—Original—

Effects of Renal Function on Urinary Excretion and Serum Concentration of Uric Acid in Patients Treated with Febuxostat for Chronic Kidney Disease

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Background: Febuxostat is recommended for lowering serum uric acid (sUA) concentration in chronic kidney disease (CKD) patients with hyperuricemia. However, it remains uncertain how febuxostat affects associations between several laboratory variables related to glomerular filtration and renal tubular reabsorption of uric acid.

Methods: We retrospectively analyzed the records of 148 patients with CKD and hyperuricemia: 122 were treated with febuxostat, and 26 were not. Clinical and laboratory variables were used to calculate estimated glomerular filtration rate (eGFR), fractional excretion of uric acid (FEUA), and estimated 24-h urinary excretion of uric acid (eEUA). We examined correlations of those variables and compared patients who did and did not receive febuxostat.

Results: eGFR and FEUA were significantly inversely regardless of febuxostat-treatment status. eGFR was significantly inversely correlated with sUA in patients who received febuxostat, but not in those who did not. Similarly, there was a significant positive correlation between FEUA and eEUA only in patients treated with febuxostat.

Conclusions: FEUA increased as eGFR decreased in our patients. Febuxostat changed correlation patterns for clinical and laboratory variables. Additional administration of uricosuric agents might help further lower sUA by increasing FEUA and eEUA in patients treated with febuxostat.

(J Nippon Med Sch 2022; 89: 360–367)

Key words: hyperuricemia, chronic kidney disease, febuxostat

Introduction

Uricosuric agents and urate synthesis inhibitors are classes of hyperuricemia drugs. In patients with normal renal function, 90% of uric acid is reabsorbed through proximal renal tubules and returns to renal blood flow[1,2]. Uricosuric agents inhibit uric acid reabsorption through proximal renal tubules, which results in elevated urinary excretion of uric acid and a decrease in serum uric acid (sUA) concentration. Conversely, xanthine oxidase inhibitors, which attenuate production of uric acid, have been widely prescribed to patients with hyperuricemia as urate synthesis inhibitors. Of these two drug types, urate synthesis inhibitors are recommended for chronic kidney disease (CKD) patients with hyperuricemia[3].

The urate synthesis inhibitor, febuxostat is a xanthine oxidase inhibitor, that is recommended for treatment[3]. However, it remains to be determined how glomerular and renal tubular dysfunction affects uric acid filtration by glomeruli, reabsorption through proximal renal tubules, and sUA concentration in patients with CKD treated with febuxostat. Moreover, data are limited on whether additional administration of uricosuric agents is effective in patients treated with febuxostat.

Here, we investigated the effects of renal glomerular and tubular function on laboratory variables related to urinary excretion of uric acid and sUA concentration in patients with CKD treated with febuxostat. Moreover, we estimated the additional effect of uricosuric agents on

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https://doi.org/10.1272/jnms.JNMS.2022_89-401
Journal Website (https://www.nms.ac.jp/sh/jnms/)

sUA concentration in such patients.

Materials and Methods

Study Design

We retrospectively examined correlations among clinical and laboratory variables related to urinary excretion of uric acid, and reabsorption of uric acid through proximal renal tubules, as described below. Next, we compared these correlation patterns between patients who were and were not treated with febuxostat.

Definitions

Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2.

Hyperuricemia was defined as an sUA concentration greater than 7.0 mg/dL.

Patients

We analyzed data from 148 outpatients with CKD and hyperuricemia who were treated in our hospital during the period from January 2020 through December 2020. Of them, 122 patients were treated with febuxostat 10 mg daily, and 26 patients were not treated with a urate-lowering drug. Clinical data, including age, sex, and underlying diseases, and laboratory data were collected to calculate eGFR, fractional excretion of uric acid (FEUA), fractional excretion of sodium (FENa), urinary excretion of β2-microglobulin (β2MG), estimated 24-h urinary excretion of creatinine (eECr), and estimated 24-h urinary excretion of uric acid (eEUA) from electronic medical records in our hospital. Patients regularly receiving losartan and diuretics were excluded.

Ethical Approval

All procedures involving human participants were done in accordance with the ethical standards of the Nippon Medical School Chiba Hokusoh Hospital (IRB approval number 824) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all included participants.

Variables

eGFR was calculated using the equation of the Japanese Society of Nephrology[4], namely.

$$eGFR\ (mL/min/1.73\ m^2) = 194 \times [Cr\ (mg/dL)]^{-1.094} \times [Age\ (years)]^{-0.287}\ (\times 0.739, \text{for women})$$

FEUA was calculated by using the following equation.

$$FEUA = (U_{UA}/S_{UA}) / (U_{Cr}/S_{Cr}) \times 100\ (\%)$$

U_{UA}: urinary concentration of uric acid (mg/dL)

S_{UA}: serum concentration of uric acid (mg/dL)

U_{Cr}: urinary concentration of creatinine (mg/dL)

S_{Cr}: serum concentration of creatinine (mg/dL)

FENa was calculated by using the following equation.

$$FENa = (U_{Na}/S_{Na}) / (U_{Cr}/S_{Cr}) \times 100\ (\%)$$

U_{Na}: urinary concentration of sodium (mEq/L)

S_{Na}: serum concentration of sodium (mEq/L)

Urinary excretion of β2-microglobulin (β2MG) per gram creatinine was calculated by using the following equation.

Urinary excretion of β2MG (μg/gCr) = [Urinary concentration of β2MG (μg/L) / urinary concentration of creatinine (mg/dL)] × 100

Estimated creatinine excretion in 24-h urine (eECr) was calculated by using the equation of the Japanese Society of Hypertension[5], namely.

eECr (mg/day) = [Body weight (kg) × 14.89] + [Height (cm) × 16.14] − [Age (years) × 2.043]−2,244.45

Estimated uric acid excretion in 24-h urine (eEUA) was calculated by using the following equation.

$$eEUA\ (mg/day) = [eECr\ (mg/day)] / U_{Cr}(mg/dL)] \times U_{UA}\ (mg/dL)$$

U_{UA}: urinary concentration of uric acid (mg/dL)

U_{Cr}: urinary concentration of creatinine (mg/dL)

eECr: estimated creatinine excretion in 24-h urine (mg/day)

Analysis of Laboratory Variables

We analyzed the correlations between eGFR and FEUA, between FEUA and urinary excretion of β2MG, between FEUA and FENa, and between FEUA and the product of eGFR multiplied by sUA. Next, we analyzed correlations between eEUA and eGFR, and between eEUA and FEUA. Similarly, we analyzed correlation between sUA and eGFR. Finally, we compared these correlation patterns in patients who were and were not treated with febuxostat.

Statistical Analysis

All analyses were conducted using R version 4.0.0 (R Core Team, 2020) and IBM SPSS Statistics version 28. Data were tested for normality with the Kolmogorov-Smirnov test. For analysis of correlations among eGFR, FEUA, FENa, urinary excretion of β2MG, and the product of eGFR multiplied by sUA, Spearman's rank correlation test was used when the data distribution was skewed. The Mann-Whitney *U*-test was used for comparing the skewed continuous variables into two groups. We considered a *P*-values of less than 0.05 as statistically significant.

Table 1 Summarized clinical characteristics of the enrolled patients. There was no significant difference in the clinical background of patients treated with and without (control) febuxostat

Treatment of hyperuricemia		Febuxostat	Control	*P* value
Total, *n*		122	26	
Age (years)		63.7 ± 14.3	68.9 ± 13.6	0.099
Gender, *n* (%)	male	72 (59.0)	16 (61.5)	0.831
	female	50 (41.0)	10 (38.5)	
Hypertension, *n* (%)		74 (60.7)	21 (80.8)	0.071
Diabetes mellitus, *n* (%)		39 (32.0)	10 (38.5)	0.647
Dislypidemia, *n* (%)		41 (33.6)	12 (46.2)	0.263
eGFR (mL/min/1.73 m^2)		30.4 ± 13.4	30.4 ± 14.1	0.964

Table 2 Summarized clinical characteristics of the enrolled patients. Serum uric acid concentration (sUA) and estimated urinary excretion of uric acid (eEUA) were lower in patients with a 10 mg daily dose of febuxostat than those without it (control). The ratio of the patients whose U_{UA}/U_{Cr} was greater than 0.5 was significantly higher in those without febuxostat than those treated with it

Treatment of hyperuricemia	Febuxostat	Control	*P* value
sUA (mg/dL)	5.8 ± 1.1	8.1 ± 1.0	**P*<0.001
U_{UA}/U_{Cr}	0.22 ± 0.10	0.39 ± 0.11	**P*<0.001
>0.5, *n* (%)	3 (2.5)	4 (15.4)	**P*=0.018
≤0.5, *n* (%)	119 (97.5)	22 (84.6)	
eEUA (mg/day)	260.7 ± 130.7	438.3 ± 158.8	**P*<0.001

Results

Clinical Characteristics of Patients

The characteristics of the 148 patients are summarized in **Table 1, 2**. There was no significant difference in age between patients who were and were not treated with febuxostat or in the sex distribution or prevalences of hypertension, diabetes mellitus, or dyslipidemia (**Table 1**). sUA and eEUA were lower in patients treated with febuxostat, and the proportion of patients with U_{UA}/U_{Cr} greater than 0.5 was significantly higher in those not receiving febuxostat (**Table 2**).

Correlation Analysis

In both treatment subgroups, eGFR was significantly inversely correlated with FEUA (**Fig. 1a, b**). FEUA was significantly positively correlated with urinary excretion of β2MG (**Fig. 2a, b**). FENa was significantly positively correlated with FEUA (**Fig. 3a, b**). FEUA was significantly inversely correlated with the product of eGFR and sUA (**Fig. 4a, b**), and eGFR was significantly positively correlated with eEUA (**Fig. 5a, b**). In contrast, FEUA was significantly positively correlated with eEUA, and eGFR was significantly inversely correlated with sUA, only in patients treated with febuxostat (**Fig. 5c, d**, **Fig. 6a, b**).

Discussion

The present results show a significant inverse correlation between eGFR and FEUA in patients who did and did not receive febuxostat, and a significant positive correlation between FEUA and urinary excretion of β2MG, as well as FENa, in both groups. Urinary excretion of β2MG is an index of proximal tubular reabsorption ability[6]. Furthermore, elevated urinary excretion of β2MG is related to renal tubular dysfunction[7]. Therefore, our findings suggest that renal tubular dysfunction progresses as eGFR decreases and that FEUA might be used as an index of renal tubular dysfunction. In patients with CKD, decrease in eGFR induces a reduction in glomerular filtration of uric acid. Simultaneously, elevated FEUA promotes urinary excretion of uric acid. Thus, a reduction in glomerular filtration of uric acid is offset by the increase in uric acid excretion rate through proximal tubules.

To clarify the effects of eGFR and FEUA on glomerular filtration and tubular reabsorption of uric acid, we examined correlations among eGFR, FEUA, sUA concentration, and eEUA in patients who did and did not receive febuxostat.

We noted a significant inverse correlation between

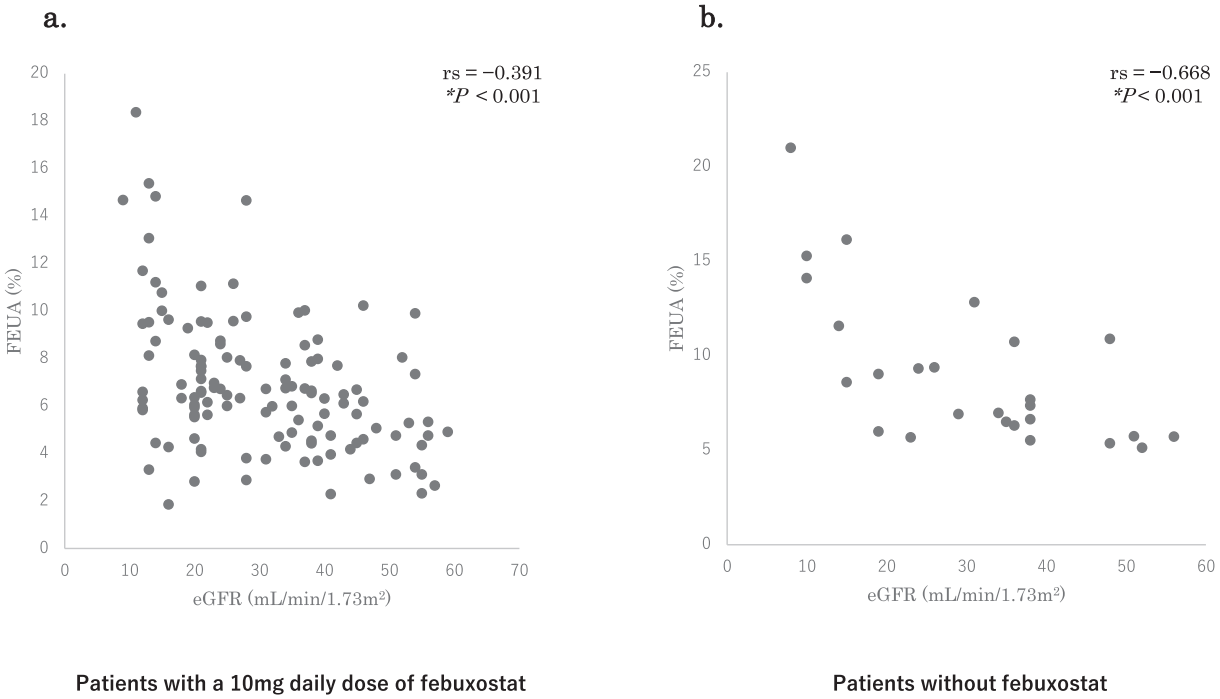

Fig. 1 Correlation between eGFR and FEUA. **a**: A significant inverse correlation was demonstrated between eGFR and FEUA in patients receiving febuxostat 10 mg daily (Spearman rank correlation coefficient: rs = –0.391, **P*<0.001). **b**: A significant inverse correlation was demonstrated between eGFR and FEUA in patients not treated with febuxostat (Spearman rank correlation coefficient: rs = –0.668, **P*<0.001).

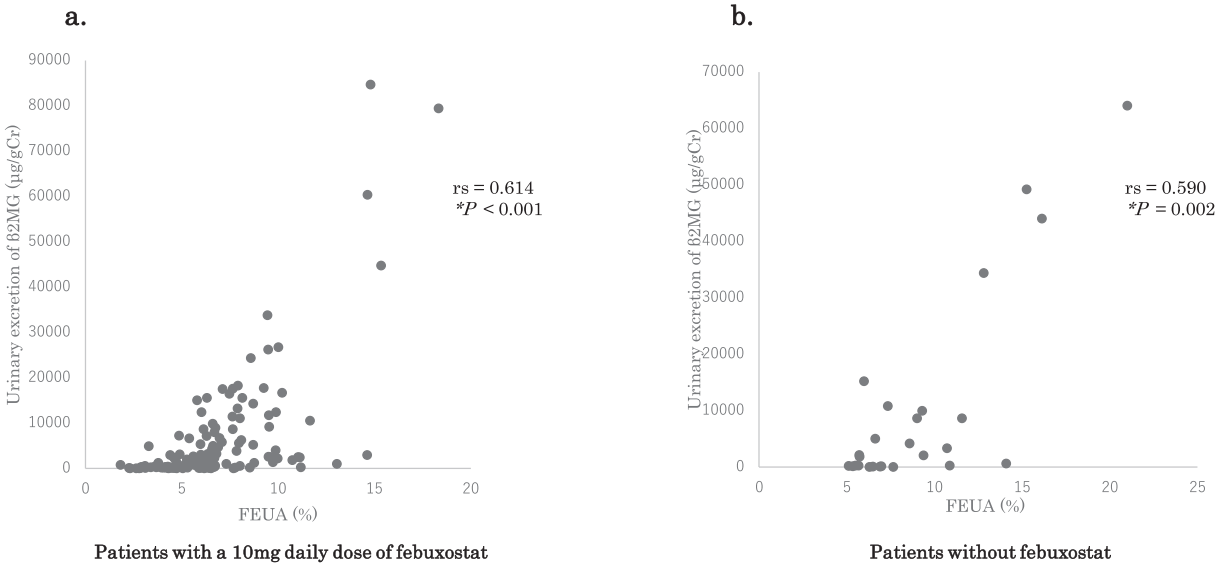

Fig. 2 Correlation between FEUA and urinary excretion of β2MG. **a**: A significant positive correlation was demonstrated between FEUA and urinary excretion of β2MG in patients receiving febuxostat 10 mg daily (Spearman rank correlation coefficient: rs = 0.614, **P*<0.001). **b**: A significant positive correlation was demonstrated between FEUA and urinary excretion of β2MG in patients not treated with febuxostat (Spearman rank correlation coefficient: rs = 0.590, **P* = 0.002).

FEUA and the product of eGFR and sUA (**Fig. 4a, b**), and a significant positive correlation between eGFR and eEUA (**Fig. 5a, b**) in both groups, and a significant positive correlation between FEUA and eEUA, and a significant inverse correlation between eGFR and sUA only in patients treated with febuxostat (**Fig. 5c, d**, **Fig. 6a, b**). To explain these phenomena, we postulate the mechanisms described below.

Figure 7 illustrates the correlations between hyperuricemia variables in patients not receiving febuxostat.

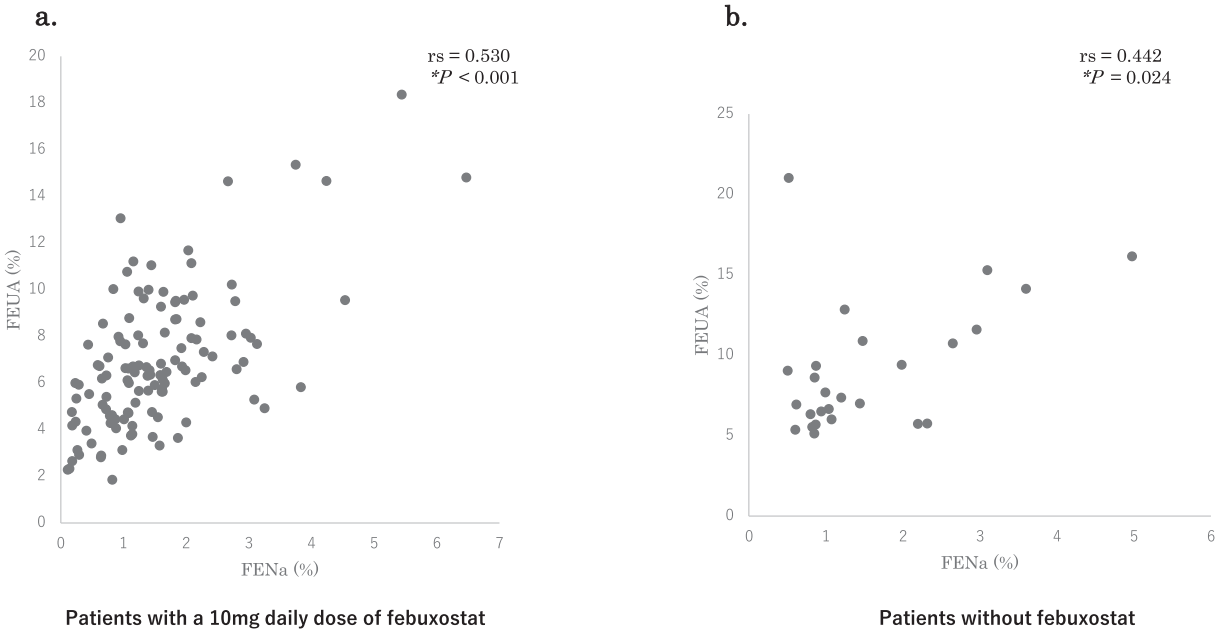

Fig. 3 Correlation between FENa and FEUA. **a**: A significant positive correlation was demonstrated between FENa and FEUA in patients receiving febuxostat 10 mg daily (Spearman rank correlation coefficient: rs = 0.530, **P*<0.001). **b**: A significant positive correlation was demonstrated between FENa and FEUA in patients not treated with febuxostat (Spearman rank correlation coefficient: rs = 0.442, **P* = 0.024).

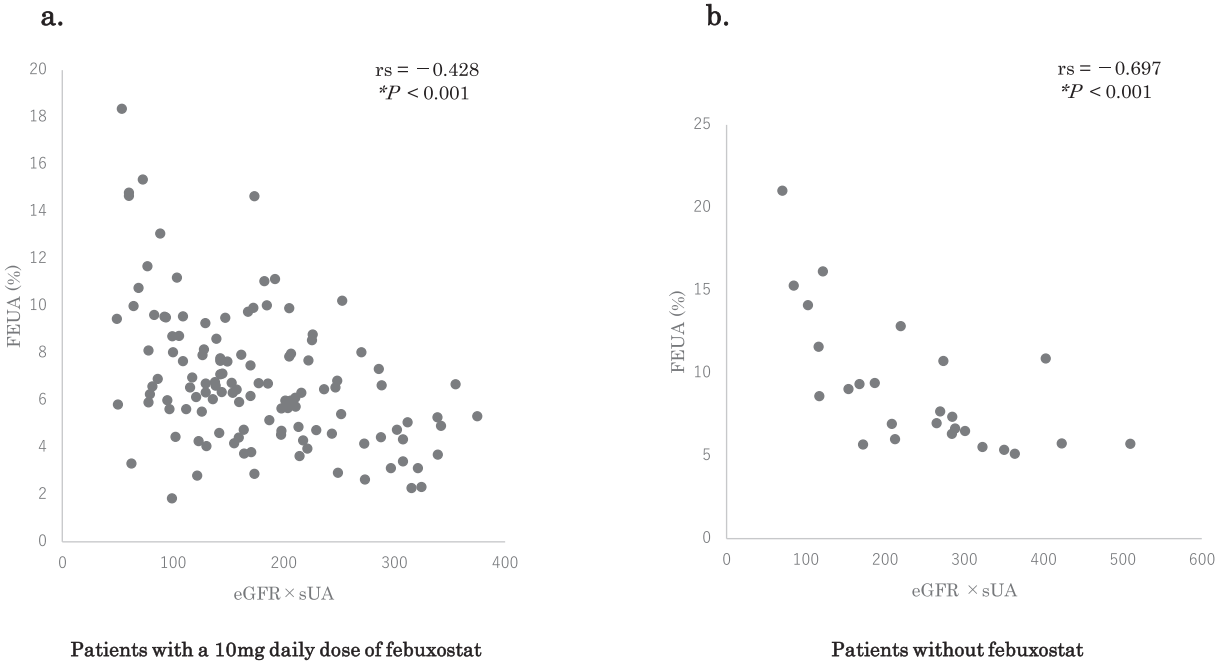

Fig. 4 Correlation between FEUA and the product of eGFR and sUA. **a**: A significant inverse correlation was demonstrated between eGFR × sUA and FEUA in patients receiving febuxostat 10 mg daily (Spearman rank correlation coefficient: rs =–0.428, **P*<0.001). **b**: A significant inverse correlation was demonstrated between eGFR × sUA and FEUA in patients not treated with febuxostat (Spearman rank correlation coefficient: rs = –0.697, **P*<0.001).

Theoretically, eEUA is proportional to the products of sUA, eGFR, and FEUA. As shown in **Figure 4b**, the product of eGFR and sUA decreased with elevation of FEUA in patients not receiving febuxostat. This offset effect led to maintenance of eEUA, regardless of FEUA (**Fig. 5d**).

Figure 8 illustrates the effect of febuxostat on the correlation between FEUA and eEUA. sUA decreased in patients receiving febuxostat 10 mg daily, leading to de-

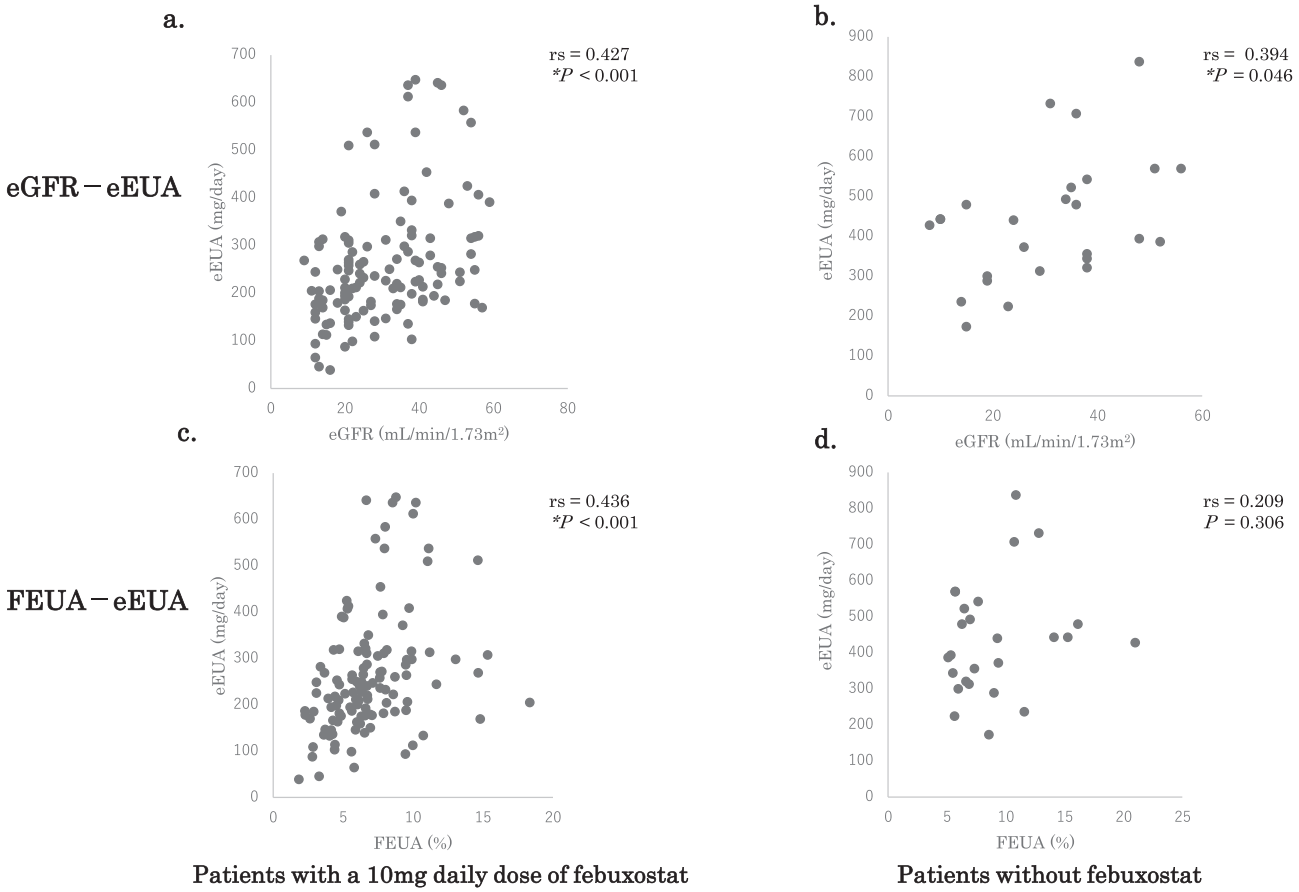

Fig. 5 Correlation between eGFR and eEUA, and FEUA and eEUA. **a**: A significant positive correlation was demonstrated between eGFR and eEUA in patients receiving febuxostat 10 mg daily (Spearman rank correlation coefficient: rs = 0.427, *P<0.001). **b**: A significant positive correlation was demonstrated between eGFR and eEUA in patients not treated with febuxostat (Spearman rank correlation coefficient: rs = 0.394, *P = 0.046). **c**: A significant positive correlation was demonstrated between FEUA and eEUA in patients receiving febuxostat 10 mg daily (Spearman rank correlation coefficient: rs = 0.436, *P<0.001). **d**: No significant correlation was demonstrated between FEUA and eEUA in patients not treated with febuxostat (Spearman rank correlation coefficient: rs = 0.209, P = 0.306).

crease in eEUA. This decrease was attenuated by elevation of FEUA, and this attenuation was responsible for the positive correlation between FEUA and eEUA in patients treated with febuxostat.

The significant positive correlation between eGFR and eEUA and the significant inverse correlation between eGFR and sUA (**Fig. 5a**, **Fig. 6a**) indicate that sUA concentration decreased as eEUA increased in patients treated with febuxostat. Therefore, the significant positive correlation between FEUA and eEUA (**Fig. 5c**, **Fig. 8**) indicates that additional administration of uricosuric agents might help lower sUA by increasing FEUA, followed by eEUA elevation in patients treated with febuxostat.

Conversely, because no significant correlation was noted between FEUA and eEUA in those not receiving febuxostat, single administration of a uricosuric agent would likely have a limited effect on eEUA (**Fig. 5d**). Despite the significant positive correlation between eGFR and eEUA (**Fig. 5b**), eGFR was not significantly correlated with sUA in those not receiving febuxostat (**Fig. 6b**). It may be that, in patients not receiving febuxostat, sUA concentration was too high to achieve a significant inverse correlation solely by glomerular filtration of uric acid.

Our findings suggest that the combination of a uricosuric agent and urate synthesis inhibitor is useful for treating hyperuricemia associated with CKD, whereas urate synthesis inhibitors, including febuxostat, are only indicated for patients with CKD[3].

This study has some limitations. First, the assessment of uric acid excretion into urine utilized spot urine instead of a 24-hour urine specimen. Clinical guidelines[3] recommended collection of a 24-hour urine sample for urinary uric acid when assessing urinary uric acid excretion; we calculated eEUA by using eECr, U_{Cr}, and U_{UA}. Urinary creatinine concentration (U_{Cr}) can be affected by

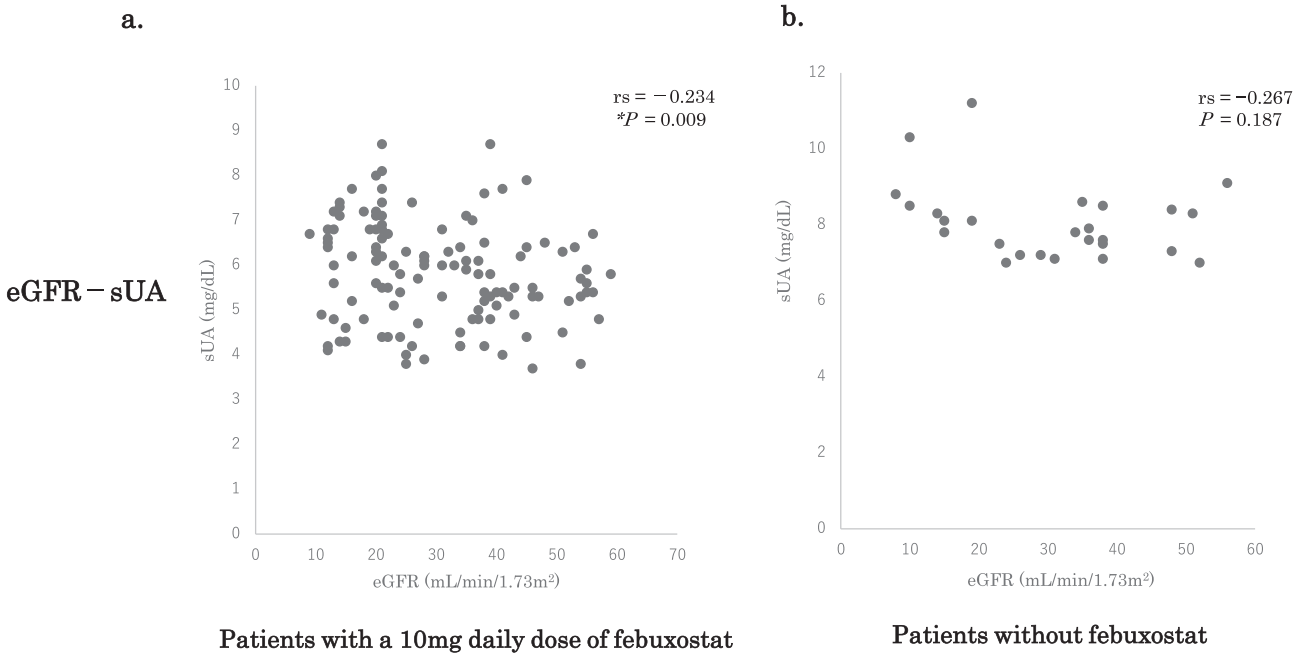

Fig. 6 Correlation between eGFR and sUA. **a**: A significant inverse correlation was demonstrated between eGFR and sUA in patients receiving febuxostat 10 mg daily (Spearman rank correlation coefficient: rs = –0.234, *P = 0.009). **b**: No significant correlation was demonstrated between eGFR and sUA in patients not treated with febuxostat (Spearman rank correlation coefficient: rs = –0.267, P = 0.187).

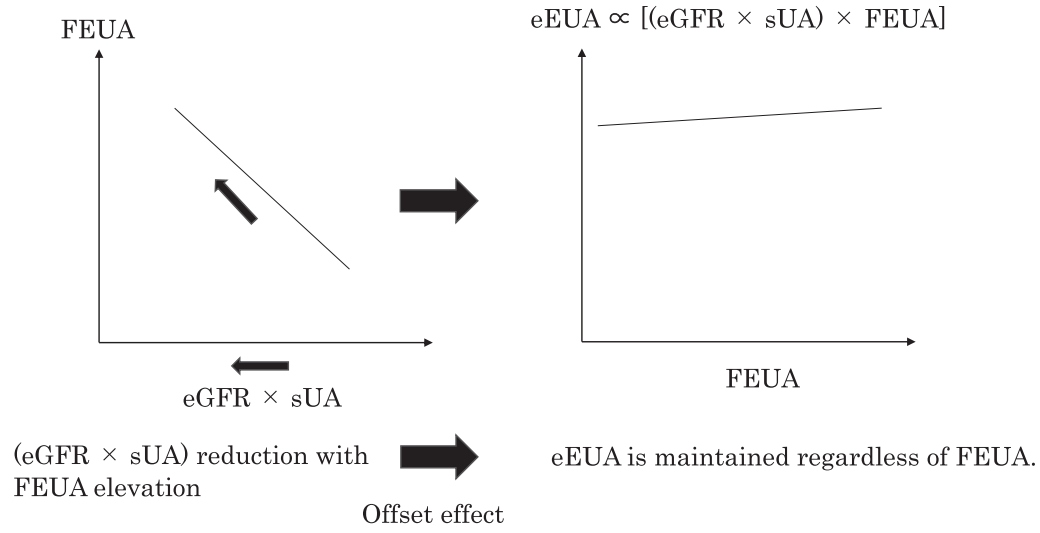

Fig. 7 Illustration of correlations among hyperuricemia variables in patients not treated with febuxostat
Theoretically, eEUA is proportional to the products of sUA, eGFR, and FEUA. As shown in Figure 4, the product of eGFR and sUA decreases as FEUA increases in patients not treated with febuxostat. This offset effect leads to maintenance of eEUA regardless of FEUA.

muscle mass. Therefore, eEUA might have been affected by muscle mass, whereas eECr was adjusted by height and body weight, as described in the Methods section. A second limitation is that uric acid excretion into stool was not assessed. Miyata et al. reported that febuxostat is a potential inhibitor of ATP-binding cassette transporter G2 (ABCG2), which is expressed in the small intestine[8]. ABCG2 promotes uric acid excretion into stool[8]. **Figure 6 a** shows the significant inverse correlation between sUA and eGFR in patients treated with febuxostat. sUA might have been susceptible to eGFR because of the attenuated uric acid excretion into stool attributable to ABCG2 inhibition in patients treated with febuxostat. Further research will be needed, as we did not evaluate ABCG2 ac-

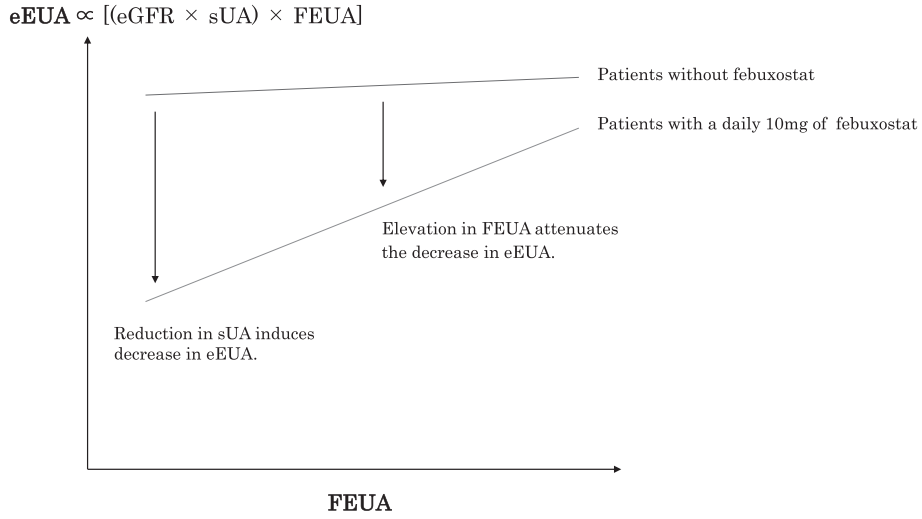

Fig. 8 Illustration of the effect of febuxostat on the correlation between FEUA and eEUA
Febuxostat caused a reduction in sUA, leading to a decrease in eEUA. This decrease is attenuated by an increase in FEUA. This attenuation explains the positive correlation between FEUA and eEUA in patients receiving febuxostat. The blue line represents patients not treated with febuxostat, and the red line represents patients treated with febuxostat 10 mg daily.

tivity in this study.

In conclusion, the significant positive correlation between FEUA and eEUA induced by febuxostat indicates that additional administration of uricosuric agents might further lower sUA by increasing FEUA and eEUA. Combined administration of urate synthesis inhibitors and uricosuric agents might be necessary to control sUA in patients with CKD and hyperuricemia. However, additional studies are necessary to confirm this hypothesis.

Acknowledgements: This study received no specific external funding.

Conflict of Interest: None declared.

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(Received, September 21, 2021)
(Accepted, October 27, 2021)
(J-STAGE Advance Publication, November 26, 2021)