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ORIGINAL RESEARCH

Response to Febuxostat in Elderly Gout Patients with Clinical Subtypes of Hyperuricemia: A Prospective Cohort Study

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Purpose: Previous clinical studies have suggested potential differences in the response of different subtypes to febuxostat treatment. However, research on elderly gout patients, particularly those with chronic kidney disease (CKD) stage 3, remains lacking. This study aims to compare febuxostat response across subtypes in elderly gout patients.

Methods: A prospective cohort study was conducted to compare the efficacy and safety of febuxostat (20 or 40 mg daily) in 490 gout patients with the clinical subtypes for 12 weeks. Hyperuricemia was defined as the renal underexcretion subtype when UUE ≤ 600 mg/d/1.73m^2 and FE_{UA} < 5.5%, the renal overload subtype when UUE > 600 mg/d/1.73m^2 and FE_{UA} ≥ 5.5%, the combined subtype when UUE > 600 mg/d/1.73m^2 and FE_{UA} < 5.5%, or the normal subtype when UUE ≤ 600 mg/d/1.73m^2 and FE_{UA} ≥ 5.5%, assessed from 24-h urine samples. The primary endpoint was the rate of achieving serum urate (SU) < 6 mg/dL at week 12.

Results: Fewer participants with combined subtype achieved the SU target, 45.57% compared with 69.69% with renal overload subtype, 63.40% with renal underexcretion subtype and 64.06% with normal subtype. Participants with the normal subtype had the lowest baseline eGFR but showed the greatest improvement after treatment (an increase of 5.67 mL/min/1.73 m^2 at week 12, P < 0.001).

Conclusion: Elderly gout patients with the combined subtype exhibit poorer response to febuxostat compared to other subtypes. Urate-lowering therapy improved renal function, particularly in patients with normal subtypes.

Keywords: Gout, Febuxostat, Clinical subtypes of hyperuricemia, Kidney function

Introduction

Gout, the archetypal purine-related disease with an estimated incidence between 2.7% and 6.7%, is caused by deposition of the monosodium form of urate (MSU) in the joints.[1,2] Inflammation at affected joints is largely induced by the recruitment of immune cells (ie infiltrating macrophages, neutrophils, etc.) and accumulation of pro-inflammatory cytokines (ie Interleukin (IL)-1β, IL-6, etc.), which leads to acute inflammation and intense pain.[3] Since gout occurs more frequently in young and middle-aged populations, clinical attention to the elderly population is insufficient. However, in recent years, as the prevalence of gout has been increasing annually,[4–7] gout demonstrates higher incidence among elderly populations, with disease burden showing linear escalation alongside advancing age.[8] Chronic gout progression predisposes to tophus formation, joint deformity, renal impairment, and subsequent exacerbation of comorbidities. Compared to gout in young and middle-aged individuals, elderly populations experience declines in the reserve and function of multiple physiological systems, leading to impaired responses to common acute stressors.[9] Consequently, they are more likely to experience polyarticular attacks and more severe clinical manifestations of gout.[10–12] Additionally, older adults with gout are more prone to comorbid conditions such as cardiovascular diseases, kidney

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diseases, diabetes, and dementia.[13] Those with gout and hyperuricemia and multiple comorbidities are at risk of issues like extended medication duration, improper dosing frequency, drug-drug interactions, or interactions with their coexisting conditions.[14,15] Therefore, the management and individualized treatment of elderly gout patients are particularly important.

Although previous studies have shown that hyperuricemia subtypes based on renal uric acid handling provide meaningful guidance for precision urate-lowering therapy, nearly all existing prospective cohorts have focused on young or middle-aged patients with preserved renal function.[9,16,17] Therefore, the applicability of hyperuricemia subtypes in elderly patients remains uncertain. Importantly, chronic kidney disease (CKD) is highly prevalent among older gout patients, yet individuals with CKD stage ≥3 have been systematically underrepresented in prior investigations.[9,16,17] Since renal dysfunction alters urate homeostasis, drug metabolism, inflammatory responses, and the risk–benefit balance of urate-lowering therapy, evidence derived from younger cohorts cannot be directly extrapolated to older patients with impaired kidney function.

A further limitation in prior research is the lack of attention to the "normal subtype", which is one of all four hyperuricemia subtypes, constituting a minority in the general gout patients.[9] It is more prevalent among older patients[18] and may represent a unique physiological state characterized by eGFR decline, altered extrarenal urate elimination, and distinct metabolic or inflammatory profiles. However, its clinical behavior, treatment response, and renal outcomes remain largely unexplored.

Therefore, we conducted a 12-week observational cohort study to compare the efficacy and safety of febuxostat dose escalation (from 20 to 40 mg daily) in elderly gout patients classified as renal underexcretion subtype, renal overload subtype, combined subtype, and normal subtype.

Materials and Methods

Study Design and Participants

A prospective cohort study was conducted to compare the efficacy and safety of febuxostat dose escalation to achieve the target SU < 6 mg/dL in elderly people with primary gout for 12 weeks.

Participants were recruited from the Gout Clinic, Affiliated Hospital of QingDao University, between September 2021 and February 2024. Diagnosis was based on the 2015 ACR/EULAR criteria. Hyperuricemia subtypes were defined using 24-h urine samples: renal underexcretion (UUE ≤ 600 mg/d/1.73m^2, FE_{UA} < 5.5%), renal overload (UUE > 600 mg/d/1.73m^2, FE_{UA} ≥ 5.5%), combined (UUE > 600 mg/d/1.73m^2, FE_{UA} < 5.5%), and normal (UUE ≤ 600 mg/d/1.73m^2, FE_{UA} ≥ 5.5%).[19]

Inclusion criteria: men aged ≥ 60 years with primary gout and SU ≥ 6.0 mg/dL, not receiving urate-lowering therapy within 2 weeks before enrollment. Exclusion criteria: febuxostat allergy, gout flare in past 2 weeks, liver enzymes > 2 × upper normal limit, or heart failure with NYHA class > II.

A formal sample size calculation was not performed because the study was intended to evaluate real-world febuxostat responses across clinical hyperuricemia subtypes in elderly gout patients, particularly those with CKD stage 3. Given the low prevalence and heterogeneity of this population, conventional power-based sample size estimation was not feasible. Accordingly, the sample size was determined pragmatically by enrolling all consecutive eligible patients within the study period. This feasibility-based approach is consistent with methodological standards for observational cohort studies in special populations.

The study complied with the Declaration of Helsinki, which was approved by the Ethics Committee of the Affiliated Hospital of QingDao University (QYFYWZLL26144) and was registered at the Chinese Clinical Trial Registration Center (ChiCTR2100043573).

Treatment and Follow-Up Procedures

All participants underwent a 14-day washout period before the study, and followed a low-purine diet (Supplementary Table 1). Participants were treated with a daily dose of 20 or 40 mg of febuxostat. Follow-up visits were conducted every 4 weeks. If serum urate (SU) remained ≥ 6 mg/dL and the participant was well tolerated, the dose of febuxostat was escalated to 40 mg

per day. In case of a gout flare, etoricoxib or colchicine was administered. No anti-inflammatory prophylaxis was used. For participants whose transaminases elevated up 1.5 times the baseline level, hepatoprotective medications (diammonium glycyrrhizinate, silibinin, or polyene phosphatidylcholine) were prescribed. Baseline information was collected as the initial visit, including age, disease duration, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), the presence of subcutaneous tophi, and comorbid conditions such as hypertension, diabetes, and hyperlipidemia.

We took several measures to ensure participant adherence. Study procedures, detailed dietary instructions, and other information were provided to patients through a WeChat channel. A patient diary was provided for patients to record their daily medications. Participant adherence was monitored at each follow-up visit through review of medication usage, interview-based compliance assessment, and confirmation of completed laboratory testing. For individuals who missed scheduled visits, telephone reminders were attempted up to three times within two weeks. Participants who remained unreachable after repeated attempts were classified as lost to follow-up. Withdrawal from the study was permitted at any time, and participants who elected to discontinue provided verbal or written notification.

During follow-up, laboratory parameters were measured, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine (Cr), SU, blood glucose (Glu), triglyceride (TG), and total cholesterol (TC). All biochemical analyses were tested using an automatic biochemical analyzer (TBA-40FR; TOSHIBA, Japan). The fractional excretion of uric acid (FEUA) = 24-h urine uric acid (uUA)/ 24-h urine creatinine (uCr) × Cr/SU × 100% and 24-h urine urate excretion (UUE) = uUA × 24-h urinary volume / [0.0061 × height (cm) + 0.0128 × weight (kg) – 0.1529) × 1.73 (mg/d/1.73m^2)].[20] Kidney function was assessed using estimated glomerular filtration rate (eGFR) (CKD-EPI design formulas).[21] Insulin resistance was calculated with TyG Index. TyG Index = ln[(Triglycerides (mg/dL) × Glucose (mg/dL)) / 2].[22] Participants with a prior diagnosis of hypertension or diabetes, or those receiving antihypertensive or antidiabetic medications, were classified as having hypertension or diabetes.[9]

Outcomes

The primary efficacy outcome was the proportion of participants achieving the target SU < 6 mg/dL at week 12. The secondary outcomes included the longitudinal changes in serum urate levels by subtype, the proportion requiring febuxostat 40 mg/day, and predictors of febuxostat response.

Safety outcomes were gout flare incidence defined as the percentage of participants who experienced patient-reported flare with pain visual analog score > 3 of a 0–10 scale, changes in liver and renal function, and the percentage of participants who needed hepatoprotective medicine throughout the study period.

Statistical Analysis

There were no missing data for baseline variables. All analyses were performed using R 4.4.3. Continuous variables were expressed as mean ± standard deviation (SD) or median (Interquartile Range, IQR), and categorical variables as frequency (%). Group comparisons used Pearson χ^2, *t*-test, one-way analysis of variance (ANOVA), or Mann–Whitney U as appropriate. Dunnett's test corrected for multiple comparisons. Logistic regression was used to identify predictors of SU target achievement; Age, baseline SU, BMI and variables with $P < 0.05$ in univariable analysis were included in multivariable models. Repeated measures ANOVA (RM-ANOVA) was used for longitudinal data, with Mauchly's test for sphericity and Greenhouse-Geisser correction as needed. When significant interactions were detected, linear mixed-effects models and Bonferroni correction were applied. For RM-ANOVA, missing values at week 4 and week 8 were imputed using the Last Observation Carried Forward (LOCF) method. For the safety analysis of gout flares, we used a complete-case approach. Participants who completed the scheduled visits but lacked a structured assessment or explicit documentation of gout flares in their medical records at any visit were excluded from the flare analysis. All tests were two sided. Statistical significance was at $P < 0.05$.

Results

Participants and Baseline Characteristics

490 participants were enrolled, and 403 participants completed (Figure 1). No participant discontinued the study due to adverse events or safety concerns. Of the 490 participants initially enrolled, 87 (17.8%) discontinued the study, all due to withdrawal of consent. The reasons included the perceived time burden associated with repeated hospital visits for follow-up assessments, and requesting withdrawal without providing a specific reason. Among all of 403 participants, 194 (48.1%) were classified as renal underexcretion type, 66 (16.4%) as renal overload type, 79 (19.6%) as combined type, and 64 (15.9%) as normal type. The clinical characteristics of all participants at baseline are shown in Table 1. Participants with the normal subtype were older, had lower SU levels, and exhibited worse renal function in all subtypes ($P < 0.05$). There were highest SU levels, BMI, triglycerides in participants with combined subtype compared to other subtypes ($P < 0.05$). However, disease duration, family history of gout, and presence of tophi were not significantly different across subtypes. More detailed baseline characteristics are presented in Table 1.

Serum Urate Lowering Efficacy

245 participants (60.7%) achieved SU < 6.0 mg/dL after 12 weeks of urate-lowering therapy.

The target achievement rates demonstrated significant variation across distinct urate phenotypes throughout the follow-up period. At week 4, the rates were 46.84% for the renal underexcretion subtype, 30.61% for the renal overload subtype, 40.98% for the combined subtype, and 54.54% for the normal subtype. By week 8, the achievement rates for the

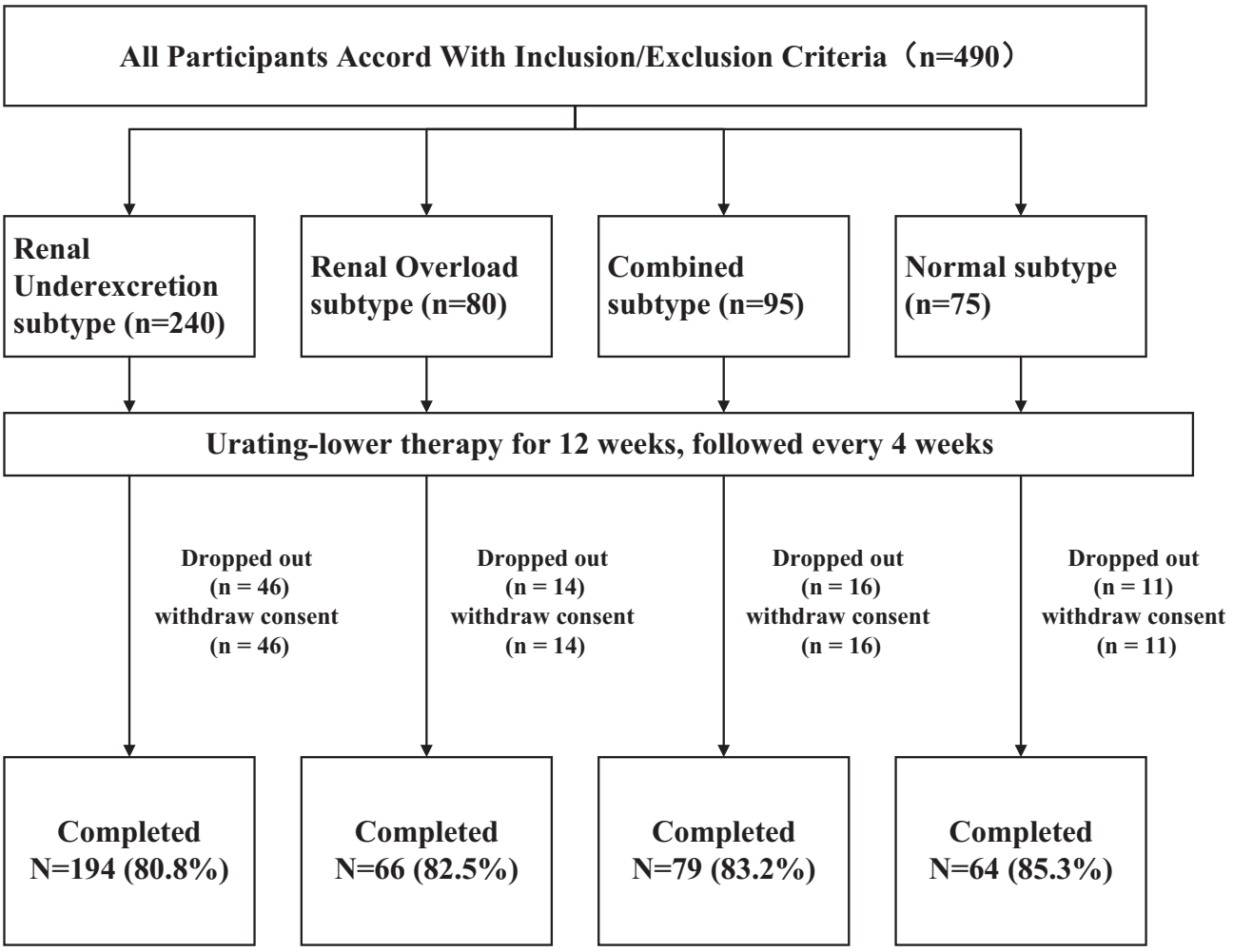

Figure 1 Participant flow throughout study.

Table 1 Clinical Characteristics of Elderly Gout Participants by Different Subtypes

Parameters	All Participants (n = 403)	Renal Under Excretion (n = 194)	Renal Overload (n = 66)	Combined (n = 79)	Normal (n = 64)	P value	Statistic
Demographic and general characteristics							
Age, years	66.17 ± 5.46	65.64 ± 4.89	66.57 ± 5.38	65.10 ± 4.89	68.71 ± 6.93	<0.001	F=6.63
Height, m	171.54 ± 5.73	172.05 ± 5.55	172.72 ± 5.86	171.46 ± 5.14	168.91 ± 6.11	<0.001	F=6.20
Weight, kg	78.45 ± 10.13	77.99 ± 9.59	80.06 ± 10.93	80.95 ± 9.86	75.13 ± 10.34	0.003	F=4.71
BMI, kg/m^2	26.62 ± 2.93	26.32 ± 2.69*	26.81 ± 3.17*	27.46 ± 3.06	26.28 ± 3.04**	0.022	F=3.26
SBP, mmHg	141.96 ± 18.54	139.91 ± 18.29	146.20 ± 18.01	143.53 ± 19.81	141.86 ± 17.69	0.094	F=2.15
DBP, mmHg	87.70 ± 11.25	86.60 ± 11.18	89.36 ± 10.47	89.45 ± 10.37	87.14 ± 12.97	0.146	F=1.80
Biochemical parameters							
ALT, U/L	23.00 (17.00, 30.00)	22.50 (17.00,28.00)	24.00 (19.00,33.75)	26.00 (19.00,31.00)	22.50 (16.00,32.00)	0.125	χ^2=5.73
AST, U/L	21.00 (17.00, 25.00)	20.00 (17.00,24.00)	22.00 (18.00,27.75)	22.00 (18.00,26.00)	20.50 (17.00,24.00)	0.066	χ^2=7.19
Blood glucose, mmol/L	5.99 ± 0.97	5.90 ± 0.82	6.09 ± 1.03	5.91 ± 0.65	6.27 ± 1.49	0.044	F=2.72
Triglyceride, mmol/L	1.93 ± 1.21	1.90 ± 1.05	1.77 ± 0.93	2.38 ± 1.80	1.63 ± 0.82	0.001	F=5.52
Total cholesterol, mmol/L	5.11 ± 1.02	5.12 ± 1.02	5.07 ± 1.10	5.25 ± 0.96	4.93 ± 0.99	0.321	F=1.17
BUN, μmol/L	5.59 ± 1.72	5.38 ± 1.73	5.86 ± 1.47	5.54 ± 1.40	6.00 ± 2.15	0.038	F=2.83
Creatinine, μmol/L	89.98 ± 17.85	89.59 ± 18.06	91.77 ± 16.54	84.72 ± 13.40	95.80 ± 21.36	0.002	F=4.94
eGFR, $mL/min/1.73m^2$	76.51 ± 16.18	77.03 ± 16.22	74.22 ± 14.61	81.42 ± 16.12	71.26 ± 16.04	0.001	F=5.35
Gout characteristics							
Onset age, years	50.66 ± 9.54	49.91 ± 9.33	52.05 ± 7.55	48.01 ± 9.95	54.63 ± 10.20	<0.001	F=6.80
UUE, $mg/d/1.73/m^2$	566.58 ± 228.28	428.62 ± 98.40	779.55 ± 192.74	791.27 ± 255.50	487.79 ± 89.24	<0.001	F=149.08
FE_{UA}, %	0.05 ± 0.02	0.04 ± 0.01	0.07 ± 0.01	0.05 ± 0.02	0.07 ± 0.01	<0.001	F=111.09
Serum urate, mg/dL	8.60 ± 1.26	8.60 ± 1.20*	8.50 ± 1.31*	8.95 ± 1.30	8.28 ± 1.28***	0.013	F=3.61
Duration, years	16.16 ± 10.14	16.53 ± 10.19	15.30 ± 9.89	17.71 ± 10.61	14.07 ± 9.45	0.152	F=1.77
Family history of gout, n	124 (31.55)	60 (31.75)	18 (28.12)	24 (30.38)	22 (36.07)	0.807	χ^2=0.98
Tophi, n	98 (26.13)	49 (27.07)	18 (28.57)	13 (18.06)	18 (30.51)	0.348	χ^2=3.30
Coexisting conditions							
Hypertension, n	280 (70.35)	126 (65.28)	50 (75.76)	58 (75.32)	46 (74.19)	0.199	χ^2=4.65
Diabetes, n	62 (15.98)	26 (13.90)	17 (25.76)	7 (9.09)	12 (20.69)	0.030	χ^2=8.98
Hyperlipidemia, n	276 (71.13)	131 (71.20)	47 (71.21)	64 (82.05)	34 (56.67)	0.014	χ^2=10.64
Obesity, n	127 (32.40)	52 (27.81)	22 (33.33)	36 (46.15)	17 (27.87)	0.028	χ^2=9.14
TyG Index	8.98 ± 0.54	8.97 ± 0.50	8.93 ± 0.54	9.15 ± 0.58	8.86 ± 0.54	0.009	F=3.87

Notes: *, compared with combined subtype, P <0.05; **, compared with combined subtype, P <0.01; ***, compared with combined subtype, P <0.001. Adjusted for Dunnett-test; Continuous variables were expressed as mean ± SD or median (IQR), and categorical variables as frequency (%).

Abbreviations: BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; UUE, urine urate excretion; FE_{UA}, fractional excretion of uric acid; TyG Index, Triglyceride-Glucose Index.

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renal underexcretion, renal overload, combined, and normal subtypes were 60.96%, 65.30%, 43.55%, and 62.79%, respectively. By week 12, these rates further increased to 63.4%, 69.69%, 45.57%, and 64.06%. Importantly, the combined subtype demonstrated the lowest achievement rate at week 12 ($P < 0.05$) (Figure 2A).

SU significantly decreased during urate-lowering treatment among elderly gout patients of all subtypes ($P_{time} < 0.001$) (Table 2). However, no significant differences in SU were observed between subtypes at follow-up time points ($P_{subtype} = 0.109$) (Table 2). Nevertheless, a significant interaction effect indicated that the pattern of uric acid change over time differed among subtypes ($P_{interaction} = 0.012$) (Table 2). In renal underexcretion subtype, renal overload subtype and normal subtype, all pairwise differences across time points were statistically significant ($p < 0.05$) (Supplementary Table 2). Otherwise, in combined subtype, all time comparisons were significant except for the interval between week 8 and 12 (estimate = 0.358, 95% CI: −0.06 − 0.78, p = 0.147) (Supplementary Table 2).

The proportion of participants requiring febuxostat escalation to 40 mg was higher in participants with combined subtype than in participants with renal underexcretion type (31.64% vs 20.10% at week 4, P>0.05, 70.88% vs 53.09% at week 8, P = 0.021, 73.42% vs 57.21% at week 12, P = 0.036), with overload type (31.64% vs 22.72% at week 4, P>0.05, 70.88% vs

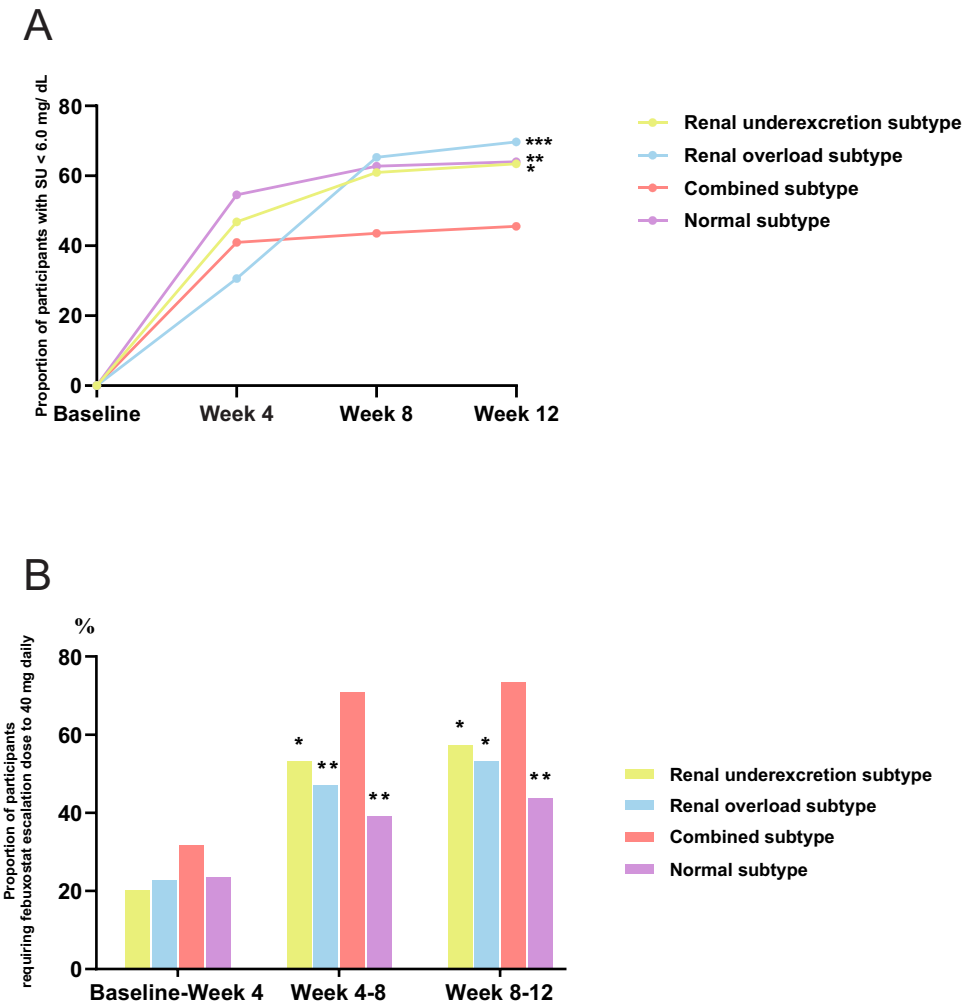

Figure 2 Serum urate lowering efficacy of febuxostat according to subtype of hyperuricemia. (**A**) Proportion of participants with SU < 6.0 mg/dL at weeks 4, 8, and 12. (**B**) Proportion of participants requiring febuxostat dose escalation to 40 mg daily. *Compared with combined subtype, P <0.05; **, compared with combined subtype, P <0.01; ***Compared with combined subtype, P <0.001. All p value was adjusted for Dunnett-test.

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Table 2 Estimated SU (LS Mean and 95% CI), Estimated SU Changes (Estimate and 95% CI), with Overall Effects From RM-ANOVA

Subtype	Baseline	4 Weeks	8 Weeks	12 Weeks	ΔBaseline-4w	ΔBaseline-8w	ΔBaseline-12w	$P_{subtype}$	P_{time}	$P_{interaction}$
Renal underexcretion subtype	8.58 (8.39, 8.76)	6.59 (6.41, 6.78)	6.09 (5.90, 6.27)	5.78 (5.60, 5.97)	1.98 (1.72, 2.25)***	2.49 (2.22, 2.76)***	2.79 (2.53, 3.06)***	0.109	<0.001	0.012
Renal overload subtype	8.50 (8.18, 8.82)	7.06 (6.74, 7.38)	6.14 (5.82, 6.46)	5.57 (5.25, 5.89)	1.44 (0.98, 1.90)***	2.37 (1.91, 2.83)***	2.93 (2.47, 3.39)***			
Combined subtype	8.95 (8.66, 9.25)	7.07 (6.78, 7.36)	6.29 (6.00, 6.58)	5.93 (5.64, 6.22)	1.88 (1.46, 2.30)***	2.66 (2.24, 3.08)***	3.02 (2.60, 3.44)***			
Normal subtype	8.28 (7.96, 8.61)	6.76 (6.44, 7.09)	6.23 (5.91, 6.56)	5.58 (5.26, 5.91)	1.52 (1.05, 1.99)***	2.05 (1.58, 2.52)***	2.70 (2.23, 3.17)***			

Notes: ***Compared with baseline, P < 0.001, adjusted for Bonferroni-test.

Abbreviations: LS, Least-Squares Mean; CI, Confidence interval; LMM, Linear Mixed-Effects Models; RM-ANOVA, Repeated Measures Analysis of Variance.

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46.96% at week 8, P = 0.009, 73.42% vs 53.03% at week 12, P = 0.033), or with normal type (31.64% vs 23.43% at week 4, P>0.05, 70.88% vs 39.06% at week 8, P = 0.003, 73.42% vs 43.75% at week 12, P = 0.003) (Figure 2B).

Predictors of Serum Urate Lowering Response

Univariate and multivariate logistic regression analyses were conducted using urate target achievement rate as the dependent variable. In unadjusted analyses, age (OR=1.03, 95% CI: 0.99–1.07, P=0.124), gout duration (OR=0.98, 95% CI: 0.96–0.99, P=0.025), BMI (OR=0.90, 95% CI: 0.84–0.97, P=0.006), SU (OR=0.67, 95% CI: 0.56–0.79, P<0.001), TyG index (OR=0.68, 95% CI: 0.47–0.99, P=0.048), BUN (OR=0.85, 95% CI: 0.76–0.96, P=0.009), and the combined subtype (OR=0.45, 95% CI: 0.28–0.75, P=0.002) exhibited significant negative correlations with urate target achievement rate.

After adjustment for age, disease duration, SU, BMI, and BUN, the combined subtype (OR=0.58, 95% CI: 0.34–0.98, P=0.043) continued to show a significant association with reduced urate target achievement rates. More details are presented on Table 3.

Safety Analysis

No serious adverse events were observed during the study. Gout flare rates were similar among all groups, affecting 65 of 129 (50.39%) participants with renal underexcretion subtype, 19 of 45 (42.22%) participants with renal overload subtype, 24 of 52 (46.15%) participants with combined subtype and 18 of 50 (36%) participants with normal subtype. (Supplementary Table 3).

Liver function and kidney function tests were monitored throughout the study (Supplementary Tables 4–7).

For ALT, there were no statistically significant effects of time (P_{time} = 0.113), subtype group ($P_{subtype}$ = 0.130), or interaction ($P_{interaction}$ = 0.389). For AST, a small but statistically significant main effect of time was observed (P_{time} < 0.001), suggesting minor changes in AST levels during follow-up. However, neither the main effect of subtype group ($P_{subtype}$ = 0.148) nor the interaction between time and subtype group ($P_{interaction}$ = 0.116) was statistically significant.

There is no difference in the demand for hepatoprotective treatment among all subtypes. (17.7% vs 8.2% vs 16.7% vs 9.4%, P = 0.074) (Supplementary Table 3).

For eGFR, significant main effects of time (P_{time} < 0.001) and subtype group ($P_{subtype}$ = <0.001), as well as a significant interaction effect ($P_{interaction}$ = 0.037), were observed, indicating eGFR longitudinal changes differed across subtypes (Supplementary Table 6). Post-hoc comparisons revealed that eGFR improvement was statistically significant only in the normal subtype during urate-lowering therapy (eg, week 0 vs week 12: estimate = −5.67, p < 0.001). In other subtypes, increases in eGFR were observed but did not reach statistical significance after multiple comparison correction (Figure 3). No patients with eGFR < 30 mL/min/1.73/m^2 were observed during the follow-up period.

Table 3 Univariate and Multivariate Logistic Regression Analyses

Parameters	Univariate Logistic Regression Analyses		Multivariate Logistic Regression Analyses	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.03 (0.99–1.07)	0.124	1.02 (0.98–1.07)	0.250
Duration	0.98 (0.96–0.99)	0.025	0.98 (0.96–1.00)	0.111
SU	0.66 (0.56–0.79)	<0.001	0.74 (0.61–0.89)	0.001
BMI	0.90 (0.84–0.97)	0.006	0.92 (0.85–0.99)	0.036
TyG Index	0.68 (0.47–0.99)	0.048	0.84 (0.56–1.26)	0.393
BUN	0.85 (0.76–0.96)	0.009	0.88 (0.77–0.99)	0.049
Combined Group	0.45 (0.28–0.75)	0.002	0.58 (0.34–0.98)	0.043

Abbreviations: OR, Odds Ratio; CI, Confidence interval; SU, serum urate.

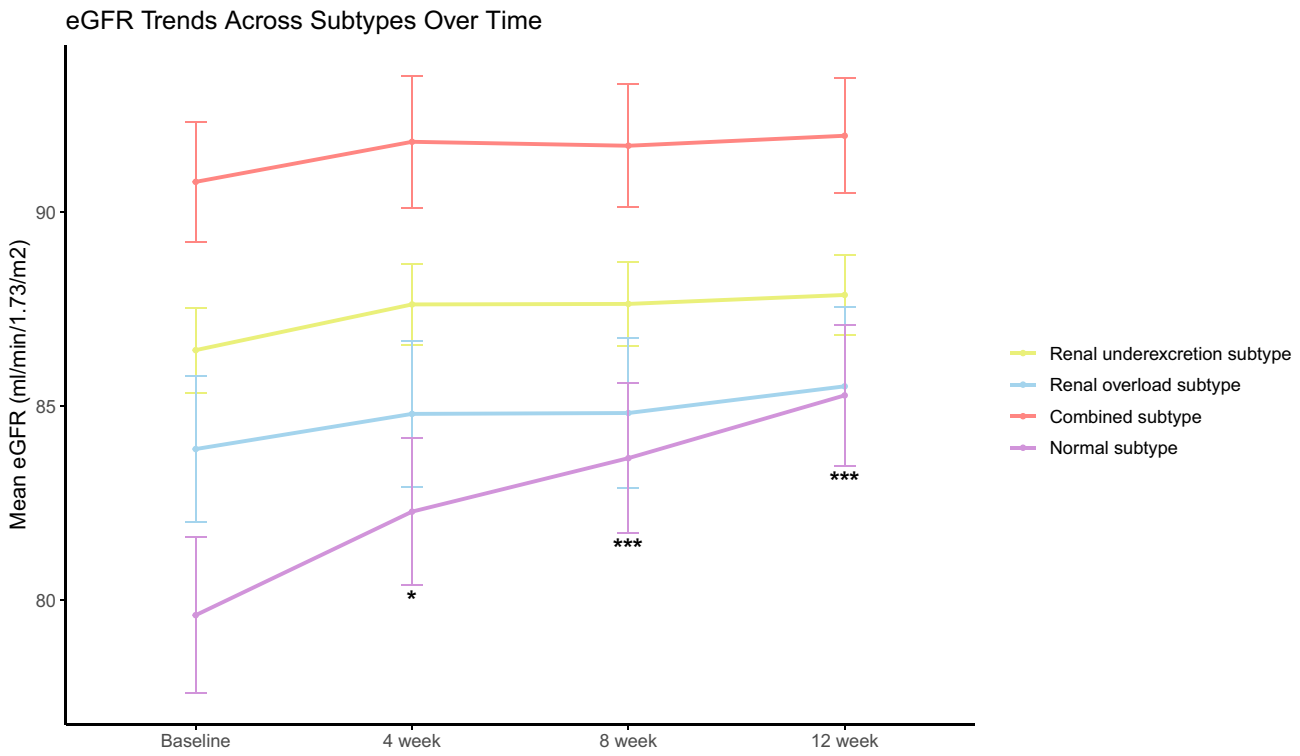

Figure 3 Estimated glomerular filtration (eGFR) trends across subtypes over time. *Compared with baseline, P <0.05; ***Compared with baseline, P <0.001. All p value was adjusted for Bonferroni -test.

Abbreviations: ALT, alanine aminotransferase; ANOVA, one-way analysis of variance; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; df, degrees of freedom; eGFR, estimated glomerular filtration rate; FEUA, fractional excretion of uric acid; IL, Interleukin; IQR, interquartile range; LMM, Linear mixed-effects models; LS, least-squares mean; MSU, monosodium form of urate; OR, odds ratio; RM-ANOVA, repeated measures analysis of variance; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; SU, serum urate; TyG Index, Triglyceride-Glucose Index; UUE, urine urate excretion.

Discussion

Major Findings

This prospective cohort study investigating febuxostat treatment in elderly gout patients revealed differential responses to febuxostat across distinct urate phenotypes. Firstly, the combined subtype exhibited the lowest target achievement rate compared to the other three subtypes, even after adjusting for BMI and baseline SU (Figure 2), which is consistent with previous findings.[9] In addition, although all subtypes showed a decrease in SU levels during treatment, there were differences in the longitudinal pattern of uric acid decline and the demand for increasing doses of febuxostat (Figure 2). Finally, during the 12-week follow-up, there was an overall tendency towards improvement in renal function among patients with all subtypes. However, a particularly noteworthy new finding is that the eGFR of patients with normal subtypes showed the greatest and statistically significant improvement, despite having the lowest baseline renal function level (Figure 3).

Pathophysiological Mechanisms

Hyperuricemia arises through heterogeneous mechanisms involving variations in renal urate reabsorption, tubular secretion, extrarenal urate disposal, and metabolic influences.[23] The combined subtype, characterized by both high UUE and low FE_{UA}, exhibited the most unfavorable urate-lowering response in this elderly cohort.[9] Baseline characteristics demonstrate this subtype's strong association with obesity and TyG index, both closely linked to insulin resistance (Table 1). Under insulin resistance conditions, elevated insulin levels further stimulate the urate-anion exchanger and the Na+-dependent anion cotransporter in the brush border membrane of the renal proximal tubule, enhancing renal urate reabsorption.[24,25] Moreover, impaired oxidative phosphorylation, caused by insulin resistance, may lead to elevated

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acidic metabolites and systemic adenosine levels.[26,27] Therefore, the low target attainment rate of this subtype is not solely due to high baseline uric acid levels but is also associated with a higher prevalence of metabolic disorders such as insulin resistance and metabolic syndrome.

A key innovation of this study lies in the inclusion of the normal subtype, which has been ignored in previous research. This subtype represents a minority in general populations but shows higher prevalence in elderly-onset gout patients, typically presenting with worse renal function.[18,23] Consequently, investigating this subtype carries particular significance for precision urate-lowering therapy in aging populations. Regarding its pathophysiology, we hypothesize two potential mechanisms: (1) declining renal function; (2) insufficient intestinal urate excretion. With advancing age, eGFR typically declines.[18] Even with normal fractional urate excretion, reduced eGFR may decrease absolute urate output, elevating serum levels. Concurrently, elevated urate levels may directly/indirectly induce glomerulosclerosis and tubulointerstitial fibrosis, exacerbating renal impairment.[28] For the latter, potential causes include ATP-binding cassette transporter G2 (ABCG2) dysfunction and gut microbiota effects. ABCG2, mainly located in the intestinal tract and renal tubule, is strongly associated with intestinal urate excretion, and dysfunction in ABCG2 results in extrarenal urate underexcretion.[9,24] Additionally, Aging modulates uric acid homeostasis through functional and spatial alterations of the gut microbiota. For instance, aging reduces the abundance of beneficial bacteria, while increasing the abundance of potential pathogens or opportunistic pathogens (eg, Escherichia coli).[29,30] The former can promote uric acid metabolism by synthesizing uric acid-metabolizing enzymes, whereas the latter may secrete xanthine oxidase (XOD), thereby increasing uric acid levels.[30] These proposed mechanisms could partially account for both the emergence of this subtype and its comparatively less severe hyperuricemia phenotype relative to other subtypes. It also helps explain this subtype's superior renal function improvement post-treatment compared to other groups. Nevertheless, these interpretations remain hypothetical and warrant further mechanistic validation through dedicated investigations.

Although gout is fundamentally an inflammatory disease driven by cytokines such as IL-1β, IL-6, and other downstream mediators,[2] the hyperuricemia subtypes are classified primarily according to renal urate transport physiology rather than inflammatory activity. As a result, differences in renal urate excretion patterns do not necessarily translate into differences in acute flare frequency. In this study, gout flares were comparable across all subtypes, consistent with previous study.[9]

Clinical Significance

Our findings carry several implications for precision urate-lowering therapy in elderly gout patients. First of all, our research further demonstrates the practicality of hyperuricemia subtypes based on renal uric acid handling for elderly gout patients, and helps identify patients, such as the combined subtype, who require more aggressive uric acid lowering treatment or closer monitoring to achieve target UA levels. Furthermore, the observed improvement in renal function in the normal type reinforces the renal protective value of achieving uric acid reduction in elderly patients, even in a short term. Although it has the lowest proportion in all gout patients, we should avoid underestimating the clinical significance of this subtype.

During the entire observational period, transaminase elevations (ALT/AST) occurred uniformly among all subtypes, with no statistically significant variations between subgroups. Previous studies have predominantly focused on patients with preserved renal function, while data on CKD stage ≥ 3 remain scarce. Given that elderly patients often present with multiple comorbidities and varying degrees of renal impairment, this study focused on individuals with CKD stage 3 to systematically evaluate the renal effects of urate-lowering therapy. The 12-week treatment period was free from acute kidney injury incidents, while demonstrating numerical improvements in renal function across subtypes. Despite the complex reciprocity between renal function and uric acid metabolism, our results indicate clinically meaningful benefits of urate reduction in geriatric gout management.

Limitations

However, several limitations of the study should be acknowledged.

1. Firstly, it was a single-center study with a male-only population, limiting the generalizability of the results, and may cause selection bias.

2. Secondly, although we included patients with CKD stage 3, which expands upon previous research, our study did not assess the effects of febuxostat treatment in patients with CKD stages 4 and 5. Further studies are needed to explore subtype-based treatment strategies in these populations. Meanwhile, this study is an observational cohort without a control group such as placebo or allopurinol. It is difficult to attribute the observed improvements in eGFR solely to febuxostat, as they could be influenced by other factors like the low-purine diet, regression to the mean, or improved management of comorbidities.
3. Thirdly, as our study population consisted of elderly patients, we were unable to titrate febuxostat to the maximum approved dose.
4. Furthermore, the use of the LOCF method for imputing missing values at weeks 4 and 8 can introduce bias.
5. Moreover, despite the significant differences in the distribution ratios of different subtypes in elderly gout patients, the unequal group sizes, especially the smaller numbers in the renal overload and normal subtypes, may reduce the precision of the estimates and widen confidence intervals for some analyses.
6. Finally, the research on the "normal subtype" of hyperuricemia is still limited. Although we discussed potential mechanisms in this study, further investigations are needed to fully understand the pathophysiological processes underlying this subtype.

Conclusion

In summary, this study delineated the therapeutic efficacy of febuxostat across distinct hyperuricemia subtypes in elderly gout patients. Patients with combined subtype demonstrated the poorest response to febuxostat. Importantly, we identified clinically meaningful renal protective effects associated with urate-lowering intervention in this geriatric gout population.

Abbreviations

ALT, alanine aminotransferase; ANOVA, one-way analysis of variance; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; df, degrees of freedom; eGFR, estimated glomerular filtration rate; FEUA, fractional excretion of uric acid; IL, Interleukin; IQR, interquartile range; LMM, Linear mixed-effects models; LS, least-squares mean; MSU, monosodium form of urate; OR, odds ratio; RM-ANOVA, repeated measures analysis of variance; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; SU, serum urate; TyG Index, Triglyceride-Glucose Index; UUE, urine urate excretion.

Data Sharing Statement

Data are available from the corresponding authors on request.

Ethics Approval and Informed Consent

The study complied with the Declaration of Helsinki, which was approved by the Ethics Committee of the Affiliated Hospital of QingDao University (QYFYWZLL26144) and was registered at the Chinese Clinical Trial Registration Center (ChiCTR2100043573). Informed consent was obtained from all participants prior to study commencement.

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Author Contributions

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Conceptualization: Ying Chen, Jingyuan Li, Shuting Di; Data curation: Jingyuan Li, Shuting Di, Xin Huang, Yang Xu, Yingluo Wang; Investigation: Jingyuan Li, Shuting Di, Xin Huang, Yang Xu, Yingluo Wang; Methodology: Jingyuan Li, Kelei Li, Ying Chen; Project administration: Ying Chen, Jingyuan Li; Resources: Ying Chen; Formal Analysis: Jingyuan Li, Kelei Li, Ying Chen, Lidan Ma, Shuhui Hu, Fei Yan, Ying Gong; Supervision: Ying Chen;

Visualization: Jingyuan Li; Writing - original draft: Jingyuan Li; Writing – review and editing: Ying Chen, Jingyuan Li, Lidan Ma, Shuhui Hu, Fei Yan, Ying Gong.

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Disclosure

The authors report no conflicts of interest in this work.

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