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ORIGINAL ARTICLE

Renoprotective effects of febuxostat in hyperuricemic patients with chronic kidney disease: a parallel-group, randomized, controlled trial

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Abstract
Background Hyperuricemia is associated with the onset of chronic kidney disease (CKD) and renal disease progression. Febuxostat, a novel, non-purine, selective xanthine oxidase inhibitor, has been reported to have a stronger effect on hyperuricemia than conventional therapy with allopurinol. However, few data are available regarding the clinical effect of febuxostat in patients with CKD.
Methods A prospective, randomized, open-label, parallel-group trial was conducted in hyperuricemic patients with stage 3 CKD. Patients were randomly assigned to treatment with febuxostat ($n = 21$) or to continue conventional therapy ($n = 19$). Treatment was continued for 12 weeks. The efficacy of febuxostat was determined by monitoring serum uric acid (UA) levels, blood pressures, renal function, and urinary protein levels. In addition, urinary liver-type fatty acid-binding protein (L-FABP), urinary albumin, urinary beta 2 microglobulin (β2MG), and serum high sensitivity C-reactive protein were measured before and 12 weeks after febuxostat was added to the treatment.
Results Febuxostat resulted in a significantly greater reduction in serum UA (−2.2 mg/dL) than conventional therapy (−0.3 mg/dL, $P < 0.001$). Serum creatinine and estimated glomerular filtration rate changed little during the study period in each group. However, treatment with febuxostat for 12 weeks reduced the urinary levels of L-FABP, albumin, and β2MG, whereas the levels of these markers did not change in the control group.
Conclusion Febuxostat reduced serum UA levels more effectively than conventional therapy and might have a renoprotective effect in hyperuricemic patients with CKD. Further studies should clarify whether febuxostat prevents the progression of renal disease and improves the prognosis of CKD.

Keywords Chronic kidney disease (CKD) · Febuxostat · Hyperuricemia · Urinary albumin · Urinary beta 2 microglobulin (β2MG) · Urinary liver-type fatty acid-binding protein (L-FABP)

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Introduction

Cardiovascular mortality is greater in patients with chronic kidney disease (CKD) than in the general population and is associated with CKD stage [1–5]. Hyperuricemia is a risk factor for the onset of CKD [6] and is associated with progression of renal dysfunction [7–9] and cardiovascular mortality [10, 11]. Chronic hyperuricemia stimulates the renin–angiotensin system and inhibits release of endothelial nitric oxide, resulting in renal vasoconstriction and hypertension; in addition, a high level of uric acid (UA) may play a pathogenic role in interstitial inflammation and progression of kidney injury [12, 13]. Allopurinol decreases serum UA levels by inhibiting the enzyme xanthine oxidase, and it has been regarded as a first-line drug for the treatment of hyperuricemia in daily practice. It has been suggested that the reduction in serum UA levels by allopurinol slows the decrease in renal function and lowers the risk of cardiovascular disease in patients with CKD [14]. Since the dosage of allopurinol, which has low lipid solubility and is metabolized by the kidney, should be lower in patients

with CKD to avoid severe adverse reactions, such as renal dysfunction, Stevens–Johnson syndrome, and hypersensitivity vasculitis [15], its efficacy could be limited in clinical practice. Febuxostat, a novel, non-purine, selective inhibitor of xanthine oxidase, is metabolized mainly by glucuronidation and oxidation in the liver, is excreted by both urinary and fecal pathways, and could be well-tolerated and effective in CKD patients with mild to moderate renal dysfunction without dose reduction. Some clinical studies have shown that febuxostat has a more potent UA lowering effect than conventional therapy with allopurinol. In addition, renoprotective effects of febuxostat have been reported in experimental [16] and clinical studies [17]. However, the clinical effects of febuxostat in CKD have not been sufficiently investigated. The objective of the present study was to evaluate the efficacy and renoprotective effects of febuxostat in hyperuricemic patients with stage 3 CKD.

Materials and methods

Study population

A total of 45 male and female adult subjects with hyperuricemia (serum UA $\geq$7.0 mg/dL) who were known to have CKD stage 3 [estimated glomerular filtration rate (eGFR) 30–59 mL/min/1.73 m^2] was recruited from Fukushima Medical University. Exclusion criteria were: (1) acute/chronic inflammatory disease and/or malignancy; (2) active gout; (3) severe cardiovascular/respiratory/digestive disease within the past 6 months; (4) pregnancy; (5) medication with febuxostat and/or benzbromarone within the past 3 months; (6) on immunosuppressive therapy; or (7) unable to give informed consent and/or other reasons making the patients unsuitable for the trial as judged by the attending physician. Patients treated with allopurinol were not excluded from the study. All patients were Japanese.

Ethics statement

This study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Fukushima Medical University (acceptance no. 1366), and the study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) UMIN000007481. All patients received an explanation of the procedures and possible risks of this study, and they gave their written informed consent to participate in this study.

Study design

This study was a 12-week, prospective, randomized, open-label, parallel-group trial conducted between April 2012 and March 2013. This study was designed to assess the effect of febuxostat in patients with stage 3 CKD. The patient flow chart (CONSORT 2010 flowchart diagram) is shown in Fig. 1. After baseline assessments and investigations, patients were randomly assigned to a control group or febuxostat treatment group. Simple randomization with a 1:1 allocation ratio was used by drawing a sealed envelope containing the intervention allocation from a box. This was repeated by each attending physician. Febuxostat treatment group patients were initially given 10 mg/day of febuxostat once daily. The dosage of febuxostat was allowed to increase to 40 mg/day to reach the target value of serum UA below 6.0 mg/dL. Patients treated with allopurinol at baseline were switched to febuxostat from allopurinol in the febuxostat treatment group and were continued on allopurinol at the same dosage as at baseline in the control group (7 patients with 100 mg/day, 3 patients with 50 mg/day, and 11 patients without allopurinol at baseline in the febuxostat group, 10 patients with 100 mg/day, 2 patients with 50 mg/day, and 7 patients without allopurinol at baseline in the control group, respectively). The dosages of antihypertensive drugs, lipid-lowering agents, and antiplatelet drugs were continued and adjusted according to each individual patient's clinical condition. The efficacy of febuxostat was determined by monitoring serum UA levels, blood pressure, renal function, and urinary protein levels. In addition, urinary liver-type fatty acid-binding protein (L-FABP), urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG), urinary albumin, urinary beta 2 microglobulin (β2MG), and serum high-sensitivity C-reactive protein (hsCRP) levels were measured before and 12 weeks after febuxostat was added to the treatment.

Data collection

Serum UA, creatinine, and urinary protein levels were measured at baseline and after 4, 8, and 12 weeks of treatment. Urinary L-FABP, urinary 8-OHdG, urinary albumin, urinary β2MG, plasma glucose, serum hsCRP, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol levels were measured at baseline and after 12 weeks of treatment. The blood pressure was a seated single measurement by an aneroid device, obtained after 5 min of rest. Blood samples were collected at the clinic by venipuncture from every patient in a fasting state, serum creatinine was measured using an

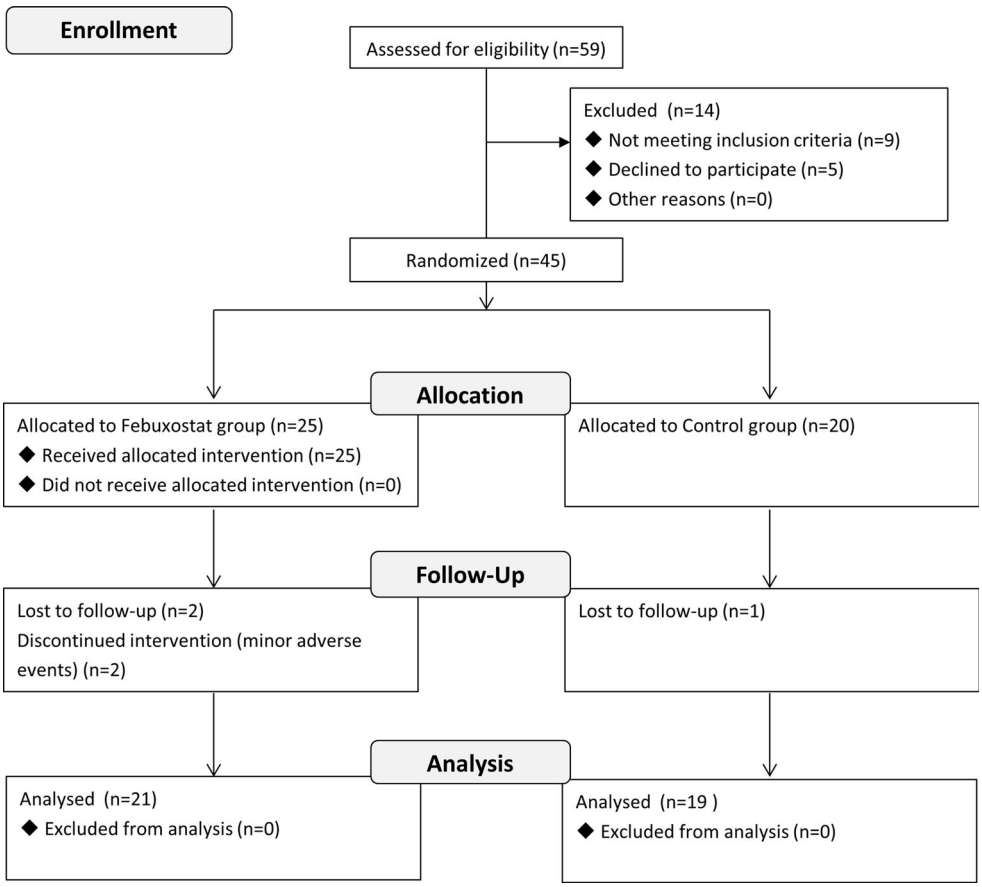

Fig. 1 Flow of participants through the study (CONSORT 2010 flowchart diagram)

enzyme-based method, and serum UA, serum albumin, plasma glucose, HDL cholesterol, and LDL cholesterol levels were measured according to the automated standardized laboratory technique in the clinical laboratory of the institution. The plasma level of hsCRP was measured by the nephelometry method using a Behring Nephelometer II (BNII) (Dade Behring, Tokyo, Japan). Urinary protein, L-FABP, 8-OHdG, albumin, and β2MG levels were measured in single-spot urine specimens collected before breakfast and were adjusted for creatinine (g/gCr for urinary protein, ng/mgCr for urinary L-FABP, and 8-OHdG, mg/gCr for urinary albumin, pg/mgCr for urinary β2MG) measured using the same urine sample. Urinary L-FABP and 8-OHdG levels were determined by the sandwich enzyme-linked immunosorbent assay kit (Mitsubishi Chemical Medience, Tokyo, Japan). Urinary albumin was determined by turbidimetric immunoassay, and urinary β2MG was determined using the latex agglutination method (Mitsubishi Chemical Medience). To estimate GFR, the estimation equation for Japanese patients with CKD was applied [18]. This equation calculates the GFR from serum creatinine, age, and sex.

Adverse events

Any adverse events considered related to the use of febuxostat were recorded during the follow-up assessment. Management of the events (discontinuation of febuxostat, etc.) was decided by the attending physician.

Statistical analysis

Statistical analysis was performed using PASW Statistics version 18.0 for Windows software. The sample size required was calculated on the basis of previous studies of the primary outcome variable, the serum UA level [14, 17]. To detect a reduction in the serum UA level of 2.0 mg/dL (SD 2.0) with a two-sided 5 % significance level and a power of 80 %, a sample size of 17 patients per group was necessary. To account for dropouts, enrollment of 30 patients per group was planned. Continuous variables are expressed as mean ± standard deviation (SD) or medians (interquartile range). Discrete data are given as counts and ratios (%). Categorical data were compared by the Chi-square test, and continuous variables were compared with

the t test. Changes in parameters during the study were compared using analysis of variance with repeated measurements. Because the distributions of urinary L-FABP, 8-OHdG, albumin, and β2MG levels were skewed rightward, the significance of any difference in these parameters was assessed by the Mann–Whitney U test. These parameters were also log transformed, which resulted in normal distributions, and significance was assessed by parametric analysis. Correlations were compared by the Spearman's rank correlation test. Multiple linear regression analysis was performed to determine the independent relationships between variables and changes in urinary parameters. Differences were considered significant at $P < 0.05$.

Results

A total of 45 patients were enrolled in the study, with 20 randomized to the control group and 25 to the febuxostat group. Febuxostat was withdrawn in two patients for rash and a systolic blood pressure decrease to below 100 mmHg, respectively. No abnormalities in liver function tests were attributed to febuxostat treatment. No hematologic alterations or serious adverse events considered related to febuxostat treatment appeared in the follow-up study. One patient in the control group and two patients in the febuxostat group were lost to follow-up during the study period. Finally, 21 patients in the febuxostat group and 19 patients in the control group were analysed after follow-up (Fig. 1). As shown in Table 1, there were no differences between the 2 groups with regard to their baseline characteristics, previous cardiovascular disease, primary renal disease, or percentage of patients taking allopurinol. The dosage of antihypertensive and lipid-lowering agents were allowed to adjust according to each individual patient's condition by the attending physicians in the present study, however, there were no change of antihypertensive and lipid-lowering treatment throughout the study period as a result.

Uric acid levels

The mean dosage of febuxostat at the end of the study was 22.4 ± 9.4 mg/day (10 mg/day, $n = 3$; 20 mg/day, $n = 14$; 40 mg/day, $n = 4$). As shown in Fig. 2, there was a significant decrease in UA levels in the febuxostat group from 4 weeks after the start of treatment, whereas the UA level was significantly lower in the febuxostat group than in the control group from 4 weeks after the start of treatment. The target UA level (<6.0 mg/dL) was achieved in 86 % of the febuxostat group. No patients achieved a UA level <6.0 mg/dL in the control group.

Blood pressure and renal function

There were no significant differences in systolic and diastolic blood pressures between the 2 groups after the start of treatment, but there was a significant decrease relative to baseline at 8 weeks in the febuxostat group ($P = 0.03$ for systolic, $P < 0.01$ for diastolic, Table 2). The changes in systolic and diastolic blood pressures at 12 weeks were +5.6 ± 17.6 and +4.7 ± 10.0 mmHg in the control group compared to −4.7 ± 13.2 and −3.7 ± 8.4 mmHg in the febuxostat group ($P = 0.041$, $P = 0.005$, respectively, Table 3). Estimated GFR was relatively lower in the febuxostat group than in the control group throughout the study period, and the eGFR level measured after 8 weeks was significantly lower compared with baseline in the febuxostat group, but there were no significant differences in eGFR between the febuxostat group and the control group throughout the study period (Table 2), and changes in eGFR and serum creatinine at 12 weeks were not significantly different between the groups (Table 3).

Plasma glucose, lipid profile, and hsCRP

There were no significant differences observed in changes in fasting plasma glucose, HDL cholesterol, and hsCRP levels, but a significant improvement in LDL cholesterol levels was seen in the febuxostat group compared to the control group (Table 3).

Urinary protein, L-FABP, 8-OHdG, albumin, and β2MG levels

The change in urinary 8-OHdG at 12 weeks was not significantly different between the 2 treatment groups, but the decreases in urinary protein, albumin, and β2MG levels were significantly greater in the febuxostat group than in the control group (Table 3). As for urinary L-FABP, a trend towards improvement with febuxostat was seen in the change at 12 weeks, although the difference was not significant ($P = 0.056$). In the febuxostat group, there were significant reductions in urinary L-FABP, albumin, and β2MG levels, whereas no changes were observed in the control group (Fig. 3). In addition, the urinary protein, L-FABP, 8-OHdG, albumin, and β2MG reduction rates were not correlated with the serum UA change rate (Fig. 4). The urinary protein, L-FABP, and 8-OHdG reduction rates were not correlated with the dosage of febuxostat at the end of the study, however, the urinary β2MG reduction rate was significantly correlated with the dosage of febuxostat ($r = -0.423$, $P = 0.010$). The urinary albumin reduction rate showed a trend for a correlation with the dosage of febuxostat ($r = -0.291$,

Table 1 Baseline characteristics of the febuxostat and control groups

	Febuxostat group ($n = 21$)	Control group ($n = 19$)	P
Age (years)	70.1 ± 9.5	66.1 ± 7.0	0.133
Sex (male/female)	19/2	16/3	0.550
Smoking (n, %)			
Current	5 (24)	3 (16)	
History	11 (52)	9 (47)	
Non	5 (24)	7 (37)	
Body mass index (kg/m^2)	24.1 ± 3.8	26.1 ± 2.9	0.061
Systolic blood pressure (mmHg)	131 ± 17	127 ± 15	0.482
Diastolic blood pressure (mmHg)	79 ± 10	76 ± 8	0.262
Heart rate (/min)	74 ± 12	67 ± 9	0.056
Serum creatinine (mg/dL)	1.39 ± 0.33	1.22 ± 0.28	0.086
eGFR (mL/min per 1.73 m^2)	41.8 ± 12.0	47.4 ± 11.0	0.129
Blood urea nitrogen (mg/dL)	23.8 ± 9.5	23.5 ± 5.4	0.910
Uric acid (mg/dL)	7.75 ± 0.84	8.18 ± 1.11	0.173
Serum albumin (g/dL)	3.98 ± 0.30	4.03 ± 0.33	0.616
Fasting plasma glucose (mg/dL)	103.3 ± 21.4	107.7 ± 22.5	0.504
Urinary protein (g/gCr)	0.91 ± 1.44	0.43 ± 0.71	0.182
HDL cholesterol (mg/dL)	53.2 ± 20.8	49.8 ± 10.7	0.526
LDL cholesterol (mg/dL)	107.0 ± 27.4	109.2 ± 26.0	0.795
hsCRP (mg/L)	1.12 ± 0.89	0.90 ± 0.99	0.484
Urinary L-FABP (μg/gCr)	9.20 (5.80, 39.20)	8.20 (4.30, 11.90)	0.286
Urinary 8-OHdG (ng/mgCr)	7.60 (6.10, 9.20)	8.10 (7.45, 10.00)	0.223
Urinary albumin (mg/gCr)	73.0 (21.2, 902.4)	82.9 (20.3, 336.1)	0.456
Urinary β2MG (pg/mgCr)	566 (158, 3048)	180 (74, 594)	0.056
Renal disease (n, %)			
Primary glomerular nephropathy	7 (33)	11 (58)	
Hypertension	11 (52)	6 (32)	
Diabetic nephropathy	1 (5)	2 (11)	
Others	2 (10)	0 (0)	
Cardiovascular disease (n, %)	3 (14)	2 (11)	0.720
Allopurinol at baseline (n, %)	10 (48)	12 (63)	0.324
50 mg/day	3 (14)	2 (11)	
100 mg/day	7 (33)	10 (53)	

Values are expressed as mean ± SD or medians (25, 75 %)

$P = 0.069$). To identify the determinants of decreases in urinary parameters such as urinary L-FABP, 8-OHdG, albumin, and β2MG, multivariate regression analyses with the changes in these urinary parameters as dependent variables and age, sex, eGFR, and the presence or absence of febuxostat as independent variables were performed (Table 4). The results showed that the decreases in urinary L-FABP, albumin, and β2MG levels were independently related to febuxostat treatment after adjustment by age, sex, and eGFR. The urinary L-FABP and 8-OHdG reduction rates did not correlate with the changes of systolic blood pressure at 12 weeks, however, the urinary albumin and β2MG change rates had significant correlations with the changes of systolic blood pressure ($r = 0.481$, $P = 0.002$, and $r = 0.379$, $P = 0.023$, respectively). Therefore, the additional multivariate regression analyses including the change of systolic blood pressure as an independent variable were performed to identify the independent determinants of urinary albumin and β2MG changes (the changes of systolic blood pressure were added to multivariate regression models in Fig. 4 as a dependent variable). Both urinary albumin and β2MG decreases still had independent relationships to febuxostat treatment after adjustment by the changes of systolic blood pressure ($\beta = -0.326$, $P = 0.029$ for ΔLn urinary albumin, $\beta = -0.389$, $P = 0.029$ for ΔLn urinary β2MG).

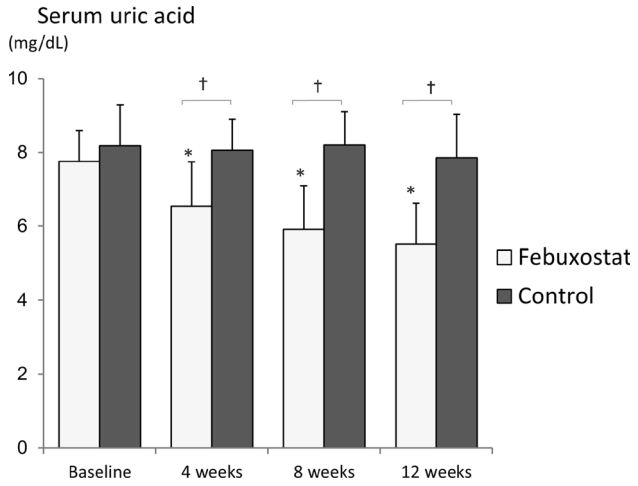

Fig. 2 Changes in serum uric acid levels. *$P < 0.001$ vs. baseline. †$P < 0.001$ between the treatment groups

Discussion

In this study, febuxostat exerted a reliable and stable clinical effect that was far greater than that of allopurinol and other conventional treatments in reducing serum UA in CKD patients with hyperuricemia, with 86 % of patients in the febuxostat group achieving the target serum UA level of <6 mg/dL. There were also significant improvements in urinary protein, L-FABP, albumin, and β2MG levels in the febuxostat group compared with the control group, suggesting the possibility of a renoprotective effect. In this study, the permitted dose of febuxostat was up to 40 mg/day if necessary, but no serious adverse events appeared, and tolerability was excellent in the CKD patients. According to a number of previous studies, febuxostat produces a better rate of reduction of the serum UA level and a higher rate of achievement of a serum UA level

Table 2 Changes in blood pressure levels and eGFR in the two groups

	Systolic BP (mmHg)	Diastolic BP (mmHg)	eGFR (mL/min per 1.73 m^2)
Febuxostat group			
Baseline	131 ± 17	79 ± 11	41.8 ± 12.0
4 weeks	125 ± 18	74 ± 10	41.0 ± 11.5
8 weeks	125 ± 19*	73 ± 11*	40.0 ± 11.8*
12 weeks	126 ± 17	75 ± 10	40.5 ± 11.4
Control group			
Baseline	127 ± 15	76 ± 8	47.4 ± 11.0
4 weeks	132 ± 19	78 ± 11	46.0 ± 9.8
8 weeks	124 ± 18	74 ± 10	45.8 ± 9.5
12 weeks	133 ± 18	80 ± 12	47.0 ± 9.3

Values are expressed as mean ± SD. * $P < 0.05$ vs. baseline within each experimental group

Table 3 Comparisons of changes in parameters between treatment groups at 12 weeks

	Febuxostat group	Control group	*P*
ΔSystolic BP (mmHg)	−4.7 ± 13.2	5.6 ± 17.6	0.041
ΔDiastolic BP (mmHg)	−3.7 ± 8.4	4.7 ± 10.0	0.005
ΔSerum creatinine (mg/dL)	0.04 ± 0.14	0.00 ± 0.15	0.299
ΔeGFR (mL/min per 1.73 m^2)	−1.3 ± 4.0	−0.4 ± 5.8	0.592
ΔUric acid (mg/dL)	−2.2 ± 0.8	−0.3 ± 1.0	<0.001
ΔFasting plasma glucose (mg/dL)	−2.3 ± 5.9	−2.1 ± 10.9	0.947
ΔUrinary protein (g/gCr)	−0.36 ± 0.66	0.07 ± 0.38	0.018
ΔHDL cholesterol (mg/dL)	−3.3 ± 7.7	−0.3 ± 6.0	0.178
ΔLDL cholesterol (mg/dL)	−6.5 ± 15.3	5.1 ± 16.7	0.027
ΔhsCRP (mg/L)	0.06 ± 0.95	0.05 ± 0.16	0.312
ΔUrinary L-FABP (μg/gCr)	−4.5 (−30.4, −1.3)	−1.1 (−4.0, 4.2)	0.056
ΔUrinary 8-OHdG (ng/mgCr)	0.5 (−1.4, 1.4)	−0.2 (−1.4, 1.6)	0.645
ΔUrinary albumin (mg/gCr)	−25.3 (−357.0, 4.8)	5.2 (−71.4, 105.5)	0.035
ΔUrinary β2microglobulin (pg/mgCr)	−96 (−803, 53)	43 (−19, 340)	0.007

Values are expressed as mean ± SD or medians (25, 75 %)

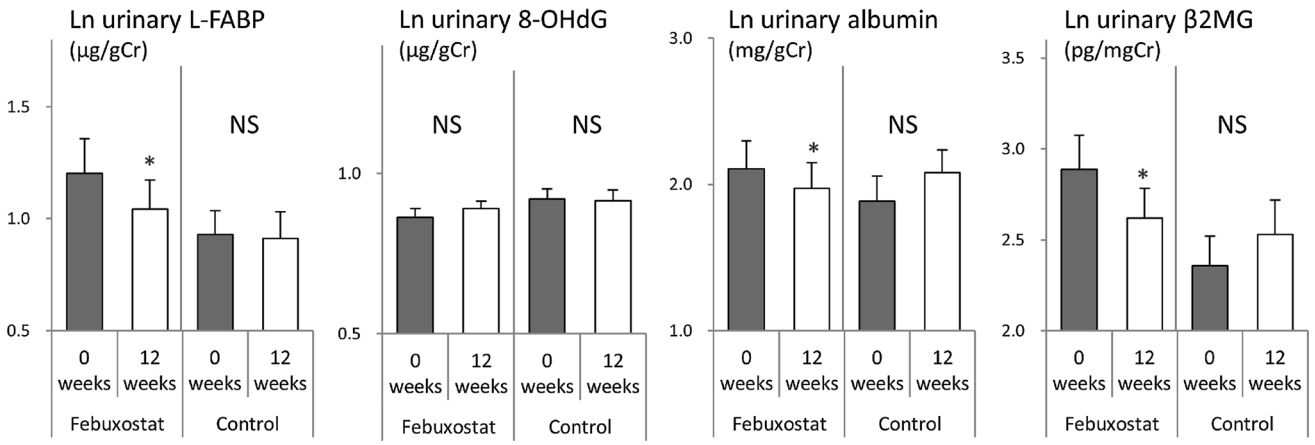

Fig. 3 Changes in log-transformed values of urinary parameters in patients with 12 weeks of treatment. After log transformation of the concentrations of the markers, urinary L-FABP, albumin, and β2MG are significantly decreased in patients in the febuxostat treatment group, whereas these markers change little during the treatment period in control group patients. Data are shown as mean ± SEM. *$P < 0.05$ vs. baseline

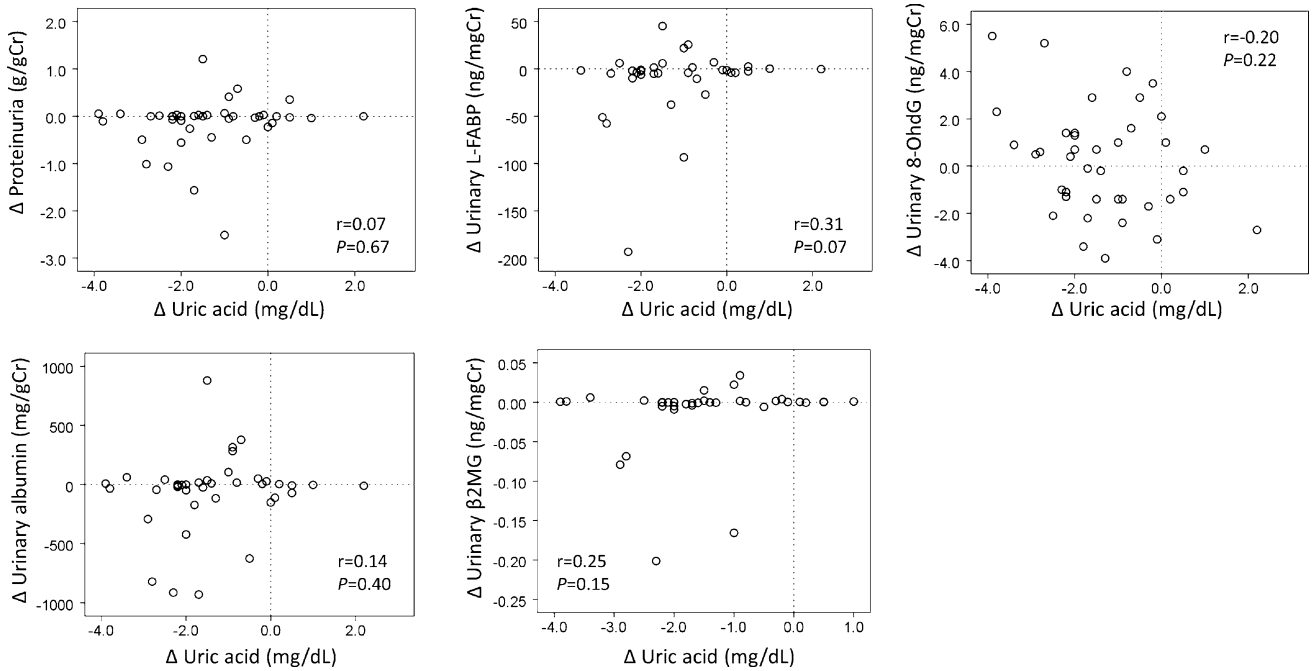

Fig. 4 Correlation between the change in uric acid levels and changes in urinary parameters. No significant correlations are seen between the changes in these urinary parameters and the changes in uric acid levels before and after treatment

<6 mg/dL than allopurinol, the main drug used in conventional treatment, and safety is not a major problem in patients with renal dysfunction of moderate or lower severity [17, 19]. Oxypurinol, a metabolic product of allopurinol, accumulates in patients with renal dysfunction, increasing the incidence of serious side effects such as Stevens–Johnson syndrome and hypersensitivity vasculitis, and this imposes a major restriction on the dose that can be used in patients with impaired renal function. Febuxostat, on the other hand, is metabolized in the liver and undergoes glucuronidation, after which it is excreted in both feces and urine. It can therefore be used in normal amounts with no dose adjustment in patients with renal dysfunction of moderate or lower severity, making it an agent that can exert a more effective action in CKD patients who could not formerly be treated adequately.

The association between hyperuricemia and kidney damage has been the subject of a number of epidemiological studies. In an epidemiological survey of healthy individuals, Iseki et al. [6] found that a serum UA

Table 4 Multivariate analyses of independent factors for improvement of urinary parameters

	ΔLn urinary L-FABP	ΔLn urinary 8-OHdG	ΔLn urinary Albumin	ΔLn urinary β2MG
Age (years)				
Standardized β	−0.073	−0.154	−0.049	−0.182
95 % CI	−0.016 to 0.010	−0.007 to 0.003	−0.015 to 0.011	−0.029 to 0.008
P value	0.634	0.363	0.741	0.255
Male sex				
Standardized β	0.485	−0.095	0.173	0.089
95 % CI	0.232 to 0.983	−0.165 to 0.092	−0.138 to 0.522	−0.346 to 0.616
P value	0.003	0.567	0.245	0.571
eGFR (mL/min/1.73 m^2)				
Standardized β	−0.375	0.202	−0.221	−0.210
95 % CI	−0.021 to −0.002	−0.002 to 0.006	−0.017 to 0.003	−0.023 to 0.005
P value	0.019	0.240	0.151	0.206
Febuxostat treatment				
Standardized β	−0.321	0.224	−0.513	−0.495
95 % CI	−0.454 to −0.002	−0.032 to 0.146	−0.606 to −0.147	−0.794 to −0.154
P value	0.048	0.205	0.002	0.005
R^2	0.302	0.081	0.189	0.191

level of ≥6 mg/dL was a risk factor for end-stage renal disease in women. Bellomo et al. [20] also reported that, in a study of healthy blood donors, the higher the serum UA level, the greater the decline in eGFR, with serum UA level being an independent risk factor for renal dysfunction. In addition, improving hyperuricemia with allopurinol has been reported to be effective in maintaining renal function [14, 21]. Studies of the clinical effect of febuxostat in patients with gout or hyperuricemia following heart surgery have all reported a renoprotective effect [17, 22], but there have been only limited studies involving CKD patients. In the present study, febuxostat not only improved serum UA levels but also showed a renoprotective effect by improving levels of urinary protein, L-FABP, albumin, and β2MG, suggesting that febuxostat may improve the renal prognosis of CKD patients, but further studies of larger numbers of patients are required. There were no significant correlations between the change in serum UA levels and changes in these urinary parameters after 12-week treatment with febuxostat, whereas the urinary β2MG reduction rate was significantly related to the dosage of febuxostat in the present study. These results suggest that the renoprotective effect of febuxostat might be independent of an effect on serum UA reduction. Indeed, animal experiments have suggested that the mechanism underlying this renoprotective effect may not consist solely of reducing the serum UA level to correct hyperuricemia, but it may also include the direct improvement of tubulointerstitial impairment by febuxostat and the suppression of oxidative stress [16, 23]. However, our results did not show the significant improvement of the urinary level of 8-OHdG, a marker of oxidative stress, by febuxostat treatment, therefore, more detailed studies of the mechanism of febuxostat's renoprotective effect are required.

In the present study, a decline in eGFR was evident in the febuxostat group at the 8-week point, when a significant decrease in blood pressure compared with baseline was seen. It returned to its original level as blood pressure increased at the 12-week point when the experiment was ended, and the change was regarded as a transient hemodynamic effect associated with reduced blood pressure. Systolic blood pressure dropped below 100 mmHg in one patient in the febuxostat group, for whom this drug was discontinued. Blood pressure returned to normal in that patient after febuxostat was discontinued, but the fact that it may result in hemodynamic effects in some patients should be borne in mind, and blood pressure must be very carefully monitored after the start of febuxostat administration. Feig et al. [24] found that allopurinol significantly lowered blood pressure in adolescents with newly diagnosed hypertension, and a recent meta-analysis study showed that allopurinol was associated with a small but significant reduction in blood pressure (−3.3 mmHg in systolic and −1.3 mmHg in diastolic) [25]. Sezai et al. [17] reported that a reduction of serum UA level by febuxostat reduced blood pressure, however, a conflicting result was also reported [26]. In addition, the precise mechanism by which these xanthine oxidase inhibitors lowered blood pressure remains unclear, although some hypotheses have been proposed to explain the association between serum

UA and hypertension, such as reduction of plasma renin activity, inhibition of oxidative stress, and improvement of endothelial dysfunction [27–30]. Therefore, association between febuxostat and blood pressure should be closely investigated in further studies.

LDL cholesterol levels were improved in the febuxostat group compared to the control group in the present study. It has been reported that there is a positive correlation between xanthine oxidase, triglycerides, and total lipids [31–33], and a recent article showed that febuxostat significantly reduced triglyceride and total cholesterol levels in 10 gouty patients [34]. The present study also included only a small number of patients, therefore, further studies with sufficient sample size and better statistical methods are still necessary to verify the possibility to improve dyslipidemia with febuxostat.

This study had certain limitations. The first consisted of issues with the study design and sample size. The sample size in the present study was small, it was an open-label study that used surrogate markers as endpoints, and the follow-up period was also short. In addition, some differences were seen in baseline characteristics such as age and renal function between the febuxostat group and the control group, although these differences were not significant, and the decreases in urinary parameters were independently related to febuxostat treatment after adjustment by age, sex, and renal function. A randomized, controlled trial with a better design and adequate sample size is required to verify the renoprotective effect of febuxostat in CKD and its effect on improving prognosis. In this respect, the FEATHER study, which is a multicenter, placebo-controlled, double-blind, randomized trial of febuxostat, is currently underway in Japan [35]. If these issues can be resolved, then febuxostat, which has far better tolerability and is more clinically effective than allopurinol, the main conventional treatment for CKD, may have a major role to play in risk management for CKD patients to improve not only renal prognosis but also survival prognosis and QOL.

The results of the present study demonstrated that, compared with conventional treatment, febuxostat exerted a more stable and reliable action in reducing serum UA levels. It also showed a renoprotective effect, improving levels of urinary protein, urinary albumin, and tubulointerstitial markers. This suggests that febuxostat may be effective in improving renal prognosis in CKD.

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