



Association Between Kidney Function Decline and Baseline TNFR Levels or Change Ratio in TNFR by Febuxostat Chiefly in Non-diabetic CKD Patients With Asymptomatic Hyperuricemia

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Background: The levels of circulating tumor necrosis factor receptor (TNFR) 1 and 2 help predict the future decline of estimated glomerular filtration rate (eGFR) chiefly in patients with diabetes. It has been recently reported that the change ratio in TNFR1 by SGLT2 inhibitor treatment is also related with future GFR decline in patients with diabetes. The aims of this study are to investigate the association between baseline TNFR levels and early change in TNFR levels by the non-purine selective xanthine oxidase inhibitor, febuxostat, and future eGFR decline chiefly in chronic kidney disease (CKD) patients without diabetes.

Methods: We conducted a *post-hoc* analysis of the FEATHER study on patients with asymptomatic hyperuricemia and CKD stage 3, who were randomly assigned febuxostat 40 mg/day or matched placebo. This analysis included 426 patients in whom baseline stored samples were available. Serum TNFR levels at baseline were measured using enzyme-linked immunosorbent assay. Those levels were also measured using 12-week stored samples from 197 randomly selected patients.

Results: Compared with placebo, short-term febuxostat treatment significantly decreased the median percent change from baseline in serum uric acid (−45.05, 95% CI −48.90 to −41.24 mg/dL), TNFR1 (1.10, 95% CI −2.25 to 4.40), and TNFR2 (1.66, 95% CI −1.72 to 4.93), but not TNFR levels. Over a median follow-up of 105 weeks, 30 patients (7.0%) experienced 30% eGFR decline from baseline. In the Cox multivariate

model, high levels of baseline TNFR predicted a 30% eGFR decline, even after adjusting for age, sex, systolic blood pressure, high sensitivity C-reactive protein, uric acid, and presence or absence of febuxostat treatment and diabetes, in addition to baseline albumin to creatinine ratio and eGFR.

Conclusion: Early change in circulating TNFR levels failed to predict future eGFR decline; however, regardless of febuxostat treatment, the elevated baseline level of TNFR was a strong predictor of 30% eGFR decline even in chiefly non-diabetic CKD patients with asymptomatic hyperuricemia.

Keywords: TNF receptor, CKD, uric acid, xanthine oxidase inhibitor, eGFR

INTRODUCTION

Hyperuricemia was previously considered to occur because of reduced renal clearance of uric acid in patients with decreased renal function; therefore, treatment of asymptomatic hyperuricemia has received less attention from researchers. However, several recent epidemiological studies demonstrated that the high levels of serum uric acid increased the risk of renal function decline in the general population (1, 2). In patients with type 1 diabetes, high-normal serum uric acid was reported to predict estimated future decline in glomerular filtration rate (eGFR) (3). However, recent randomized controlled clinical trials (RCTs) demonstrated that the reduction of serum uric acid with allopurinol did not prevent renal function decline in patients with type 1 diabetes and mild to moderate diabetic kidney disease (DKD) or stage 3 and 4 chronic kidney disease (CKD), both of which are high risk factors for eGFR decline (4, 5). Data on halting the progression of CKD using non-purine selective xanthine oxidase inhibitor to lower uric acid have been insufficient (6, 7), although a number of studies demonstrated that uric acid was associated with the pathogenesis of kidney injury through endothelial dysfunction and inflammation (8, 9).

Studies indicated that the elevated levels of circulating tumor necrosis factor receptor (TNFR), which is one of the inflammatory markers, predicted the progression of renal function decline and mortality in a broad range of diseases (10–13). However, the mechanisms that modulate TNFR levels are not fully understood, although the *post-hoc* analyses of several clinical trials reported that several therapeutic agents altered serum TNFR levels (14, 15). We and other researchers previously

demonstrated that serum TNFR level was associated with serum uric acid level in patients with type 2 diabetes (16, 17).

Therefore, in the current *post-hoc* analysis of the previously reported FEATHER study, we investigated whether baseline TNFR levels and early change in circulating TNFR levels predicted 30% eGFR decline chiefly in non-diabetic CKD patients with asymptomatic hyperuricemia.

METHODS

Study Patients

The FEATHER trial design, baseline characteristics of the participants, and primary results have been previously described (6). This was a *post-hoc* analysis of a multicenter, prospective, double-blind, randomized, placebo-controlled parallel group trial to test and compare the efficacy of the xanthine oxidase inhibitor (febuxostat) with placebo in preventing the progression of CKD. Briefly, in this study, 467 patients aged ≥ 20 years, in CKD stage 3 (eGFR 30–60 mL/min/1.73 m²) with asymptomatic hyperuricemia were eligible for enrollment. Moreover, participants were required to have a uric acid concentration between 7.0 and 10.0 mg/dL. The study patients were randomized to receive febuxostat 40 mg/day or placebo for up to 108 weeks. In this study, we included 426 patients whose baseline samples were available.

Measurement of Circulating TNFR Concentrations

Direct sandwich enzyme-linked immunosorbent assay was used for quantifying TNFR1 and TNFR2 (R&D systems, Minneapolis, Minnesota), as previously described (18, 19). To assess the effect of febuxostat, we measured serum TNFR levels using baseline and 12-week stored samples from 197 randomly selected patients. Moreover, the baseline TNFR levels were measured in 426 patients to examine whether they predicted renal function decline.

Statistical Analysis

Data were expressed as mean \pm standard deviation (SD) or as median (25th–75th percentile). Categorical variables were then assessed using the chi-square test. Moreover, baseline demographics and clinical characteristics were assessed

Abbreviations: ACR, albumin to creatinine ratio; ANCOVA, analysis of covariance; BMI, body mass index; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; FEATHER, Febuxostat vs. Placebo Randomized Controlled Trial Regarding Reduced Renal Function in Patients With Hyperuricemia Complicated by Chronic Kidney Disease Stage 3; HbA1c, glycated hemoglobin; hsCRP, high sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; JAK, janus kinase; NLRP3, NOD, LRR, and pyrin domain-containing protein 3; PERL, Preventing Early Renal Loss in Diabetes; RCT, randomized controlled trial; SD, standard deviation; SGLT, sodium glucose cotransporter; TNE, tumor necrosis factor; TNFR, TNF receptor.

according to the baseline TNFR level. The Wilcoxon rank-sum test was also applied for comparison between two groups.

Percentages of change in uric acid, TNFR1, and TNFR2 over the intervention period from baseline to 12 weeks were assessed for the febuxostat and placebo groups. Moreover, we calculated percentages of change in the albumin to creatinine ratio (ACR) and eGFR from baseline to end of study. The effect of febuxostat compared to placebo on circulating ACR, eGFR, uric acid, and TNFR levels was determined by the Wilcoxon rank-sum test. The median differences between groups and 95% CIs were estimated with the Hodges–Lehmann method. Cumulative incidence of 30% eGFR decline was estimated using Kaplan–Meier curves. Univariate and multivariate Cox proportional hazard regression analyses were applied to analyze the association between baseline TNFR levels and $\geq 30\%$ eGFR decline, with adjustments for age, sex, presence of diabetes, systolic blood pressure (BP), high sensitivity C-reactive protein (hsCRP), ACR, eGFR, uric acid, and febuxostat treatment at baseline. The slope of eGFR (mL/min/1.73 m²/year) was determined using a random coefficient model in which the regression coefficients (intercept and slope) were assumed to be a random effect. In this model, an unstructured covariance matrix was specified for random intercept and slope effects, and all measurements were used to compute regression slopes; i.e., at baseline, at 4, 8, and 12 weeks, and then every 12 weeks until week 108 or until discontinuation of treatment. Moreover, multivariate linear regression analysis was performed to evaluate the independent association between TNFR levels and the slope of eGFR change, with adjustments for age, sex, presence of diabetes, systolic BP, hsCRP, ACR, eGFR, uric acid, and febuxostat treatment at baseline.

Statistical analyses were performed with SAS software version 9.3 (SAS Institute, Cary, NC, USA). A *P*-value of < 0.05 was considered to be statistically significant.

RESULTS

Characteristics of the Study Patients According to the Baseline TNFR Level

Table 1 shows the demographic and baseline characteristics. Compared with patients in the lowest tertile of TNFR2 level, those in the highest tertile of TNFR2 level comprised fewer men; had higher systolic BP, uric acid, and ACR; and had lower eGFR at baseline. However, age, body mass index (BMI), diastolic BP, glycosylated hemoglobin (HbA1c), hsCRP, presence of diabetes, and febuxostat treatment did not differ between both groups.

Effect of Febuxostat on Uric Acid, TNFR1, and TNFR2 Levels

The characteristics of the 197 randomly selected patients in the febuxostat and placebo groups are shown in **Supplementary Table 1**. Compared with patients on placebo treatment at week 12, those on febuxostat treatment had a more pronounced reduction in median uric acid level (-45.05 , 95% CI -48.90 to -41.24 mg/dL) but had similar serum TNFR levels (**Table 2**).

Effect of TNFR Levels on Future eGFR Decline: Univariate and Multivariate Cox Proportional Hazards Regression Analyses

The mean eGFR slope significantly differed between patients with TNFR2 level in the highest tertile (-1.24 ± 2.21 mL/min/1.73 m² per year) and those in the two lowest tertile (0.20 ± 1.91 mL/min/1.73 m² per year) groups (difference, -1.43 ; 95% CI, -1.84 to -1.03 ; $P < 0.001$). A similar result was observed according to TNFR1 level (difference, -1.54 ; 95% CI, -1.95 to -1.14 ; $P < 0.001$) (**Supplementary Table 2**).

During the median follow-up period of 105 weeks, 12 (2.8%) and 30 (7.0%) patients developed the 40 and 30% eGFR decline, respectively. Therefore, we investigated the impact of circulating TNFRs on renal disease progression (i.e., 30% eGFR decline from baseline) using Cox proportional hazards regression model. In the univariate Cox regression model, high levels of TNFR2 and ACR at baseline significantly increased the incidence for 30% eGFR decline (**Table 3**). The cumulative incidence of 30% eGFR decline for the highest tertile of TNFRs steeply increased from start of observation (**Figure 1**). Overall, the risk of renal progression significantly increased in patients in the highest tertile of TNFR2 than in those in lowest two tertiles of TNFR2, after adjustment for age, sex, presence of diabetes, systolic BP, hsCRP, febuxostat treatment, ACR, and eGFR (HR 4.76, 95% CI 1.79–12.64, $P = 0.002$) (**Table 3**). Similar results were obtained when TNFR1 was included instead of TNFR2 in the model (**Supplementary Table 3**).

Next, multivariate regression model was used to examine the factors associated with the slope of eGFR rather than 30% eGFR decline. After adjusting all relevant variables in the multivariate regression model, baseline TNFR2, in addition to baseline eGFR and ACR, was significantly associated with the eGFR slope (**Table 4**). Moreover, similar results were obtained when TNFR1 was included rather than TNFR2 in the model (**Supplementary Table 4**).

DISCUSSION

In this *post-hoc* analysis, we tested the hypothesis that treatment with the xanthine oxidase inhibitor (febuxostat) would lower serum TNFR levels, and early change in circulating TNFR levels predicts future eGFR decline in patients with CKD stage 3. Our hypothesis was derived from the subsequent results of previous clinical and experimental studies: (1) uric acid stimulated renal inherent cells, such as mesangial cell, tubular cell, and endothelial cells, to produce inflammatory cytokines (20–23); (2) xanthine oxidase inhibitor treatment decreased uric acid level, resulting in attenuating macrophage infiltration to the kidney in diabetic rat (24); and (3) there was positive correlation between serum uric acid and circulating TNFR levels in patients with IgA nephropathy and diabetes (16, 17). In this study, serum TNFR level was not altered after 12 weeks of febuxostat treatment, although the baseline circulating TNFR level predicted the risk for 30% eGFR decline and was associated with eGFR slope, even after adjustment for relevant factors, including baseline eGFR and ACR.

TABLE 1 | Characteristics of the study patients according to the circulating TNFR2 levels.

| Variables | All | T1 + T2 | T3 | p-value* |
|----------------------------------|----------------------|----------------------|----------------------|----------|
| | (n = 426) | (n = 284) | (n = 142) | |
| TNFR1, pg/mL | 2039 (1,585, 2,513) | 1,733 (1,480, 2,094) | 2,776 (2,395, 3,171) | <0.001 |
| TNFR2, pg/mL | 4,194 (3,339, 5,228) | 3,582 (2,993, 4,194) | 5,662 (5,228, 6,474) | <0.001 |
| Febuxostat treatment, n (%) | 214 (50.2) | 146 (51.4) | 68 (47.9) | 0.493 |
| Age, yr | 65.4 ± 12.0 | 64.6 ± 11.5 | 66.9 ± 12.8 | 0.062 |
| Male, n (%) | 331 (77.7) | 235 (82.8) | 96 (67.6) | <0.001 |
| Presence of diabetes, n (%) | 131 (30.8) | 85 (29.9) | 46 (32.4) | 0.603 |
| BMI, kg/m ² | 24.8 ± 4.0 | 24.8 ± 3.8 | 24.8 ± 4.5 | 0.881 |
| Systolic BP, mmHg | 131.1 ± 15.1 | 130.0 ± 14.4 | 133.1 ± 16.2 | 0.046 |
| Diastolic BP, mmHg | 77.5 ± 11.1 | 77.9 ± 10.7 | 76.8 ± 12.0 | 0.346 |
| Uric acid, mg/dL | 7.8 ± 0.9 | 7.7 ± 0.8 | 8.0 ± 1.1 | <0.001 |
| HbA1c (%) | 5.9 (5.6, 6.3) | 5.9 (5.6, 6.3) | 5.9 (5.6, 6.5) | 0.299 |
| HsCRP, ng/mL | 590 (237, 1,400) | 567 (242, 1,190) | 660 (229, 2,080) | 0.085 |
| ACR, mg/gCr | 118 (17, 534) | 61 (11, 394) | 372 (78, 735) | <0.001 |
| eGFR, mL/min/1.73 m ² | 45 ± 10 | 48 ± 9 | 39 ± 8 | <0.001 |

Data are presented as mean ± SD, median (quartiles) or as %.

T1–T3, tertiles 1–3. *T1 + T2 vs. T3. Tertile boundaries are as follows. TNFR1 (pg/mL): 1,728 for the 33.3th and 2,326 for the 66.6th percentiles; TNFR2 (pg/mL): 3,582 for the 33.3th and 4,785 for the 66.6th percentiles.

ACR, ratio of urinary albumin to creatinine; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HsCRP, high sensitivity C-reactive protein; SD, standard deviation; TNFR, tumor necrosis factor receptor.

TABLE 2 | Percent changes in uric acid, TNFR1, and TNFR2 from baseline to week 12.

| Variables | Placebo | Febuxostat | Difference | p-value |
|----------------------------------|-----------------------|-------------------------|-------------------------|---------|
| | (n = 98) | (n = 99) | (95% CI) | |
| ACR, mg/gCr* | 13.79 (–24.77, 93.50) | 8.70 (–37.07, 76.68) | –6.17 (–30.14, 15.60) | 0.575 |
| eGFR, mL/min/1.73 m ² | 0.00 (–5.56, 4.69) | –1.49 (–6.98, 6.67) | –0.13 (–2.63, 2.38) | 0.876 |
| Uric acid, mg/dL | –1.33 (–6.49, 4.35) | –46.24 (–57.35, –35.00) | –45.05 (–48.90, –41.24) | <0.001 |
| TNFR1, pg/mL | 1.89 (–5.29, 9.43) | 3.51 (–3.89, 10.90) | 1.10 (–2.25, 4.40) | 0.550 |
| TNFR2, pg/mL | 1.55 (–6.51, 7.22) | 3.42 (–6.08, 10.14) | 1.66 (–1.72, 4.93) | 0.338 |

Abbreviations used in this table are the same as in **Table 1**.

Data are presented as median (quartiles).

The median differences between groups and 95% CI were estimated with the Hodges–Lehmann method.

P-values were computed from the Wilcoxon rank-sum test.

*Percent change in ACR from baseline to end of study.

TABLE 3 | Univariate and multivariate Cox regression analyses of the risk factors for 30% eGFR decline from baseline.

| Variables | Unadjusted | p-value | Adjusted | p-value |
|---|--------------------|---------|--------------------|---------|
| | HR (95%CI) | | HR (95%CI) | |
| TNFR2 (T3 vs. T1 + T2) | 5.68 (2.50, 12.89) | <0.001 | 4.76 (1.79, 12.64) | 0.002 |
| Age (per 1 increase) | 1.00 (0.97, 1.03) | 0.908 | 1.00 (0.96, 1.03) | 0.812 |
| Male | 1.21 (0.49, 3.00) | 0.677 | 2.09 (0.77, 5.67) | 0.150 |
| Systolic BP (per 1 increase) | 1.00(0.98, 1.03) | 0.901 | 0.99 (0.96, 1.02) | 0.388 |
| Presence of diabetes | 1.06 (0.48, 2.33) | 0.892 | 0.85 (0.37, 1.95) | 0.701 |
| Treatment (Febuxostat vs. Placebo) | 1.22 (0.59, 2.53) | 0.601 | 1.35 (0.65, 2.84) | 0.422 |
| Uric acid (per 1 increase) | 0.93 (0.62, 1.42) | 0.746 | 0.76 (0.50, 1.14) | 0.180 |
| log _e hsCRP (per 1 increase) | 1.25 (0.95, 1.63) | 0.108 | 1.18 (0.90, 1.55) | 0.226 |
| eGFR (per 1 increase) | 0.96 (0.92, 1.00) | 0.072 | 0.99 (0.95, 1.04) | 0.789 |
| log _e ACR (per 1 increase) | 1.42 (1.14, 1.78) | 0.002 | 1.31 (1.02, 1.69) | 0.034 |

Abbreviations used in this table are the same as in **Table 1**.

log_e, log-transformed.

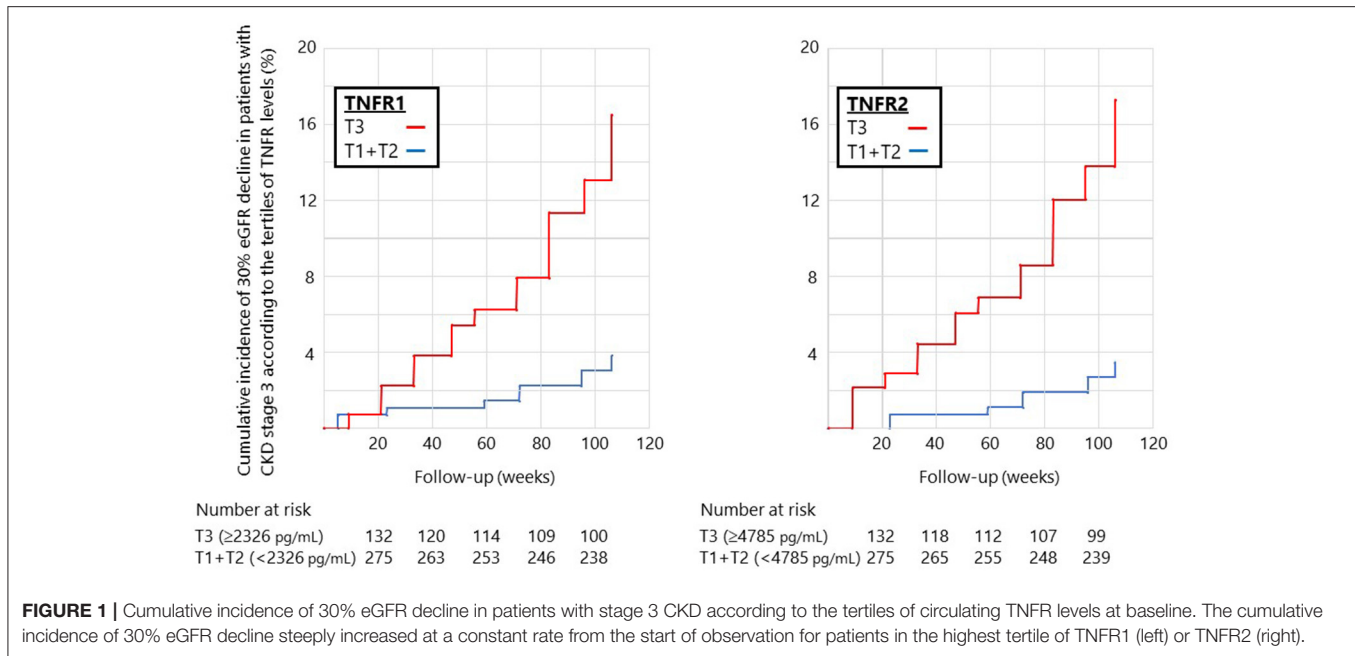


FIGURE 1 | Cumulative incidence of 30% eGFR decline in patients with stage 3 CKD according to the tertiles of circulating TNFR levels at baseline. The cumulative incidence of 30% eGFR decline steeply increased at a constant rate from the start of observation for patients in the highest tertile of TNFR1 (left) or TNFR2 (right).

TABLE 4 | Multivariate regression analysis of the factors associated with eGFR slope in the study patients.

| Variables | Unstandardized coefficient | | Standardized coefficient Beta | p-values |
|-----------------------|----------------------------|-------|----------------------------------|----------|
| | B | SE | | |
| TNFR2 (T3 vs. T1, T2) | -0.547 | 0.233 | -0.121 | 0.019 |
| Age | 0.000 | 0.009 | -0.002 | 0.963 |
| Male sex | -0.130 | 0.232 | -0.026 | 0.575 |
| Systolic BP | 0.000 | 0.006 | 0.004 | 0.938 |
| Presence of diabetes | 0.148 | 0.207 | 0.032 | 0.477 |
| Febuxostat treatment | 0.249 | 0.183 | 0.059 | 0.175 |
| Uric acid | 0.051 | 0.104 | 0.022 | 0.627 |
| log_hsCRP | 0.058 | 0.073 | 0.035 | 0.423 |
| eGFR | 0.049 | 0.011 | 0.225 | < 0.001 |
| log_ACR | -0.335 | 0.051 | -0.316 | < 0.001 |

Abbreviations used in this table are the same as in **Table 1**.
log_, log-transformed.

A number of studies have shown the association of uric acid with inflammation, oxidative stress, and endothelial dysfunction in experimental models (20, 24, 25). Recently, Zhou et al. (26) showed that, compared with healthy individuals, even young patients with asymptomatic hyperuricemia had significantly higher inflammation and oxidative stress. Chronic inflammation plays a critical role in the development and/or progression of CKD. In human kidney biopsy samples, independent of crystal deposition, hyperuricemia was shown to be associated with tubular atrophy and interstitial inflammation and fibrosis (27). In animal models of several kidney diseases, hyperuricemia was demonstrated to induce macrophage infiltration, which was alleviated by treatment with xanthine oxidase inhibitor (24, 28). Although several studies indicated that treatment with allopurinol attenuated the increase in intercellular adhesion

molecule-1 (ICAM-1) levels after acute ischemic stroke or decreased hsCRP in asymptomatic hyperuricemia (29, 30), recent placebo-controlled RCTs demonstrated that treatment with allopurinol did not improve endothelial function, oxidative stress, and inflammation in patients with stage 3 CKD (31). We previously demonstrated that serum uric acid is negatively associated with eGFR and positively associated with TNF-related markers such as TNF α and TNFRs in patients with IgA nephropathy and type 2 diabetes (16, 17). To date, therapeutic agents that modulate TNFR levels remain to be completely elucidated; however, several studies have revealed that treatment with sodium glucose cotransporter (SGLT2) inhibitor or Janus kinase (JAK) 1/2 inhibitor may decrease serum TNFR levels in patients with early and advanced DKD, respectively, whereas renin-angiotensin system inhibitor treatment did not alter TNFR

levels in patients with early DKD (15). In this study, there were no differences in the TNFR levels between the intervention and non-intervention group.

Many observational studies demonstrated that high levels of uric acid predicted eGFR decline in patients with diabetes, CKD, and the general population (1–3). However, the FEATHER study reported that urate-lowering therapy failed to prevent renal function decline in patients with hyperuricemia and stage 3 CKD (6). One of the limitations of this study is that the eGFR decline in patients who received placebo is less (-0.47 ± 4.48 mL/min/1.73 m²), making it difficult to confirm the effect on renal function. Therefore, if we restrict the study patients whose baseline TNFR levels are high (i.e., patients whose eGFR steeply declines), the urate-lowering therapy may prevent renal function decline. However, in this study, use of febuxostat fails to prove this hypothesis (**Supplementary Table 5**).

To date, a growing body of evidence, including our research, demonstrated that circulating TNFR levels predict future eGFR decline chiefly in patients with diabetes. Similar to previous studies, our study expanded the prognostication value of TNFR on the renal function decline in part in non-diabetic population (32, 33). It is important to consider whether elevated circulating TNFR levels only reflect impaired renal processing of these proteins. Indeed, these levels are elevated in patients with advanced renal failure or hemodialysis patients (12, 13, 34). We demonstrated that increased TNFR production of any tissue, including kidneys, partly contributes to the elevation of those levels considering the measurements of fractional excretion TNFR (35). On the other hand, Niewczas et al. (15) demonstrated that overproduction of TNFR occurs chiefly outside the kidneys and suggests that leukocytes are one plausible non-kidney source of TNFR from elegant studies (36, 37).

The limitations of the study should be acknowledged. First, it is not clear whether long-term febuxostat treatment would lower serum TNFR levels, although those levels did not change after a relatively short-term (12 weeks) treatment. Second, our multivariate model may not be appropriately adjusted because inflammatory markers other than hsCRP are not measured. Finally, we use 30% decline in eGFR from baseline as alternative end point to ESRD or 57% decline in eGFR from baseline (doubling of serum creatinine level). Therefore, this endpoint may not accurately reflect future renal function decline. Nevertheless, the strength of the study is that baseline TNFR levels are shown to predict eGFR reduction despite limited reduction in eGFR in the study period.

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CONCLUSIONS

Elevated baseline TNFR levels were associated with eGFR decline; however, early change in circulating TNFR levels failed to predict future eGFR decline chiefly in non-diabetic CKD patients with asymptomatic hyperuricemia. Therefore, additional studies are required to identify treatments that modulate circulating TNFR levels.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Juntendo University Faculty of Medicine, Tokyo, Japan (No. H18-0204). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

TG and NY helped to design the study, oversee its execution, and write the manuscript. YO, IO, YSh, NI, SI, HH, KK, and TH helped to provide clinical data and write the manuscript. MM, YN, SN, SU, and YSu helped to interpret data. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2021.634932/full#supplementary-material>

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