rate using the cystatin C-based eGFR. Dotinurad significantly decreased serum cystatin C levels from 2.00 mg/L (1.35–3.82) to 1.84 mg/L (1.28–3.63 mg/L) ($p = 0.030$) and improved the cystatin C-based eGFR (29.0 ± 10.7 to 31.2 ± 11.8 mL/min/1.73 m^2; $p = 0.049$) (Table 6).

Correlation between changes in renal function and UA

Because we observed a significant increase in the eGFR after dotinurad treatment, we investigated the factors that influence this improvement. A univariate correlation analysis of the dotinurad group revealed that the decrease in UA was significantly associated with renal function improvement (r = 0.398; $p = 0.032$) (Table 7). A multivariate analysis that included age, sex, baseline eGFR, and metabolomic parameters revealed that the decrease in UA (stdβ = 0.381; $p = 0.037$) influenced renal function improvement (Table 8).

Discussion

This study provided insights regarding the impact of different UA-lowering drugs on the renal function. We demonstrated that dotinurad and febuxostat effectively decreased the serum UA level in patients with CKD and asymptomatic hyperuricemia. Dotinurad significantly improved the eGFR without increasing urinary protein or tubular injury markers, whereas febuxostat did not change the eGFR. These results suggest that dotinurad has renoprotective effects other than the ability to lower UA.

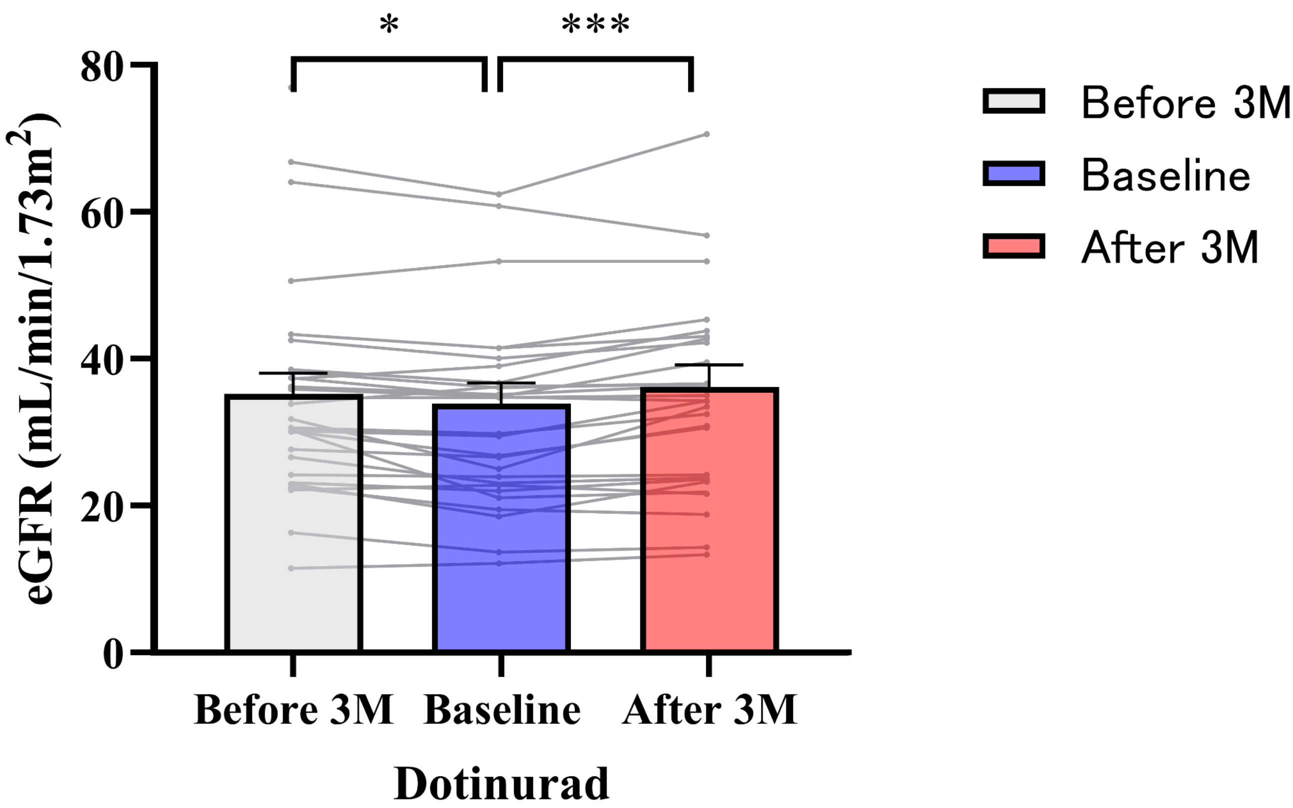

Fig. 3. Dotinurad improved glomerular filtration rate. Estimated glomerular filtration rates before treatment, at baseline, and after 3 months of treatment of the dotinurad group are shown. *$p < 0.05$ and ***$p < 0.001$ (post hoc Tukey test).

	Baseline	After 3 months	*P*
UPCR (g/gCr)			
Dotinurad	0.26 (0.01–4.91)	0.35 (0.01–3.35)	0.26
Febuxostat	1.08 (0.01–15.87)	1.18 (0.03–5.97)	0.44
Urinary NAG (g/dL)			
Dotinurad	7.41 ± 4.87	9.02 ± 9.04	0.28
Febuxostat	12.25 ± 10.00	9.51 ± 7.48	0.32

Table 5. Effects of UA-lowering drugs on urinalysis results. NAG, *N*-acetyl-β-D-glucosaminidase; UA, uric acid; UPCR, urinary protein-to-creatinine ratio.

	Baseline	After 3 months	*P*
Serum cystatin C (mg/L)	2.00 (1.35–3.82)	1.84 (1.28–3.63)	0.030
eGFRcys (mL/min/1.73 m^2)	29.0 ± 10.7	31.2 ± 11.8	0.049

Table 6. Effects of dotinurad on cystatin C. eGFRcys, cystatin C-based estimated glomerular filtration rate.

Based on the finding that hyperuricemia is a modifiable risk factor for the development and progression of CKD, UA-lowering drugs are expected to mitigate CKD progression[32]. Several observational studies and randomized controlled trials have reported that UA-lowering drugs are beneficial for preventing CKD progression[19–23,33,34], whereas others have found no significant effect[24–26]. Notably, these studies included XOIs, thus highlighting the need for research of other types of drugs such as URAT1 inhibitors. Verinurad, a selective URAT1 inhibitor, in combination with febuxostat lowered serum UA and reduced albuminuria in patients with type 2 diabetes[35]. However, when combined with allopurinol for patients with CKD and gout, verinurad did not reduce albuminuria or slow the decline of the eGFR[36]. Observational studies that included dotinurad and combination therapy with XOIs reported effective reductions in UA; however, renal function changes

Variables	r	*P*
Age (years)	− 0.051	0.79
Body mass index (kg/m^2)	0.340	0.077
eGFR at Baseline (mL/min/1.73m2)	− 0.165	0.39
Uric acid at baseline (mg/dL)	0.362	0.054
Uric acid at 3 months (mg/dL)	− 0.118	0.54
UUCR at baseline (g/gCr)	− 0.021	0.92
UUCR at 3 months (g/gCr)	− 0.062	0.77
Decrease in uric acid (mg/dL)	0.398	0.032

Table 7. Univariate correlations with eGFR improvement. eGFR, estimated glomerular filtration rate; UUCR, urinary uric acid-to-creatinine ratio.

Variable	Standardized β coefficient	P
Decrease in UA (mg/dL)	0.381	0.037
Body mass index (kg/m^2)	0.339	0.065
eGFR at baseline (mL/min/1.73 m^2)	− 0.298	0.099

Table 8. Multivariate analysis of renal function improvement. eGFR, estimated glomerular filtration rate; UA, uric acid.

were variable[29–31]. Only one study reported that dotinurad monotherapy effectively decreased serum UA and improved the eGFR decline in patients with CKD[37]. By comparing the efficacy of both dotinurad and febuxostat during this study, we found that dotinurad had a greater impact on renal function improvement. Because of the progressive nature of renal injury in our cohort, the absence of improvement in the eGFR after febuxostat may indicate that febuxostat prevented CKD progression. In contrast, patients treated with dotinurad exhibited eGFR improvement. These findings suggest that dotinurad may provide additional benefits when used to manage hyperuricemia in patients with CKD. The relatively short duration of the three-months follow-up may limit our conclusions. However, a longer-term investigation of 12 months with dotinurad reported an improvement in the eGFR slope[30]. Although further studies are necessary to confirm that dotinurad has renoprotective effects, these findings are consistent with our results.

Because the kidney is the main regulator of UA through urinary excretion, renal underexcretion-type hyperuricemia is common in patients with CKD[9,17]. Two mechanisms that could be involved in renal underexcretion-type hyperuricemia are reduced glomerular filtration and accelerated tubular reabsorption. During this study, both the eGFR and FEUA were strongly associated with the UUCR, suggesting that accelerated tubular reabsorption may also contribute to renal underexcretion. Another cohort study also reported accelerated tubular reabsorption in patients with CKD[16], in line with the fact that benzbromarone, a uricosuric drug, effectively reduced UA levels in patients with CKD[38]. Significant increases in the UUCR and FEUA followed by a significant decrease in UA were observed with dotinurad treatment during this study. In contrast, the UUCR and FEUA decreased after febuxostat treatment, thus indicating accelerated tubular reabsorption of UA. Diminished tubular reabsorption was associated with favorable renal outcomes[16]. The dissociation of tubular reabsorption after dotinurad and febuxostat treatments may partly explain why renal function improvement could be observed only with dotinurad. The pathophysiology of renal injury associated with hyperuricemia includes monosodium urate monohydrate deposition in the interstitium[39,40]. Accelerated urinary UA excretion by dotinurad may prevent toxic deposition of monosodium urate monohydrate in the kidneys. Although pathological confirmation by renal biopsy is needed to conclude, our study highlighted the importance of further research on the association between reabsorbed UA and renal injury. It should be noted that accelerated urinary uric acid excretion potentially increase the risk of urinary stone formation. Among the various risk factors for the urolithiasis such as dehydration, dietary habits, body, shape, urinary glycoprotein, or advanced glycation end products, urinary pH needs to be monitored and corrected in patients predisposed to kidney stone[41–47]. Although urinary pH in the dotinurad group did not change, and no patient developed nephrolithiasis during the treatment, alkali supplementation was prescribed for some patients due to the acidified urine at baseline. Ensuring adequate water intake and considering urinary alkalization are important in preventing kidney stones in susceptible individuals. Metabolic effect may be the other explanation of the improvement in renal function after dotinurad. URAT1 is expressed in various organs other than the kidney including heart and hepatocyte. URAT1 inhibition improved insulin resistance in murine model[48]. Although no significant changes could be observed in metabolic parameters, we do not exclude the possibilities of metabolic effects of dotinurad on renal function. Further study is needed to elucidate the association between metabolic abnormalities and URAT1 inhibition.

This study had several limitations. First, the increase in the eGFR may have reflected glomerular hyperfiltration. Although we did not observe an increase in urinary protein excretion, whether favorable changes are sustained with long-term dotinurad treatment should be confirmed. Concomitant use of the other medications may have affected our results. RAS-i and SGLT2-i prevent CKD progression by correcting glomerular hyperfiltration. In addition, several medications such as SGLT2-i, losartan, and atorvastatin have uricosuric effect. Therefore, it is necessary to consider these medications to interpret our results. Although the difference was not significant, the higher baseline proteinuria in the febuxostat group compared with the dotinurad group might contribute to the more rapid deterioration of eGFR. Second, urinary creatinine excretion may change after dotinurad treatment, thus affecting the eGFR. However, we confirmed renal function improvement using the cystatin C-based eGFR. Third, because of the relatively small sample size and retrospective single-center design of this study, we could not eliminate the selection bias in the determination of treatment drugs. Prospective studies with larger populations are necessary to confirm our findings that dotinurad exerted renoprotective effect beyond the reduction of serum UA. In this study, multiple comparisons between groups have been performed. The analysis of multiple variables increases the risk of type I error. Therefore, a multiple testing correction in larger populations would reinforce the favorable effect of dotinurad in renal function.

In conclusion, this study revealed the efficacy of dotinurad for the management of hyperuricemia in patients with CKD. Renal function improvement observed during this study indicates that selective urate reabsorption inhibitors could be therapeutic options for the prevention of renal function decline in patients with CKD and hyperuricemia.

Materials and methods

Study population

This study included patients with CKD who newly initiated UA-lowering drug treatment for hyperuricemia at Tottori University Hospital between January 2023 and August 2024. Patients who switched from other UA-lowering drugs, underwent dialysis, underwent renal transplantation, or experienced acute kidney injury during follow-up were excluded from the study. CKD was defined as an eGFR < 60 mL/min/1.73 m^2[49] or UPCR > 0.15 g/gCr. UA-lowering agents were prescribed by the responsible physician according to the guidelines for the management of hyperuricemia[50]. Hyperuricemia was defined as a UA level ≥ 7.0 mg/dL or any prescription of UA-lowering drugs. Characteristics of the patients, including age, sex, height, body weight, body mass index, systolic blood pressure, diastolic blood pressure, and history of gout, were obtained from the medical records. Informed consent was obtained from all patients. We determined that a total number of 46 participants would provide the study with 95% power ($P = 0.05$; effect size: 0.80). The target number of participants was calculated as previously reported using G*Power software (version 3.1.9.6; Germany)[51,52].

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tottori University Hospital (approval number: 23A079).

Laboratory data

Data regarding serum UA, creatinine, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, HbA1c, urinary pH, urinary creatinine, urinary protein, urinary *N*-acetyl-β-D-glucosaminidase, urinary UA at treatment initiation (baseline), and urinary UA at 3 months after the initiation of UA-lowering drugs were collected. Additionally, data regarding the eGFR 3 months before treatment were collected. The observation period consists of three distinct phases: the pre-treatment phase (3 months before drug initiation), the baseline (at the point of drug initiation), and the post-treatment phase (3 months after drug initiation). Serum cystatin C levels were measured using a human cystatin C enzyme-linked immunosorbent assay kit (BioVender, Brno, Czech Republic). Urinary UA excretion was assessed based on the UUCR and FEUA.

Statistical analysis

Continuous variables were reported as the mean ± standard deviation or median (range). The Kolmogorov–Smirnov test was used to assess the normality of data distribution. Differences between two groups were analyzed using Student's t-test or the paired t-test for normally distributed variables and the Mann–Whitney test or Wilcoxon test for non-normally distributed variables. Changes in the eGFR were analyzed using a two-way analysis of variance with a post hoc Tukey test. Correlations between parameters were analyzed using Pearson's correlation coefficient. A multiple linear regression analysis in which baseline eGFR and metabolic parameters were selected using the stepwise forward selection method was performed to investigate factors that influence renal function improvement. A two-tailed $P < 0.05$ was considered statistically significant. All analyses were performed using StatFlex (version 7.0 for Windows; Artec, Osaka, Japan).

Data availability

The datasets of this study are available from the corresponding author on reasonable request.

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Author contributions

TT and TS conceptualized the study. TT and YM analyzed and interpreted the data. TT, ST, YM, KK, YF, TI, and KH acquired the data. TT drafted the manuscript. HI supervised the study. All authors read and approved the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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