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Febuxostat and Renal Outcomes in Stage 3-4 CKD Patients with Asymptomatic Hyperuricemia: A Prospective Observational Study

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Submission Date : 20 Nov 2025
Accepted Date : 05 Feb 2026
Published Date : 30 March 2026
DOI: https://doi.org/10.3329/jrpmc.v11i1.89919

Abstract

Background:
Chronic kidney disease (CKD) is commonly accompanied by asymptomatic hyperuricemia, which has been linked to faster renal deterioration.

Objective:
This study evaluated whether febuxostat provides renal benefit compared with standard care in adults with stage 3–4 CKD and elevated serum uric acid.

Methods:
This prospective observational study was conducted in the Department of Nephrology at the National Institute of Kidney Diseases & Urology (NIKDU), Dhaka, from February to July 2016, on 150 adults with chronic kidney disease (CKD) Stage 3-4 and asymptomatic hyperuricemia (serum uric acid ≥7 mg/dL), allocated in equal numbers by a closed-envelope technique to either a Febuxostat group (40 mg once daily after breakfast) or a conventional-therapy group receiving standard CKD care without Febuxostat (75 patients in each group). Participants were followed at baseline, 2 months, and 4 months with repeat clinical and biochemical assessments. The primary outcome was a ≥10% decline from baseline eGFR at 4 months. Secondary outcomes included between-group differences in CKD stage distribution, mean eGFR, and serum creatinine at 2 and 4 months, change in serum uric acid, and significant adverse events (myocardial infarction, stroke, heart failure, mortality).

Results:
Over four months, febuxostat was associated with better preservation of kidney function: eGFR remained higher, creatinine rose more slowly, and progression to CKD stage 5 was markedly lower. The primary endpoint, a ≥10% eGFR decline, occurred far less frequently with febuxostat, corresponding to a substantially reduced adjusted risk. Serum uric acid decreased to near-target levels, and cardiovascular events were infrequent and comparable between groups.

Conclusion:
These findings indicate the short-term renoprotective potential of febuxostat in selected CKD patients, underscoring the need for longer controlled trials.

Keywords: Febuxostat, Asymptomatic hyperuricemia, Chronic kidney disease (CKD), EGFR, And Renal Outcomes

Citation: Paul RS,Roy DK,Chowdhury HS.Febuxostat and Renal Outcomes in Stage 3-4 CKD Patients with Asymptomatic Hyperuricemia: A Prospective Observational Study.J Rang Med Col.2026 Mar;11(1):3-8.doi: https://doi.org/10.3329/jrpmc.v11i1.89919

Introduction:

Chronic kidney disease (CKD) continues to impose a substantial global health burden, with progressive loss of kidney function leading to increased cardiovascular morbidity and premature mortality. Extensive epidemiologic analyses, including data from the Global Burden of Disease Study, highlight CKD as a leading contributor to years of life lost worldwide and a priority condition for targeted intervention.[1] In parallel, population-based studies from Asia demonstrate a high prevalence of CKD, particularly in rapidly

urbanizing countries such as China and India, where approximately 1 in 10 adults fulfil diagnostic criteria.[2,3] Within this high-risk landscape, asymptomatic hyperuricemia has emerged as a recurring clinical feature in CKD and has been implicated in diverse pathways of renal and cardiovascular injury. A substantial body of experimental and observational evidence links elevated serum uric acid (SUA) with endothelial dysfunction, afferent arteriolar vasoconstriction, glomerular hypertension, tubular inflammation, and activation of the renin–angiotensin system.[4,5] Meta-analytic data reinforce these mechanistic findings: a synthesis of 13 prospective cohorts with more than 190,000 participants showed that each 1 mg/dL increase in SUA was associated with a measurable rise in incident CKD risk, and categorical hyperuricemia more than doubled the likelihood of new-onset CKD.[6] These associations extend to accelerated eGFR decline, increased proteinuria, and heightened cardiovascular events, all of which converge in the clinical trajectory of stage 3–4 CKD. Pharmacologic urate-lowering has therefore gained attention as a potential reno protective strategy. Febuxostat, a non-purine-selective xanthine oxidase inhibitor (XOI), provides a potent and predictable reduction in SUA across a wide range of kidney functions. Phase III randomized trials established its superior biochemical efficacy relative to allopurinol, particularly in achieving target SUA levels in individuals with mild to moderate renal impairment.[7] Moreover, early prospective data from Japanese CKD cohorts suggested that febuxostat may slow renal functional decline in asymptomatic hyperuricemia. However, most studies were limited by short follow-up durations and incomplete representation of advanced CKD.[8] Despite strong biologic plausibility and supportive early signals, real-world prospective evidence evaluating febuxostat's effect on renal trajectories in stage 3-4 CKD without gout remains limited. This gap is clinically relevant, given the high prevalence of hyperuricemia in moderate to advanced CKD and the ongoing debate about whether urate-lowering therapy should be routinely offered in asymptomatic individuals. The present study addressed this evidence gap by examining whether febuxostat therapy is associated with improved renal outcomes in adults with stage 3-4 CKD and asymptomatic hyperuricemia.

Method:

This prospective observational study was conducted in the Department of Nephrology at the National Institute of Kidney Diseases & Urology (NIKDU), Dhaka, from February to July 2016, following Institutional Review Board approval. Consecutive adults with chronic kidney disease (CKD) Stage 3–4 and asymptomatic hyperuricemia (serum uric acid ≥7 mg/dL) were screened. The inclusion criteria were age 18-65 years, either sex, CKD Stage 3 or 4, and the absence of gout symptoms. Exclusion criteria comprised primary disorders of uric acid metabolism, autosomal dominant polycystic kidney disease, pregnancy or lactation, and symptomatic hyperuricemia/gout. After consent, 150 eligible participants were allocated in equal numbers by a closed-envelope technique to either a Febuxostat group (40 mg once daily after breakfast) or a conventional-therapy group receiving standard CKD care without Febuxostat (75 patients in each group).

Baseline demographics (age, sex, weight, height), comorbidities (diabetes mellitus, hypertension, ischemic heart disease, tobacco use), medications (loop diuretics, calcium-channel blockers, ACE inhibitors/ARBs), and laboratory variables (serum creatinine, estimated glomerular filtration rate [eGFR], serum uric acid, total cholesterol, albuminuria) were recorded. eGFR was calculated using the laboratory's standard equation, and CKD stages were defined according to prevailing criteria. Participants were followed at baseline, 2 months, and 4 months with repeat clinical and biochemical assessments. The primary outcome was a ≥10% decline from baseline eGFR at 4 months. Secondary outcomes included between-group differences in CKD stage distribution, mean eGFR, and serum creatinine at 2 and 4 months, change in serum uric acid, and significant adverse events (myocardial infarction, stroke, heart failure, mortality).

Data analyses were performed using standard statistical software, SPSS (v. 26.0). Between-group comparisons used χ^2 tests for categorical variables and t-tests or nonparametric equivalents for continuous variables, as appropriate; longitudinal within- and between-group changes were assessed with repeated-measures analyses. Univariable and multivariable logistic regression identified predictors of ≥10% eGFR decline, including

clinically relevant covariates (treatment group, baseline renal indices, CKD stage, diuretic use, and tobacco use). Two-sided p <0.05 indicated statistical significance.

Results:

At baseline, both groups had similar distributions of age, sex, and significant comorbidities, although tobacco use was more frequent in the conventional group (56.0% vs 40.0%, p=0.048) (Table-I). Renal function was comparable except for slightly higher serum creatinine in Group II (2.9±0.6 vs 2.5±0.6 mg/dL, p=0.001). Diuretic use was also more common in the conventional group (50.7% vs 33.3%, p=0.032) (Table-II). By 2 months, clinically meaningful differences had already emerged. Group I demonstrated higher mean eGFR (28.1±7.7 vs 20.1±8.1 ml/min/1.73m , p<0.001) and lower serum creatinine (2.5±0.6 vs 3.2±0.8 mg/dL, p<0.001). These advantages persisted at 4 months, with the febuxostat group maintaining significantly better renal function (eGFR 27.2±8.9 ml/min/1.73m) compared with the conventional group (16.5±7.0 ml/min/1.73m; p<0.001). Likewise, serum creatinine remained substantially lower (2.8±0.7 vs 4.1±1.5 mg/dL; p<0.001). Febuxostat also produced stronger urate control, reducing SUA to 6.1±0.2 mg/dL versus 7.9±1.1 mg/dL (p<0.001). Progression to CKD stage 5 was markedly less frequent with febuxostat (2.7% vs 22.7%, p<0.001) (Table-III). Overall, only 30.7% of febuxostat patients experienced ≥10% decline in eGFR over 4 months, compared with 89.3% in the conventional group (p<0.001) (Table-IV). Logistic regression confirmed febuxostat therapy as a strong independent protective factor against rapid renal decline (aOR 0.18; 95% CI 0.09–0.36; p<0.001). Higher baseline creatinine modestly increased the risk (aOR 1.18 per 0.5 mg/dL; p=0.028) (Table-V).

Table-I: Baseline demographic and clinical characteristics (N=150)

Baseline characteristics	Group I (Febuxostat, n=75) no. (%)	Group II (Conventional, n=75) no. (%)	p-value
Age (years), mean±SD	48±10	47±13	0.401
Age <40 years	22(29.3)	20(26.7)	
Age 40–49 years	18(24.0)	17(22.7)	
Age 50–59 years	20(26.7)	19(25.3)	
≥60 years	15(20.0)	19(25.3)	
Male sex	46(61.3)	41(54.7)	0.408
Diabetes mellitus	33(44.0)	29(38.7)	0.496
Hypertension	49(65.3)	52(69.3)	0.612
Ischemic heart disease	12(16.0)	15(20.0)	0.523
Tobacco use	42(56.0)	30(40.0)	0.048

Table-II: Baseline renal and biochemical status (N=150)

Baseline renal and biochemical status	Group I (Febuxostat, n=75) no. (%)	Group II (Conventional, n=75) no. (%)	p-value
CKD Stage 3	29(38.7)	25(33.3)	0.496
CKD Stage 4	46(61.3)	50(66.7)	
eGFR (ml/min/1.73m)	26.9±7.4	25.3±6.2	0.223
Serum creatinine (mg/dL)	2.5±0.6	2.9±0.6	0.001
Serum uric acid (mg/dL)	8.3±1.2	7.9±0.9	0.231
Total cholesterol (mg/dL)	197.3±48.5	191.1±41.9	0.405
Loop diuretics	25(33.3)	38(50.7)	0.032
ARB/ACEi	45(60.0)	51(68.0)	0.307

Table-III: Renal outcomes at 2 and 4 months (N=150)

Renal outcomes	Group I	Group II	p-value
eGFR (ml/min/1.73m)			
2 months	28.1±7.7	20.1±8.1	<0.001
4 months	27.2±8.9	16.5±7.0	<0.001
Serum creatinine (mg/dL)			
2 months	2.5±0.6	3.2±0.8	<0.001
4 months	2.8±0.7	4.1±1.5	<0.001
Serum uric acid (mg/dL)			
2 months	7.5±0.6	7.6±0.9	0.569
4 months	6.1±0.2	7.9±1.1	<0.001
CKD Stage 5 at 4 months	2(2.7)	17(22.7)	<0.001

Table-IV: Primary outcome and CKD progression (N=150)

Primary outcome	Group I no. (%)	Group II no. (%)	p-value
≥10% decline in eGFR	23(30.7)	57(89.3)	<0.001
CKD Stage 3 at 4 months	27(36.0)	1(1.3)	<0.001
CKD Stage 4 at 4 months	46(61.3)	57(76.0)	0.054
CKD Stage 5 at 4 months	2(2.7)	17(22.7)	<0.001
Death	0(0.0)	1(1.3)	0.5

Table-V: Predictors of ≥10% eGFR decline at 4 months (Logistic Regression, N=150)

Predictor	Adjusted OR (95% CI)	p-value
Febuxostat therapy (vs conventional)	0.18(0.09–0.36)	<0.001
Baseline eGFR (per 5 ml/min higher)	0.92(0.78–1.08)	0.31
Baseline serum creatinine (per 0.5 mg/dL higher)	1.18(1.02–1.38)	0.028
CKD Stage 4 (vs Stage 3)	1.34(0.66–2.73)	0.41
Loop diuretic use	1.29 (0.66–2.52)	0.46
Tobacco use	1.22(0.64–2.34)	0.54

Discussion:

In this prospective study on adults with stage 3–4 CKD and asymptomatic hyperuricemia, febuxostat therapy was associated with significantly better short-term renal outcomes compared with conventional management. Patients receiving febuxostat demonstrated higher eGFR, lower serum creatinine, reduced progression to CKD stage 5, and markedly lower odds of≥10% eGFR decline over 4 months. These benefits were observed despite comparable baseline clinical features, and a higher burden of tobacco use in the febuxostat group. The findings are consistent with a growing body of evidence suggesting that urate-lowering therapy may confer reno-protective effects in CKD. Epidemiologic studies have shown that elevated serum uric acid is independently associated with accelerated renal decline and incident CKD, supporting a mechanistic link through endothelial dysfunction, afferent arteriolar injury, and oxidative stress pathways.[9,10] Longitudinal observational data in hypertensive and obese populations similarly demonstrate that higher urate levels predict faster eGFR loss and higher cardiovascular risk.[9,10] These pathophysiologic insights provide a biologically plausible foundation for therapeutic urate reduction as a strategy to slow CKD progression. Randomized and prospective clinical trials evaluating febuxostat in CKD populations reinforce these associations. In a landmark 6-month double-masked trial, febuxostat significantly slowed eGFR decline in stage 3–4 CKD patients with asymptomatic hyperuricemia,

without increasing serious adverse events.[11] Smaller controlled trials in moderate CKD consistently report improvements in eGFR slope and reductions in proteinuria over 8–12 weeks.[12,13] In surgical CKD cohorts, febuxostat also reduced uric acid more effectively than allopurinol and improved vascular parameters, including arterial stiffness and blood pressure, suggesting broader cardio-renal benefits.[14] A significant phase III program across hyperuricemic populations has further confirmed febuxostat's predictability in achieving serum urate targets irrespective of renal function, due to its pharmacokinetics being largely independent of renal clearance.[15,16] Our findings align with these prior observations. Achieving SUA levels near 6 mg/dL in the febuxostat group corresponded with renal stability, echoing treat-to-target advantages documented in randomized trials. Although loop diuretic exposure was higher in the conventional-therapy group, febuxostat remained independently protective in multivariable models, suggesting that the observed benefits were not attributable solely to confounding. Evidence from allopurinol trials also supports the concept of urate-lowering renoprotection. Several randomized and long-term follow-up studies demonstrated slower CKD progression and fewer cardiovascular events with allopurinol in hyperuricemic CKD patients.[17-19] Although these studies used different agents, the consistency of benefit across xanthine oxidase inhibitors reinforces urate-lowering as a potential disease-modifying strategy in CKD.

Limitations:

This single-centre, non-randomized design with a short follow-up period (4 months) and a modest sample size limits causal inference and the detection of rare outcomes. Background therapies and adherence were not standardized; proteinuria data were incomplete, indicating that residual confounding is likely. eGFR was the primary surrogate endpoint, and the findings may be generalized only to similar stage 3–4 CKD patients with asymptomatic hyperuricemia.

Conclusion:

Febuxostat therapy was associated with short-term preservation of kidney function compared with conventional management in stage 3–4 CKD patients with asymptomatic hyperuricemia. Over 4 months, febuxostat maintained higher eGFR, lowered serum creatinine, reduced progression to CKD stage 5, and markedly decreased the odds of clinically relevant decline in renal function (adjusted OR ≈0.18), despite comparable baseline profiles. Urate lowering was robust, and achieving a serum uric acid level near 6 mg/dL was associated with renal stability. Cardiovascular events and mortality rates were similar between groups throughout the study period. At the same time, these findings support febuxostat as a potential renoprotective option for carefully selected stage 3–4 CKD patients with asymptomatic hyperuricemia.

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