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Original article

Effects of fenofibrate therapy on renal function in primary gout patients

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Abstract

Objective. To investigate the incidence and potential risk factors for development of fenofibrate-associated nephrotoxicity in gout patients.

Methods. A total of 983 gout patients on fenofibrate treatment who visited the dedicated Gout Clinic at the Affiliated Hospital of Qingdao University between September 2016 and June 2020 were retrospectively enrolled from the electronic records system. Fenofibrate-associated nephrotoxicity was defined as an increase in serum creatinine (SCr) $\geq$0.3 mg/dl within 6 months of fenofibrate initiation. The change trend of SCr and uric acid levels during the treatment period were assessed by a generalised additive mixed model (GAMM). Multivariate analysis was performed for risk factors affecting elevated SCr.

Results. A total of 100 (10.2%) patients experienced an increase in SCr $\geq$0.3 mg/dl within 6 months after fenofibrate initiation. The median change of SCr in the whole cohort was 0.11 mg/dl [interquartile range (IQR) 0.03–0.20], whereas it was 0.36 (0.33–0.45) in the fenofibrate-associated nephrotoxicity group. In a multivariable regression model, chronic kidney disease (CKD) [odds ratio (OR) 2.39 (95% CI 1.48, 3.86)] and tophus [OR 2.29 (95% CI 1.39, 3.78)] were identified to be risk predictors, independent of measured covariates, of fenofibrate-associated nephrotoxicity. During the treatment period, although SCr temporarily increased, serum urate and triglyceride concentrations decreased using the interaction analysis of GAMM. Of those with fenofibrate withdrawal records, the SCr increase in 65% of patients was reversed after an average of 49 days off the drug.

Conclusions. This observational study implied that fenofibrate-associated nephrotoxicity occurs frequently in gout patients, especially in patients with tophi or CKD. The potential renal risks of fenofibrate usage in gout needs additional research.

Key words: gout, fenofibrate, nephrotoxicity

CLINICAL SCIENCE

Rheumatology key messages

- Fenofibrate-associated nephrotoxicity occurs frequently in gout patients receiving fenofibrate.
- Patients with tophus and chronic kidney disease were more susceptible to fenofibrate-associated nephrotoxicity.
- Fenofibrate-associated nephrotoxicity temporarily elevated serum creatinine while serum urate and triglyceride concentrations decreased in the interaction analysis of GAMM.

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Introduction

Gout is a chronic disease caused by deposition of monosodium urate crystals in the joints and is characterised by joint inflammation and pain [1]. The prevalence of gout is 2.7–6.7% in western developed countries and has steadily increased recently to 1.1% in mainland China [2]. One correlation is kidney damage, with nephropathy associated with gout [3, 4].

Fenofibrate is a fibric acid derivative for the treatment of hypertriglyceridaemia, which is prevalent with ∼50–70% of gout patients suffering from dyslipidaemia [5, 6]. The 2012 ACR guidelines recommend that agents other than probenecid with clinically significant uricosuric effects, such as fenofibrate and losartan, can be therapeutically useful as components of a comprehensive urate-lowering therapy (ULT) strategy [7]. In addition, the 2016 European League Against Rheumatism guidelines suggest the use of fenofibrate in gout patients [8]. However, the British Society for Rheumatology Guideline did not recommend fenofibrate as a primary ULT because of its weak uricosuric effect [9]. Moreover, the 2020 ACR guidelines recommend against adding or switching cholesterol-lowering agents to fenofibrate despite its urate-lowering effects, as the risks, including side effects of the medication, were felt to outweigh potential benefits [10]. However, the level of evidence supporting the ACR recommendation against the switch to fenofibrate is low. A combination of fenofibrate plus ULT is regarded as beneficial in the treatment of hypertriglyceridaemia and/or hypertension, as well as hyperuricaemia in gout patients with these complications [11], and has been widely used in clinical practice [12].

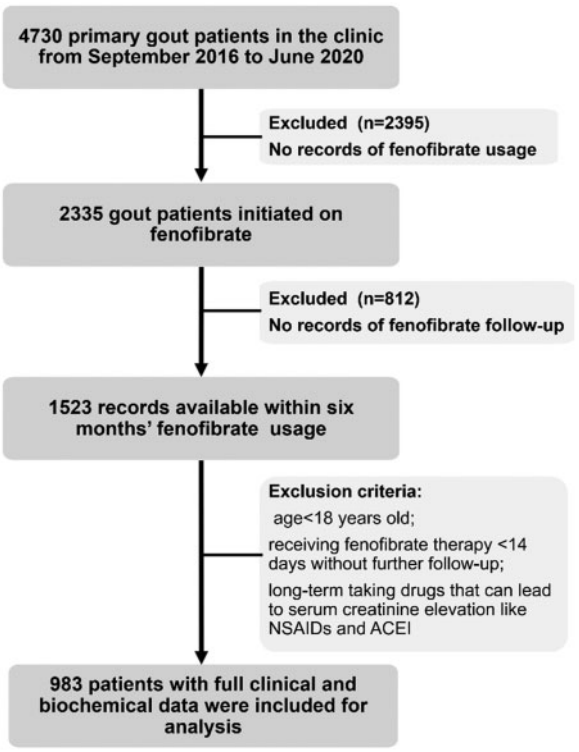
The elevation of serum creatinine (SCr) levels in some gout patients with hypertriglyceridaemia receiving fenofibrate treatment has been observed [13]. However, this adverse effect has not been thoroughly evaluated with respect to the incidence, potential risk factors and reversibility of nephrotoxicity in gout patients on fenofibrate treatment. Therefore we performed a single-centre, retrospective, observational study to investigate these questions.

Methods

Study population

This is a clinical delivery population-based cohort study. A total of 1335 gout patients with fenofibrate treatment identified from the Biobank Information Management System (BIMS; Haier, China) who visited the Gout Clinic at the Affiliated Hospital of Qingdao University between September 2016 and June 2020 were screened. Every patient voluntarily provided written informed consent to import their electronic health records into the BIMS, which could be used in further scientific research. The data set contains demographic characteristics, including age, ethnicity, birthplace, height and weight, history of gout, complications and treatment regimes.

Fig. 1 Flowchart for participant selection



All patients were diagnosed according to the 2015 ACR/EULAR gout classification criteria [14]. Patients were excluded for the following reasons: <18 years of age, receiving fenofibrate therapy <14 days without further follow-up and long-term use of SCr elevation drugs such as NSAIDs and angiotensin-converting enzyme inhibitors. A total of 983 patients were finally included (Fig. 1). The study was approved by the research ethics committee of the Affiliated Hospital of Qingdao University (QYFYWZLL 25847).

Study design and measurements

Baseline was the time of fenofibrate initiation; follow-up laboratory data were obtained from outpatient visits. Nephrotoxicity was defined as an increase in SCr of $\geq$0.3 mg/dl within the first 6 months of fenofibrate administration, according to the Acute Kidney Injury Network guidelines [15, 16]. Chronic kidney disease (CKD) was defined according to the estimated glomerular filtration rate (eGFR) measure as suggested by the Kidney Disease Outcomes Quality Initiative clinical practice guidelines [17]. Any hepatic disease was defined as the presence of fatty liver, hepatitis or liver tumours. A positive family history of gout was defined as one or more of the patient's first- or second-degree relatives affected by gout [18]. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration

formula [19]. BMI was calculated as weight in kilograms divided by height in metres squared.

Outcomes

The primary outcome was the trends and predictors for fenofibrate-associated nephrotoxicity (defined above). Secondary outcomes included medications and comorbidities that predispose to nephrotoxicity and the time course for nephrotoxicity analysed by changes in SCr during the treatment period and the temporal relationship between therapy initiation and an increase in SCr.

Statistical analysis

Data are presented as mean (S.D.), median (interquartile range) or number (percentage). The measured data were analysed by Student's *t*-tests or Wilcoxon rank sum test. Categorical data were analysed by chi-squared tests and expressed as a composition ratio. Uni- and multivariate logistic regression analyses were performed to identify factors predicting an increase in SCr (≥0.3 mg/dl, yes/no). Age, BMI and duration of gout were included as continuous variables and others were dichotomous data, all of which were included simultaneously in the logistic model. The trend of serum urate (SU), SCr and triglycerides were applied in the generalised additive mixed model (GAMM).

All statistical analyses were performed using SPSS 25.0 (IBM, Armonk, NY, USA), R (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org) and EmpowerStats (X&Y Solutions, Boston, MA, USA; www.empowerstats.com) software. With regards to the observance of performance, the missing data (36 of 983 patients lacking the duration of gout) were deleted. A two-tailed *P*-value <0.05 was used as the threshold for statistical significance.

Results

A total of 983 patients from our dedicated gout clinic were ultimately included in this retrospective cohort study with a median duration of fenofibrate therapy of 51 days (IQR 28–98) receiving a fixed dose (200 mg/day) (Fig. 1). The time points chosen to define the two studied groups were if a peak creatinine value during the follow-up period minus the baseline creatinine value was ≥0.3 mg/dl, which was defined as the nephrotoxicity group; if not, it was the non-nephrotoxicity group. The number of patients available at each time point is shown in Supplementary Fig. 1, available at *Rheumatology* online. A total of 100 (10.17%) patients experienced an increase in SCr ≥0.3 mg/dl within the first 6 months after the initiation of fenofibrate (Table 1). The median age of the fenofibrate-associated nephrotoxicity group was 51 years (IQR 37–60) *vs* 43 (36–54) for the non-nephrotoxicity group ($P = 0.001$) and the duration of gout was longer [8 years (IQR 4–12) *vs* 6 (3–11); $P = 0.028$] (Table 1). The BMI in the SCr ≥0.3 mg/dl group was lower than in the SCr <0.3 mg/dl group [26.67 kg/m^2 (IQR 24.91–29.30) *vs* 27.76 (25.74–29.84); $P = 0.013$] (Table 1). The proportions of patients with tophus (37.00% *vs* 16.87%; $P < 0.001$), CKD (58.00% *vs* 32.16%; $P < 0.001$) and hypertension (59.00% *vs* 45.64%; $P = 0.012$) were significantly higher

Table 1 Baseline patient information

Characteristics	<0.3 mg/dl increase [*n* = 883 (89.83%)]	≥0.3 mg/dl increase [*n* = 100 (10.17%)]	OR (95% CI)	*P*-value
Patient demographics, median (IQR)				
Age, years	43.00 (36.00–54.00)	51.00 (37.00–60.00)	1.03 (1.01, 1.04)	0.001
BMI, kg/m^2	27.76 (25.74–29.84)	26.67 (24.91–29.30)	0.92 (0.86, 0.98)	0.013
Duration of gout, years	6.00 (3.00–11.00)	8.00 (4.00–12.00)	1.04 (1.00, 1.07)	0.028
Medical history, *n* (%)				
Tophus	149 (16.87)	37 (37.00)	2.89 (1.86, 4.50)	<0.001
CKD	284 (32.16)	58 (58.00)	2.91 (1.91, 4.44)	<0.001
Family history of gout	181 (20.50)	21 (21.00)	1.03 (0.62, 1.71)	0.906
Hypertension	403 (45.64)	59 (59.00)	1.71 (1.13, 2.61)	0.012
Diabetes	80 (9.06)	8 (8.00)	0.87 (0.41, 1.86)	0.725
Nephrolithiasis	85 (9.63)	14 (14.00)	1.53 (0.83, 2.81)	0.171
Hypertriglyceridaemia	595 (67.38)	63 (63.00)	0.82 (0.54, 1.27)	0.378
Cardiovascular disease	19 (2.15)	3 (3.00)	1.41 (0.41, 4.84)	0.589
Any hepatic disease	155 (17.55)	10 (10.00)	0.52 (0.27, 1.03)	0.059
Concomitant medications, *n* (%)				
ULT drugs				0.084
Allopurinol	39 (4.71)	0 (0.00)		
Febuxostat	673 (81.28)	80 (87.91)		
Benzbromarone	116 (14.01)	11 (12.09)		
Etoricoxib	157 (17.78)	21 (21.00)		0.428
Colchicine	627 (71.01)	73 (73.00)		0.677
Losartan	206 (23.33)	29 (29.00)		0.208

in the fenofibrate-associated nephrotoxicity group (Table 1). Family history of gout, as well as comorbidities including any hepatic disease, cardiovascular disease, nephrolithiasis and self-reported hypertriglyceridaemia were similar between the groups (Table 1). No significant differences were detected between the two groups in concomitant medication proportions, such as ULTs, short-term etoricoxib therapy (120 mg/day for 3–5 days), colchicine and losartan (100 mg/day) (Table 1). During the follow-up period, the proportion (0.00% *vs* 2.03%; $P = 0.933$) of etoricoxib prescriptions for patients in a gout flare was similar between the nephrotoxicity and non-nephrotoxicity groups (Supplementary Table 1, available at *Rheumatology* online). Losartan (100 mg/day), an angiotensin receptor blocker, was prescribed in gout patients with hypertension. A similar proportion (4.00% *vs* 3.28%; $P = 0.295$) of patients initiated losartan during the follow-up period.

Baseline renal function

At baseline, patients in the fenofibrate-associated nephrotoxicity group had significantly higher median levels of SCr [1.01 mg/dl (IQR 0.88–1.22) *vs* 0.93 (0.84–1.03); $P < 0.001$), blood urea nitrogen [BUN; 5.80 mg/dl (IQR 4.60–7.30) *vs* 4.80 (4.00–5.80); $P < 0.001$] and BUN:SCr ratio [5.64 (IQR 4.81–6.45) *vs* 5.21 (4.26–6.25); $P = 0.008$] (Table 2). However, the eGFR [83.39 ml/min/1.73 m^2 (IQR 65.09–99.68) *vs* 94.59 (82.76–107.76); $P < 0.001$) and clearance rate of endogenous creatinine [96.00 ml/min (IQR 75.00–125.00) *vs* 122.00 (98.00–145.00); $P < 0.001$] were lower with no significant difference in SU levels between the two groups (Table 2).

Independent predictors of increased SCr in gout patients

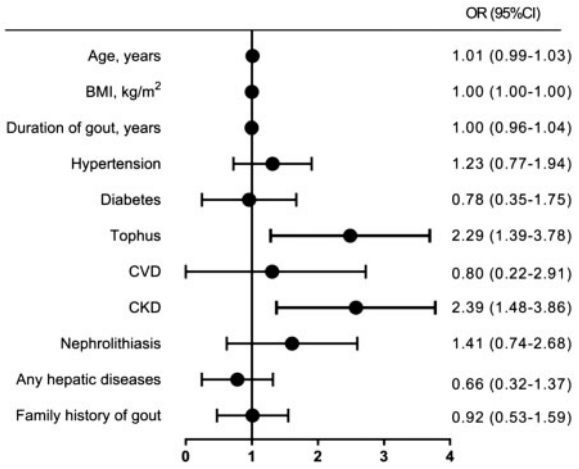
In the univariate analysis, age, BMI, duration of gout, tophus and hypertension were risk factors for nephrotoxicity (Table 1). The following covariates were introduced in a multivariate regression model: age, BMI, duration of gout, hypertension, diabetes, hypertriglyceridaemia, tophus, cardiovascular disease, CKD, nephrolithiasis, any hepatic disease and family history of gout. CKD [odds ratio (OR)2.39 (95% CI 1.48, 3.869)] and tophus [OR 2.29 (95% CI 1.39, 3.78)] were significantly related to increased SCr induced by fenofibrate in the final multivariate regression model (Fig. 2), both of which can be regarded as independent predictors of fenofibrate-associated nephrotoxicity in this cohort of gout patients.

We next explored the incidence of nephrotoxicity hierarchically in patients with tophus and/or CKD. Patients with tophus or CKD alone were susceptible to nephrotoxicity with incidences of 19.9% and 17.0%, respectively (Supplementary Fig. 2, available at *Rheumatology* online). The incidence increased to 31.0% when patients had both tophus and CKD (Supplementary Fig. 2, available at *Rheumatology* online). In a subgroup analysis based on eGFR (<60, ≥60, <90, ≥90 ml/min/1.73 m^2), we found that the lower the eGFR at baseline, the higher the incidence of nephrotoxicity after initiation of fenofibrate: 38.8%, 11.3% and 7.0%, respectively (Supplementary Fig. 2, available at *Rheumatology* online).

Time course of fenofibrate-associated nephrotoxicity

We also evaluated the trend in variables of SCr, SU and triglycerides during fenofibrate treatment in a GAMM (Fig. 3). Within 20 days after the initiation of fenofibrate, the overall SCr concentration in patients experiencing

Fig. 2 Multivariate regression analysis of risk factors for fenofibrate-associated nephrotoxicity



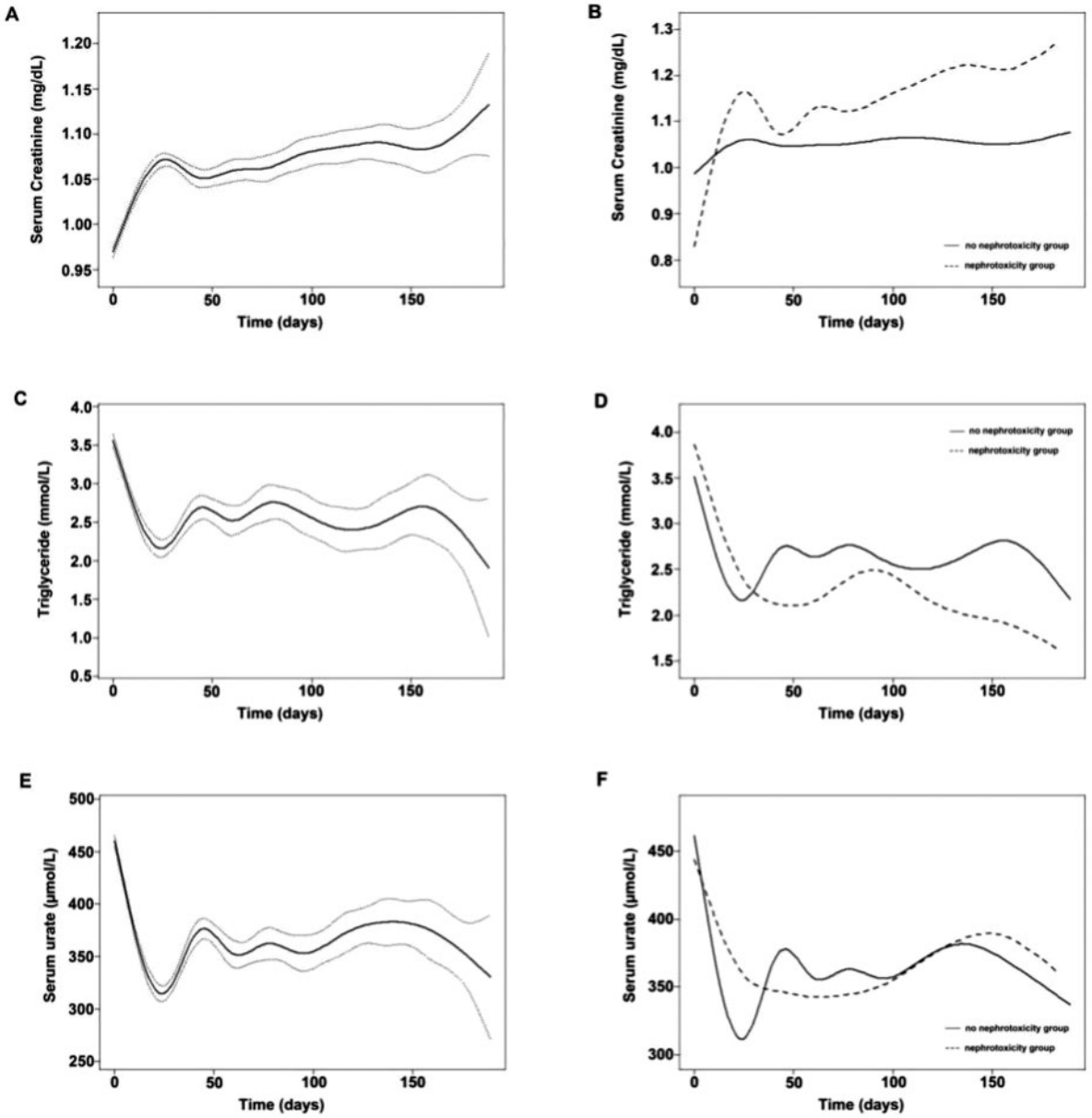
CVD: cardiovascular disease.

Table 2 Baseline renal function

Function	<0.3 mg/dl increase ($n = 883$)	≥0.3 mg/dl increase ($n = 100$)	*P*-value
SCr, mg/dl	0.93 (0.84–1.03)	1.01 (0.88–1.22)	<0.001
eGFR, ml/min/1.73 m^2	94.59 (82.76–107.76)	83.39 (65.09–99.68)	<0.001
BUN, mg/dl	4.80 (4.00–5.80)	5.80 (4.60–7.30)	<0.001
CCR, ml/min	122.00 (98.00–145.00)	96.00 (75.00–125.00)	<0.001
BUN: SCr ratio	5.21 (4.26–6.25)	5.64 (4.81–6.45)	0.008
SU, μmol/l	462.00 (359.00–566.00)	416.00 (324.75–579.75)	0.094

Values presented as median (IQR). CCR, creatinine clearance rate.

Fig. 3 Time course for creatinine and SU change on fenofibrate therapy



(**A**) Changes in SCr level over time on fenofibrate therapy in the whole population. (**B**) Changes in SCr level over time in the fenofibrate-associated nephrotoxicity group and no fenofibrate-associated nephrotoxicity group. (**C**) Changes in triglyceride levels over time on fenofibrate therapy in the whole population. (**D**) Changes in triglycerides level over time in the fenofibrate-associated nephrotoxicity group and no fenofibrate-associated nephrotoxicity group. (**E**) Changes in the SU level over time on fenofibrate therapy in the whole population. (**F**) Changes in the SU level over time in the fenofibrate-associated nephrotoxicity group and no fenofibrate-associated nephrotoxicity group. The dotted lines (A, C, E) represent the 95% CI.

nephrotoxicity was elevated (Fig. 3A). The difference in SCr elevation (from interaction analysis in the GAMM) was 0.0019 mg/dl/day (95% CI 0.0016, 0.0022; $P < 0.001$) between the fenofibrate-associated nephrotoxicity group and the non-nephrotoxic group (Fig. 3B). Both the SU concentrations (Fig. 3C) and triglyceride levels (Fig. 3E) of the entire cohort decreased at the initial stage of treatment and were stable thereafter. The difference was −0.0059 mmol/l/day (95% CI −0.0102, −0.0017; $P = 0.0063$) in triglyceride reduction (Fig. 3D) and 0.184 μmol/l/day (95% CI −0.097, 0.465; $P = 0.20$) in SU reduction (Fig. 3F) between the two groups.

The median change in SCr in the whole cohort was 0.11 mg/dl (IQR 0.03–0.20). The peak SCr in patients

TABLE 3 Renal function trends on fenofibrate therapy

Function	<0.3 mg/dl increase ($n = 883$)	≥0.3 mg/dl increase ($n = 100$)	*P*-value
Peak SCr, mg/dl	1.02 (0.93–1.14)	1.35 (1.26–1.63)	<0.001
Change in SCr, mg/dl	0.10 (0.03–0.17)	0.36 (0.33–0.45)	<0.001
Peak SU, μmol/l	329.00 (277.00–391.00)	334.50 (278.50–415.25)	0.248
Change in SU[a], μmol/l	−116.00 (−235.00 to −18.00)	−87.00 (−179.00–6.75)	0.083
Minimum SU, μmol/l	295.00 (252.00–345.00)	285.50 (241.25–334.75)	0.157
Change in SU[b], μmol/l	142.00 (47.00–259.00)	116.00 (43.75–253.25)	0.152
Peak eGFR, ml/min/1.73 m^2	84.85 (73.22–95.64)	58.84 (45.97 – 67.60)	<0.001
Change in eGFR[a], ml/min/1.73 m^2	−10.14 (−16.77 to −3.51)	−25.20 (−34.79 to −17.96)	<0.001
Minimum eGFR, ml/min/1.73 m^2, mean (S.D.)	83.89 (16.87)	55.58 (16.40)	<0.001
Change in eGFR[b], ml/min/1.73 m^2	10.25 (3.70–16.81)	25.50 (17.96–34.79)	<0.001

Values presented as median (IQR) unless stated otherwise. [a]Value is the change from baseline to peak SCr. [b]Value is the change from baseline to the minimum value over 6 months.

who presented with nephrotoxicity was 1.35 mg/dl (IQR 1.26–1.63) (Table 3), resulting from an increase of 0.36 mg/dl from initiation of fenofibrate to peak. The eGFR at the time of peak SCr decreased from 83.39 ml/min/1.73 m^2 (IQR 65.09–99.68) to 58.84 (45.97–67.60), falling by 29.5% in patients with nephrotoxicity, a greater reduction than in the non-nephrotoxic group ($P < 0.001$; Table 3). The change in SU concentration from baseline to the peak SCr was −116 μmol/l in the non-nephrotoxicity group and −87 μmol/l in the nephrotoxicity group, which was not significantly different ($P = 0.083$; Table 3). Moreover, the minimum SU and eGFR in patients with nephrotoxicity was 285.50 μmol/l (IQR 241.25–334.75) and 55.58 ml/min/1.73 m^2 (S.D. 16.40), respectively (Table 3).

Reversible effects of fenofibrate-associated nephrotoxicity

Most of the patients with fenofibrate-associated nephrotoxicity recovered after fenofibrate therapy withdrawal, as seen by the SCr decreasing back to the baseline level (Supplementary Fig. 3A, available at *Rheumatology* online). Of the 163 cases with records of fenofibrate discontinuation in this cohort, peak SCr returned to baseline in 107 (65.6%) patients after a mean time of 49 days (Supplementary Fig. 3B, available at *Rheumatology* online). However, 16 of 21 patients experiencing fenofibrate-associated nephrotoxicity did not return to the baseline SCr during the follow-up. Complications and renal function at baseline were similar in patients whose SCr returned to baseline and those whose did not (data not shown). In addition, the regimen of fenofibrate combined with the ULT febuxostat had a stronger effect on lowering SU levels than when combined with allopurinol and benzbromarone (−138.70 *vs* −75.18 *vs* −58.83 μmol/l; $P < 0.05$; Supplementary Fig. 4A, available at *Rheumatology* online), but no differences in renal function were indicated by SCr levels (Supplementary Fig. 4B, available at *Rheumatology* online).

Discussion

Fenofibrate-associated nephrotoxicity is often overlooked in the treatment of gout patients with hypertriglyceridaemia. Our retrospective study suggests that 10.2% of gout patients initiated on fenofibrate will develop an increase in SCr of ≥0.3 mg/dl. The incidence was higher when gout patients had the complications of tophus and/or CKD. The elevated SCr was reversible in 65.6% patients after fenofibrate withdrawal.

Fenofibrate, which can activate the nuclear transcription factor peroxisome proliferator-activated receptor (PPAR)-α [20], is a good option to lower SU concentrations in gout patients with hypertriglyceridaemia [21]. Fenofibrate induces an elevation in SCr in some individuals with mild renal insufficiency shortly after taking the drug [22]. A population-based study that included 80 453 patients reported that in the first 90 days of treatment, fenofibrate was associated with a 2.4-fold risk of hospitalization due to increased SCr compared with ezetimibe [23]. In this cohort, 9.1% of fenofibrate users had an increase of SCr >50% [23]. However, in some experimental cases, fenofibrate presents a renoprotective effect against nephropathy in the case of attenuating tubulointerstitial fibrosis and inflammation [24–26]. The application of fenofibrate in gout patients is also ubiquitous owing to its ability to reduce SU levels and the risk of gout attacks [12]. However, the renal safety of fenofibrate in gout patients is still unclear.

This study confirmed that fenofibrate-related nephrotoxicity occurs in >10% in a general cohort of gout patients and >30% in patients with tophus and CKD. Previously eGFR declined ∼1 ml/min/1.73 m^2/year, from 120–130 ml/min/1.73 m^2 in younger patients; those that declined >4 ml/min/1.73 m^2/year were considered 'fast progressors' [17, 27]. In our study, the fenofibrate-related nephrotoxicity group had an eGFR reduction of ∼25 ml/min/1.73 m^2 after fenofibrate initiation, whereas the predicted progression of CKD or chronic gouty nephropathy is generally <12 ml/min/1.73 m^2/year [28]. This indicates that the majority of nephrotoxicity during gout management is caused by fenofibrate.

Our results showed 18.9% of the patients had tophi and 16.7% had nephrolithiasis. Other studies have documented elevated SCr and decreased eGFR in gout patients complicated with tophi or CKD [29–31]. The increased risk of tophi for nephrotoxicity may result from increased urine urate excretion, which would cause renal overload during ULT in tophaceous gout. Additionally, urate stones deposited in the kidney result in renal interstitial fibrosis and renal tubular atrophy, further leading to renal arteriolar thickening, lumen stenosis and glomerulosclerosis [32]. As the presence of tophi, indicative of chronic refractory gout and renal dysfunction, inhibits both creatinine and urate clearance, it may predispose to the onset of fenofibrate-associated nephrotoxicity by this mechanism.

In this study, 65.6% of gout patients had a decrease in SCr to baseline levels after fenofibrate withdrawal, consistent with other studies. Lee *et al.* [13] found that SCr was temporarily increased after fenofibrate therapy but resolved after drug withdrawal. In the ACCORD Lipid Trial, after 5 years of continuous on-trial fenofibrate therapy, case subjects had the highest adjusted SCr *vs* control subjects [33]. After 51 days off the drug, SCr in the fenofibrate therapy group was comparable to that of control subjects [33]. Our and these studies support that fenofibrate-associated SCr elevation may be a short-term kidney event, and mainly reversible.

Our data also suggest a stronger effect on lowering urate of fenofibrate combined with febuxostat than with allopurinol or benzbromarone. Yamamoto *et al.* [34] reported that co-administration of allopurinol with fenofibrate was able to increase oxypurinol (an active allopurinol metabolite) clearance in addition to urate clearance. Fenofibrate and benzbromarone were both supposed to promote renal urate excretion by inhibiting URAT1 [35]. However, a more effective urate-lowering function of febuxostat in a Han Chinese cohort has been demonstrated [36].

A limitation of this study is its retrospective, observational design. Further, although it is useful to explore the incidence of adverse events, we were limited in our ability to evaluate any long-term effects. Moreover, the gout patients in the current study are Han Chinese, which potentially limits the generalizability.

Given fenofibrate administration is widely used in gout patients for the management of hypertriglyceridaemia, the current study provided significant evidence to the notion that prescribing fenofibrate to gout patients should be done cautiously in clinical practice, especially with tophi and renal dysfunction. Our evidence-based study may contribute to the development of guidelines.

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Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Dalbeth N, Choi HK, Joosten LAB *et al.* Gout. Nat Rev Dis Primers 2019;5:69.

2 Liu R, Han C, Wu D *et al.* Prevalence of hyperuricemia and gout in mainland China from 2000 to 2014: a systematic review and meta-analysis. Biomed Res Int 2015;2015:762820.

3 Choi HK, De Vera MA, Krishnan E. Gout and the risk of type 2 diabetes among men with a high cardiovascular risk profile. Rheumatology (Oxford) 2008;47:1567–70.

4 Roughley MJ, Belcher J, Mallen CD *et al.* Gout and risk of chronic kidney disease and nephrolithiasis: meta-analysis of observational studies. Arthritis Res Ther 2015;17:90.

5 Lee SJ, Hirsch JD, Terkeltaub R *et al.* Perceptions of disease and health-related quality of life among patients with gout. Rheumatology (Oxford) 2008;48:582–6.

6 Gao Q, Cheng X, Merriman TR *et al.* Trends in the manifestations of 9754 gout patients in a Chinese clinical center: a 10-year observational study. Joint Bone Spine 2020;105078.

7 Khanna D, Fitzgerald JD, Khanna PP *et al.* 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64:1431–46.

8 Richette P, Doherty M, Pascual E *et al.* 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76:29–42.

9 Hui M, Carr A, Cameron S *et al.* The British Society for Rheumatology guideline for the management of gout. Rheumatology (Oxford) 2017;56:e1–20.

10 FitzGerald JD, Dalbeth N, Mikuls T *et al.* American College of Rheumatology guideline for the management of gout. Arthritis Rheumatol 2020;72:879–95.

11 Takahashi S, Moriwaki Y, Yamamoto T *et al.* Effects of combination treatment using anti-hyperuricaemic agents with fenofibrate and/or losartan on uric acid metabolism. Ann Rheum Dis 2003;62:572–5.

12 Jung JY, Choi Y, Suh CH *et al.* Effect of fenofibrate on uric acid level in patients with gout. Sci Rep 2018;8: 16767.

13 Lee YH, Lee CH, Lee J. Effect of fenofibrate in combination with urate lowering agents in patients with gout. Korean J Intern Med 2006;21:89–93.

14 Neogi T, Jansen TL, Dalbeth N *et al.* 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2015;74: 1789–98.

15 Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. Crit Care Med 2008;36(4 Suppl):S216–23.

16 Attridge RL, Linn WD, Ryan L *et al.* Evaluation of the incidence and risk factors for development of fenofibrate-associated nephrotoxicity. J Clin Lipidol 2012;6:19–26.

17 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39(2 Suppl 1):S1–266.

18 Kuo CF, Grainge MJ, See LC *et al.* Familial aggregation of gout and relative genetic and environmental contributions: a nationwide population study in Taiwan. Ann Rheum Dis 2015;74:369–74.

19 Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.

20 Vu-Dac N, Schoonjans K, Kosykh V *et al.* Fibrates increase human apolipoprotein A-II expression through activation of the peroxisome proliferator-activated receptor. J Clin Invest 1995;96:741–50.

21 Takahashi S, Inokuchi T, Kobayashi T *et al.* Relationship between insulin resistance and low urinary pH in patients with gout, and effects of PPARalpha agonists on urine pH. Horm Metab Res 2007;39:511–4.

22 Hottelart C, el Esper N, Achard JM *et al.* [Fenofibrate increases blood creatinine, but does not change the glomerular filtration rate in patients with mild renal insufficiency]. Nephrologie 1999;20:41–4.

23 Zhao YY, Weir MA, Manno M *et al.* New fibrate use and acute renal outcomes in elderly adults: a population-based study. Ann Intern Med 2012;156:560–9.

24 Chen LL, Zhang JY, Wang BP. Renoprotective effects of fenofibrate in diabetic rats are achieved by suppressing kidney plasminogen activator inhibitor-1. Vascul Pharmacol 2006;44:309–15.

25 Li L, Emmett N, Mann D *et al.* Fenofibrate attenuates tubulointerstitial fibrosis and inflammation through suppression of nuclear factor-κB and transforming growth factor-β1/Smad3 in diabetic nephropathy. Exp Biol Med (Maywood) 2010;235:383–91.

26 Emami F, Hariri A, Matinfar M *et al.* Fenofibrate-induced renal dysfunction, yes or no? J Res Med Sci 2020;25: 39.

27 Stevens LA, Greene T, Levey AS. Surrogate end points for clinical trials of kidney disease progression. Clin J Am Soc Nephrol 2006;1:874–84.

28 Badve SV, Pascoe EM, Tiku A *et al.* Effects of allopurinol on the progression of chronic kidney disease. N Engl J Med 2020;382:2504–13.

29 Ma L, Sun R, Jia Z *et al.* Clinical characteristics associated with subcutaneous tophi formation in Chinese gout patients: a retrospective study. Clin Rheumatol 2018;37:1359–65.

30 Lu CC, Wu SK, Chen HY *et al.* Clinical characteristics of and relationship between metabolic components and renal function among patients with early-onset juvenile tophaceous gout. J Rheumatol 2014;41:1878–83.

31 Roughley M, Sultan AA, Clarson L *et al.* Risk of chronic kidney disease in patients with gout and the impact of urate lowering therapy: a population-based cohort study. Arthritis Res Ther 2018;20:243.

32 Turner JJ, Stacey JM, Harding B *et al.* UROMODULIN mutations cause familial juvenile hyperuricemic nephropathy. J Clin Endocrinol Metab 2003;88: 1398–401.

33 Mychaleckyj JC, Craven T, Nayak U *et al.* Reversibility of fenofibrate therapy-induced renal function impairment in ACCORD type 2 diabetic participants. Diabetes Care 2012;35:1008–14.

34 Yamamoto T, Moriwaki Y, Takahashi S *et al.* Effect of fenofibrate on plasma concentration and urinary excretion of purine bases and oxypurinol. J Rheumatol 2001;28:2294–7.

35 Derosa G, Maffioli P, Sahebkar A. Plasma uric acid concentrations are reduced by fenofibrate: a systematic review and meta-analysis of randomized placebo-controlled trials. Pharmacol Res 2015;102: 63–70.

36 Liang N, Sun M, Sun R *et al.* Baseline urate level and renal function predict outcomes of urate-lowering therapy using low doses of febuxostat and benzbromarone: a prospective, randomized controlled study in a Chinese primary gout cohort. Arthritis Res Ther 2019;21:200.