Effects of renal function on the urinary excretion and serum concentration of uric acid in patients with chronic kidney disease treated with febuxostat

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Abstract

Background: Febuxostat is recommended for patients with chronic kidney disease (CKD) associated with hyperuricemia to lower the serum uric acid (sUA) concentration. However, it remains uncertain how this drug affects correlations between several laboratory parameters regarding glomerular filtration and renal tubular reabsorption of uric acid.

Methods: We enrolled 148 patients with CKD with hyperuricemia. Of them, 122 were treated with febuxostat, and 26 were treated without it. Clinical and laboratory parameters were recorded to calculate the estimated glomerular filtration rate (eGFR), fractional excretion of uric acid (FEUA), and the estimated 24-h urinary excretion of uric acid (eEUA). We retrospectively examined the correlations between those parameters to compare the patients treated with febuxostat to those without it.

Results: A significant inverse correlation between eGFR and FEUA was demonstrated in both patients treated with febuxostat and those without it. In patients treated with febuxostat, a significant inverse correlation was demonstrated between eGFR and sUA, whereas no significant correlation was demonstrated in those without it. There was a significant positive correlation between FEUA and eEUA in patients treated with febuxostat, whereas no significant correlation was revealed in those without it.
**Conclusions:** FEUA increased as eGFR declined in our study population. Febuxostat changed the correlation patterns between the clinical laboratory parameters. An additional administration of uricosuric agents would be helpful for further sUA lowering by increasing both FEUA and eEUA in patients treated with febuxostat.

**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 the proximal renal tubules and returns to the renal blood flow. Uricosuric agents inhibit uric acid reabsorption through proximal renal tubules, which results in elevated urinary excretion of uric acid and a decrease in the serum uric acid (sUA) concentration. Conversely, xanthine oxidase inhibitors, which attenuate the 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 to be prescribed to patients with chronic kidney disease (CKD) associated with hyperuricemia.

Among urate synthesis inhibitors, febuxostat, one of the xanthine oxidase inhibitors, is recommended to be prescribed. However, it remains uncertain how glomerular and renal tubular dysfunction affects uric acid filtration by the glomeruli, reabsorption through the proximal renal tubules, and sUA concentration in patients with CKD treated with febuxostat. Moreover, it remains unclear whether an additional administration of uricosuric agents is effective in those treated with febuxostat.

Here, we investigated the effects of renal glomerular and tubular function on laboratory parameters regarding the urinary excretion of uric acid and sUA
concentration in patients with CKD treated with febuxostat. Moreover, we tried to predict the additional effect of uricosuric agents on sUA concentration in those treated with febuxostat.
Materials and methods

Study design: We retrospectively examined the correlations between clinical laboratory parameters regarding the urinary excretion of uric acid, and the reabsorption of uric acid through the proximal renal tubules as described below. Next, we compared the patients treated with febuxostat to those without it in terms of these correlation patterns.

Definition:

Chronic kidney disease (CKD): CKD was defined as an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m².

Hyperuricemia: sUA concentration greater than 7.0 mg/dL was diagnosed as hyperuricemia.

Patients: We enrolled 148 outpatients with CKD with hyperuricemia in our hospital from January 2020 to December 2020. Of them, 122 patients were treated with a 10 mg daily dose of febuxostat, and 26 patients were not treated with any urate-lowering drug. Clinical information, including age, gender, 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), the estimated 24-h urinary excretion of creatinine (eECr), and the estimated 24-h urinary excretion of uric acid (eEUA) from the electronic medical records in our hospital. Patients who were
taking losartan and diuretics regularly were excluded.

**Ethical approval**: All procedures performed in this study involving human participants were in accordance with the ethical standards of the Nippon Medical School Chiba Hokusho Hospital (IRB approval number 824) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent**: Written informed consent was obtained from all the participants included in this study.

**eGFR**

eGFR was calculated using the equation advocated below by the Japanese Society of Nephrology⁴.

\[
eGFR \text{ (mL/min/1.73 m²)} = 194 \times [\text{Cr (mg/dL)}]^{-1.094} \times [\text{Age (years)}]^{-0.287} \times 0.739, \text{ (for women)}
\]

**FEUA**

FEUA was calculated using the equation below.

\[
\text{FEUA} = \left( \frac{U_{UA}}{S_{UA}} \right) / \left( \frac{U_{Cr}}{S_{Cr}} \right) \times 100 \%
\]

\(U_{UA}\): 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**

FENa was calculated using the equation below.

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

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

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

**Urinary excretion of β2-microglobulin (β2MG)**

The urinary excretion of β2MG per gram creatinine was calculated using the equation below.

$$
\text{Urinary excretion of β2MG (μg/gCr)} = \left[\frac{\text{Urinary concentration of β2MG (μg/L)}}{\text{Urinary concentration of creatinine (mg/dL)}}\right] \times 100
$$

**Estimated creatinine excretion in 24-h urine (eECr)**

The eECr was calculated using the equation advocated below by the Japanese Society of Hypertension$^5$.

$$
eECr \, (mg/day) = [\text{Body weight (kg) } \times 14.89] + [\text{Height (cm) } \times 16.14] - [\text{Age (years)} \times 2.043] - 2244.45
$$

**Estimated uric acid excretion in 24-h urine (eEUA)**

The eEUA was calculated using the equation below.
\[ e\text{EUA} \text{ (mg/day)} = \frac{[e\text{ECr} \text{ (mg/day)}]}{U_Cr \text{ (mg/dL)}} \times U_{UA} \text{ (mg/dL)} \]

- \( U_{UA} \): urinary concentration of uric acid (mg/dL)
- \( U_Cr \): urinary concentration of creatinine (mg/dL)
- \( e\text{ECr} \): estimated creatinine excretion in 24-h urine (mg/day)

**Analysis of laboratory parameters**

We analyzed the correlations between eGFR and FEUA, FEUA and urinary excretion of \( \beta_2 \text{MG} \), FEUA and FENa, and FEUA and the product of eGFR multiplied by \( sUA \). Next, we analyzed the correlation between eEUA and eGFR, as well as that between eEUA and FEUA. Similarly, we analyzed the correlation between \( sUA \) and eGFR. Finally, we compared the patients treated with febuxostat to those treated without it in respect to these correlation patterns.

**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 using the Kolmogorov-Smirnov test. Regarding the correlation between eGFR, FEUA, FENa, urinary excretion of \( \beta_2 \text{MG} \), 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 $P$-values $< 0.05$ as statistically significant.
Results

Clinical characteristics of the patients

The characteristics of the enrolled 148 patients are summarized in Table 1 and Table 2.

We revealed no significant difference in the age between the patients treated with febuxostat and those without it. We also demonstrated no significant difference in the distribution of gender and the numbers of hypertension, diabetes mellitus, and dyslipidemia between the two groups (Table 1). It was observed that sUA and eEUA were lower in patients treated with febuxostat than those without it. 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 (Table 2).

Correlation between eGFR and FEUA

A statistically significant inverse correlation was demonstrated between eGFR and FEUA in both patients treated with febuxostat and those without it (Fig. 1a, b).

Correlation between FEUA and urinary excretion of β2MG

A statistically significant positive correlation was demonstrated between FEUA and urinary excretion of β2MG in both patients treated with febuxostat and those without it (Fig. 2a, b).

Correlation between FENa and FEUA
A statistically significant positive correlation was demonstrated between FENa and FEUA in both patients treated with febuxostat and those without it (Fig. 3a, b).

**Correlation between FEUA and the product of eGFR and sUA**

A statistically significant inverse correlation was demonstrated between FEUA and the product of eGFR and sUA in both patients treated with febuxostat and those without it (Fig. 4a, b).

**Correlation between eGFR and eEUA, and FEUA and eEUA**

A statistically significant positive correlation was demonstrated between eGFR and eEUA in both patients treated with febuxostat and those without it (Fig. 5a, b). A statistically significant positive correlation was demonstrated between FEUA and eEUA in patients treated with febuxostat, whereas no significant correlation was demonstrated in those without it (Fig. 5c, d).

**Correlation between eGFR and sUA**

A statistically significant inverse correlation was demonstrated between eGFR and sUA in patients treated with febuxostat, whereas no significant correlation was demonstrated in those without it (Fig. 6a, b).
Discussion

In the present study, we demonstrated a significant inverse correlation between eGFR and FEUA in both patients treated with and without febuxostat. Next, we demonstrated a significant positive correlation between FEUA and urinary excretion of β2MG, as well as FENa in both groups. Urinary excretion of β2MG represents proximal tubular reabsorption ability. Furthermore, elevated urinary excretion of β2MG is related to renal tubular dysfunction. Therefore, these data indicated that renal tubular dysfunction progressed as eGFR declined and that FEUA could be used as an index of renal tubular dysfunction. In patients with CKD, the decline in eGFR induced the reduction in the glomerular filtration of uric acid. Simultaneously, the elevated FEUA promoted the urinary excretion of uric acid. It meant that the reduction in the glomerular filtration of uric acid was offset by the increase in uric acid excretion rate through the proximal tubule.

To elucidate the effects of eGFR and FEUA on the glomerular filtration and tubular reabsorption of uric acid, we examined the correlation among eGFR, FEUA, sUA concentration, and eEUA in patients treated with and without febuxostat.

First, we revealed a significant inverse correlation between FEUA and the product of eGFR and sUA in both groups (Fig. 4a, b). Next, we demonstrated a significant positive correlation between eGFR and eEUA in both groups (Fig. 5a, b).
Subsequently, we revealed a positive significant correlation between FEUA and eEUA in patients treated with febuxostat, whereas no significant correlation was shown in those not treated with febuxostat (Fig. 5c, d). Finally, we revealed a significant inverse correlation between eGFR and sUA in patients treated with febuxostat, whereas no significant correlation was demonstrated in those without it (Fig. 6a, b). To explain these phenomena, we postulated the mechanisms described below.

Fig. 7 demonstrates the schematic drawing of the correlation between parameters regarding hyperuricemia in patients without febuxostat. Theoretically, eEUA is proportional to the products of sUA, eGFR, and FEUA. As shown in Fig. 4b, the product of eGFR and sUA decreased with the elevation of FEUA in patients without febuxostat. This offset effect led to the maintained eEUA regardless of FEUA (Fig. 5d).

Fig. 8 demonstrates the schematic drawing of the effect of febuxostat on the correlation between FEUA and eEUA. In patients with a 10 mg daily dose of febuxostat, febuxostat caused a reduction in sUA, leading to a decrease in eEUA. This decrease was attenuated by the elevation of FEUA. This attenuative effect induced a positive correlation between FEUA and eEUA in patients treated with febuxostat.

A significant positive correlation between eGFR and eEUA and a significant inverse correlation between eGFR and sUA (Fig. 5a, Fig. 6a) indicated that sUA
concentration decreased as eEUA increased in those treated with febuxostat. Therefore, the significant positive correlation between FEUA and eEUA (Fig. 5c, Fig. 8) indicates that the additional administration of uricosuric agents would be helpful for further sUA lowering by increasing FEUA followed by eEUA elevation in patients treated with febuxostat.

Conversely, a single administration of a uricosuric agent would not have enough effect on eEUA because no significant correlation was revealed between FEUA and eEUA in those without febuxostat (Fig. 5d). Despite the significant positive correlation between eGFR and eEUA (Fig. 5b), no significant correlation was revealed between eGFR and sUA in those without it (Fig. 6b). The possibility was that sUA concentration was too high to achieve a significant inverse correlation by only the glomerular filtration of uric acid without febuxostat.

This study suggests that uricosuric agents combined with urate synthesis inhibitors are useful for the treatment of hyperuricemia with CKD, whereas urate synthesis inhibitors, including febuxostat, are only recommended to be prescribed to patients with CKD3.

There are some limitations of this study. The first one is that the assessment of uric acid excretion into urine was done with spot urine instead of 24-hour specimen of
urine. In the clinical guideline\textsuperscript{3}, collecting a 24-hour urine sample for urinary uric acid is recommended to assess the urinary uric acid excretion, whereas we calculated eEUA by using eECr, UCr, and UA as described in the Materials and methods section. Urinary concentration of creatinine (UCr) could be influenced by muscle mass. Therefore, we should mention that eEUA could be affected by muscle mass, whereas eECr was adjusted by the height and the body weight as described in the Materials and methods section.

The second limitation is that uric acid excretion into stool was not assessed. Miyata et al. reported that febuxostat acts as a potential inhibitor of ATP-binding cassette transporter G2 (ABCG2), which is expressed in the small intestine\textsuperscript{8}. ABCG2 promotes uric acid excretion into stool\textsuperscript{8}. Fig. 6a demonstrated a significant inverse correlation between sUA and eGFR in patients treated with febuxostat. The possibility was that sUA was susceptible to eGFR because of the attenuated uric acid excretion into stool due to ABCG2 inhibition in patients treated with febuxostat. Further research will be needed since we did not evaluate the ABCG2 activity in this study.

In conclusion, the significant positive correlation between FEUA and eEUA induced by febuxostat indicates that the additional administration of uricosuric agents would be helpful for further sUA lowering by increasing FEUA and eEUA. Both urate synthesis inhibitors and uricosuric agents would be necessary for controlling sUA in
patients with CKD with hyperuricemia. Further research will be needed to reveal the validity of our conclusion.

**Conflict of interest:** The authors declare that they have no conflict of interest.

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Figure legends

**Fig. 1: Correlation between eGFR and FEUA.**

**a:** A statistically significant inverse correlation was demonstrated between eGFR and FEUA in patients with a 10 mg daily dose of febuxostat (Spearman’s rank correlation coefficient: $r_s = -0.391$, *$P<0.001$). **b:** A statistically significant inverse correlation was demonstrated between eGFR and FEUA in patients without febuxostat (Spearman’s rank correlation coefficient: $r_s = -0.668$, *$P<0.001$).

**Fig. 2: Correlation between FEUA and urinary excretion of β2MG.**

**a:** A statistically significant positive correlation was demonstrated between FEUA and urinary excretion of β2MG in patients with a 10 mg daily dose of febuxostat (Spearman’s rank correlation coefficient: $r_s = 0.614$, *$P<0.001$). **b:** A statistically significant positive correlation was demonstrated between FEUA and urinary excretion of β2MG in patients without febuxostat (Spearman’s rank correlation coefficient: $r_s = 0.590$, *$P=0.002$).

**Fig. 3: Correlation between FENa and FEUA.**

**a:** A statistically significant positive correlation was demonstrated between FENa and FEUA in patients with a 10 mg daily dose of febuxostat (Spearman’s rank correlation coefficient: $r_s = 0.530$, *$P<0.001$). **b:** A statistically significant positive correlation was demonstrated between FENa and FEUA in those without febuxostat. (Spearman’s rank correlation coefficient: $r_s = 0.442$, *$P=$...
Fig. 4: Correlation between FEUA and the product of eGFR and sUA. 

a: A statistically significant inverse correlation was demonstrated between eGFR × sUA and FEUA in patients with a 10 mg daily dose of febuxostat (Spearman’s rank correlation coefficient: rs = −0.428, *P < 0.001). 

b: A statistically significant inverse correlation was demonstrated between eGFR × sUA and FEUA in patients without febuxostat (Spearman’s rank correlation coefficient: rs = −0.697, *P < 0.001).

Fig. 5: Correlation between eGFR and eEUA, and FEUA and eEUA. 

a: A statistically significant positive correlation was demonstrated between eGFR and eEUA in patients with a 10 mg daily dose of febuxostat (Spearman’s rank correlation coefficient: rs = 0.427, *P < 0.001). 

b: A statistically significant positive correlation was demonstrated between eGFR and eEUA in patients without febuxostat (Spearman’s rank correlation coefficient: rs = 0.394, *P = 0.046). 

c: A statistically significant positive correlation was demonstrated between FEUA and eEUA in patients with a 10 mg daily dose of febuxostat (Spearman’s rank correlation coefficient: rs = 0.436, *P < 0.001). 

d: No significant correlation was demonstrated between FEUA and eEUA in patients without febuxostat (Spearman’s rank correlation coefficient: rs = 0.209, P = 0.306).

Fig. 6: Correlation between eGFR and sUA. 

a: A statistically significant inverse
correlation was demonstrated between eGFR and sUA in patients treated with febuxostat (Spearman’s rank correlation coefficient: rs = −0.234, *P = 0.009). b: No significant correlation was demonstrated between eGFR and sUA in patients without febuxostat. (Spearman’s rank correlation coefficient: rs = −0.267, P = 0.187).

Fig. 7: Schematic drawing of the correlation among parameters regarding hyperuricemia in patients without febuxostat.

Theoretically, eEUA is proportional to the products of sUA, eGFR, and FEUA. As shown in Fig. 4, the product of eGFR and sUA decreases with the elevation in FEUA in patients without febuxostat. This offset effect leads to the maintained eEUA regardless of FEUA.

Fig. 8: Schematic drawing of the effect of febuxostat on the correlation between FEUA and eEUA. In patients with febuxostat, febuxostat caused a reduction in sUA, leading to a decrease in eEUA. This decrease is attenuated by the elevation in FEUA. This attenuative effect induces a positive correlation between FEUA and eEUA in patients with febuxostat. The blue line represents the patients without febuxostat, whereas the red line represents the patients with a 10 mg daily dose of febuxostat.
Table captions

**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.

**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 $\text{U}_{\text{UA}}/\text{U}_{\text{Cr}}$ was greater than 0.5 was significantly higher in those without febuxostat than those treated with it.
Patients with a 10mg daily dose of febuxostat

Patients without febuxostat

**Graph a.**
- rs = −0.391
- *P < 0.001

**Graph b.**
- rs = −0.668
- *P < 0.001
Patients with a 10mg daily dose of febuxostat

Patients without febuxostat

a. $rs = 0.614$  
$^*P < 0.001$

b. $rs = 0.590$  
$^*P = 0.002$
Patients with a 10mg daily dose of febuxostat

- Scatter plot (a): $r_s = 0.530$, $*P < 0.001$
- Scatter plot (b): $r_s = 0.442$, $*P = 0.024$

Patients without febuxostat
Patients with a 10mg daily dose of febuxostat

\[ rs = -0.428 \]
\[ *P < 0.001 \]

Patients without febuxostat

\[ rs = -0.697 \]
\[ *P < 0.001 \]
Patients with a 10mg daily dose of febuxostat

Patients without febuxostat

\[ \text{rs} = 0.436 \quad *P < 0.001 \]

\[ \text{rs} = 0.209 \quad P = 0.306 \]

\[ \text{rs} = 0.427 \quad *P < 0.001 \]

\[ \text{rs} = 0.394 \quad *P = 0.046 \]
Patients without febuxostat

Patients with a 10mg daily dose of febuxostat

eGFR – sUA

\[ rs = -0.234 \]
\[ *P = 0.009 \]

\[ rs = -0.267 \]
\[ P = 0.187 \]
(eGFR × sUA) reduction with FEUA elevation

Offset effect

eEUA is maintained regardless of FEUA.
eEUA $\propto \left[(e\text{GFR} \times s\text{UA}) \times \text{FEUA}\right]$

Reduction in sUA induces decrease in eEUA.

Elevation in FEUA attenuates the decrease in eEUA.

Patients with a daily 10mg of febuxostat

Patients without febuxostat

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| Treatment of hyperuricemia | Febxostat | 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 m²)    | 30.4 ± 13.4 | 30.4 ± 14.1 | 0.964    |
| 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     |