Effect of fenofibrate on uric acid level in patients with gout

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Gout is a chronic disease associated with deposition of monosodium urate crystals and accompanied by diabetes, hypertension, and dyslipidemia. Hyperuricemia is common among patients with gout, and fenofibrate is usually used to reduce triglyceride levels. The aim of this study is to determine the effect of uric acid reduction by fenofibrate in patients with gout administered uric acid lowering agents (viz., the xanthine oxidase inhibitors allopurinol and febuxostat). Data from 863 patients with gout were collected from electronic medical records comprising information on underlying diseases, laboratory findings, and drug histories. Among all the patients, 70 (8.11%) took fenofibrate with allopurinol or febuxostat. Male and young patients took fenofibrate more frequently, and hypertension was less frequent in patients administered xanthine oxidase inhibitors and fenofibrate than in those administered only xanthine oxidase inhibitors. After the treatment, serum uric acid levels more significantly decreased (−1.81 ± 2.41 vs. −2.40 ± 2.28 mg/dL, p = 0.043) in patients with fenofibrate cotreatment, than in those administered allopurinol or febuxostat alone. The effect of uric acid reduction was larger (b = −1.098, p < 0.001) in patients taking glucocorticoids than in those administered other treatments. There was no difference in the levels of creatinine, blood urea nitrogen, and aminotransferases between patients treated with and without fenofibrate. Fenofibrate additionally reduced uric acid levels without showing any change in the results of renal or liver function tests, suggesting that the addition of fenofibrate is a reasonable option for treating gout in patients having high triglyceride levels.
it enhances the oxidation of fatty acids in the liver and muscle and reduces hepatic lipogenesis13,14. Fibrates are fibric acid derivatives that activate the nuclear transcription factor peroxisome proliferator-activated receptor (PPAR)-α, which controls fatty acid transport and β-oxidation and results in a reduction in triglyceride levels and an increase in high-density lipoprotein cholesterol levels15,16. Fenofibrate is widely used to modify the lipid profile of patients with hypertriglyceridemia or type 2 diabetes and has a preventive effect on the progression of atherosclerosis in those patients17,18.

In clinical practice, physicians have prescribed fenofibrate for the treatment of hypertriglyceridemia in patients with gout. Fenofibrate has been reported to reduce serum uric acid levels in other populations19. However, the effect on the uric acid level or the adverse effect of fenofibrate coadministered with xanthine oxidase inhibitors has rarely been investigated in patients with gout. Only a few studies have examined by how much the uric acid level could be reduced by adding fenofibrate to patients with gout who received standard therapy.

Therefore, we sought to determine the effect of fenofibrate on the serum uric acid level in patients with gout by comparing serial serum uric acid levels between patients receiving xanthine oxidase inhibitors and fenofibrate and those receiving only xanthine oxidase inhibitors. In addition, we investigated whether fenofibrate coadministration affects renal or hepatic function in these patients.

### Results

#### Basic characteristics of patients with gout.

Table 1 shows the comparison of characteristics between patients administered allopurinol or febuxostat and patients cotreated with fenofibrate. Of the 863 patients with gout, 70 (8.1%) and 793 (91.9%) had prescriptions for allopurinol plus fenofibrate or febuxostat plus fenofibrate and allopurinol or febuxostat, respectively. Among them, 789 patients (91.4%) were men; the mean age was 50.6 ± 14.9 years; and 394 (45.7%) and 127 (14.7%) patients had hypertension and diabetes, respectively. The patients with gout on allopurinol plus fenofibrate or febuxostat plus fenofibrate were younger (46.9 ± 12.0 vs. 50.9 ± 15.1 years, \( p = 0.012 \)) and had less hypertension (22/70, 31.4 vs. 372/793, 46.9%, \( p = 0.013 \)) than those with gout who were not on fenofibrate. The levels of serum triglyceride decreased from 418.4 ± 190.0 to 316.2 ± 185.2 mg/dL, \( p = 0.002 \), suggesting good fenofibrate treatment adherence of the patients.

#### Comparison of uric acid reduction between patients treated with and without fenofibrate.

Changes in serum uric acid levels with and without fenofibrate are shown in Fig. 1. Before the medication, the average uric acid level did not differ between the patients on allopurinol or febuxostat and those on allopurinol plus fenofibrate or febuxostat plus fenofibrate (8.89 ± 2.01 vs. 8.74 ± 1.66 mg/dL, \( p = 0.548 \)). After treatment, both groups showed decreased serum uric acid levels, which more significantly decreased in patients cotreated with fenofibrate than in those on allopurinol or febuxostat alone (−1.81 ± 2.41 vs. −2.40 ± 2.28 mg/dL, \( p = 0.043 \)).

Table 2 shows the results of the linear multiple regression, which assessed the association between the types of medication and change in serum uric acid levels. Even after adjusting for the confounders, we found that the serum uric acid level decreased more in patients on allopurinol plus fenofibrate or febuxostat plus fenofibrate than it did in patients with gout but not treated with fenofibrate (\( b = -0.879, p = 0.003 \)). Furthermore, serum uric acid levels decreased more in patients with gout who were administered glucocorticoids than in patients who were not (\( b = -1.098, p < 0.001 \)).

The levels of serum uric acid at enrolment were compared to the levels before the index measure to exclude spontaneous changes of serum uric acid. Pre-enrollment levels of serum uric acid were collected at the closest measurement between 30 and 150 days prior to the time of enrolment. There was no difference in the levels of serum uric acid between before and at enrolment (Supplementary Table 1).

#### Comparison of the results of renal and liver function tests between patients treated with and without fenofibrate.

Table 3 shows the results of the liver and renal function tests before and after the use of medication according to the treatment groups. Mean creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels before and after medication were not significantly different between patients on allopurinol or febuxostat and those on allopurinol plus fenofibrate or febuxostat plus fenofibrate.

### Discussion

In addition to gout, hyperuricemia also leads to hypertension, diabetes, and dyslipidemia, and has become a public health burden worldwide because of its high prevalence and clinical significance20. Although uric acid has a beneficial effect as an oxygen radical scavenger, hyperuricemia correlates closely with cardiovascular risk and all-cause mortality21,22,11.12. The aging society and decreased human physical activity caused by social development, have increased the incidence of gout with obesity, dyslipidemia, diabetes, hypertension, and hyperuricemia23.

In this study, we analyzed the clinical data of 863 patients with gout who were administered xanthine oxidase inhibitors, and fenofibrate decreased the uric acid level by approximately 0.73 mg/dL. Furthermore, cotreatment with fenofibrate and xanthine oxidase inhibitors did not affect the serum levels of the kidney and liver function markers.

Several studies have examined the effect of fenofibrate on uric acid levels in gout. The studies showed that uric acid levels decreased by 19 and 23% after fenofibrate treatment of patients with gout who were on urate-lowering agents24,25. However, although the reduction of urate levels was assessed in a small number (10 and 14) of patients with gout, this study collected sufficient clinical data to evaluate the general effect of fenofibrate. Furthermore, in the previous studies, patients treated with only allopurinol were enrolled, whereas our patients were prescribed allopurinol or febuxostat. Febuxostat is considered more effective than allopurinol in achieving target uric acid level23,26.
The uric acid levels were reduced in patients taking xanthine oxidase inhibitors and fenofibrate compared with those taking only xanthine oxidase inhibitors (−1.81 vs. −2.4 mg/dL, \( p = 0.043 \)). Fenofibrate decreases serum uric acid levels by increasing urinary excretion of uric acid by inhibiting the renal organic anion transporter urate transporter 1 (URAT1; solute carrier family 22 member 12, SLC22A12) \(^{19,27} \). Moreover, it was shown to raise urinary pH, and acidic urinary pH could be associated with the formation of uric acid stones, which is one of the comorbidities of gout and a common complication of uricosuric agents \(^{28} \). Therefore, the addition of fenofibrate is reasonable, considering that agents that increase the renal excretion of uric acid are likely to lead to the development of uric acid stones.

More studies on the effect of fenofibrate on uric acid reduction were carried out in patients with hypertriglyceridemia or diabetes \(^{19,29,30} \). The characteristics of study participants by treatment groups are shown in Table 1. SD: standard deviation; NSAIDs: nonsteroidal anti-inflammatory drugs; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA.

![Table 1. Characteristics of study participants by treatment groups. SD: standard deviation; NSAIDs: nonsteroidal anti-inflammatory drugs; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA.](https://example.com/table1.png)
diabetes (FIELD) study conducted to determine the effect of fenofibrate on type 2 diabetes, uric acid levels were decreased by 10.3% in 622 patients with diabetes who took allopurinol. In addition, the first gout event in 5 years was more frequent with placebo treatment than with fenofibrate among patients with diabetes.

Treatment strategies for acute gout such as the use of anti-inflammatory drugs including colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids are frequently maintained because of the need for prophylaxis to prevent further recurrent gout flares. In this study, among the treatments with anti-inflammatory drugs, statins, and angiotensin receptor modulating agents, glucocorticoids were correlated significantly with uric acid reduction. This finding could be explained by the fact that glucocorticoids enhance urinary excretion of uric acid by directly acting on uric acid transport in the renal tubules. Moreover, the effect of glucocorticoids on lowering uric acid was similar to that of allopurinol in previous reports.

Since mild liver biochemical abnormalities are known to occur in 5–10% of patients on fenofibrate, baseline and regular periodic aminotransferase testing is recommended. Fenofibrate-induced hepatotoxicity is hepatocellular, cholestatic, or of a mixed pattern, and ranges from an acute and self-limiting to chronic liver injury. However, in this study, there was no differences in the levels of AST and ALT between patients treated with and without fenofibrate. Furthermore, previous studies showed the beneficial effects of fenofibrate on levels of liver enzymes in patients with fatty liver and its preventive effects on fatty liver disease in mice.

A limitation of this study is the lack of data on gout flares, which should ultimately be prevented in the treatment of gout. However, this is a novel study that investigated the effect of fenofibrate on the reduction of uric acid in a large population of patients with gout who were administered febuxostat and allopurinol. The status of these patients is significant because it is similar to that in the current clinical situation, indicating that it could be applied to the management of patients with gout and elevated triglycerides. Another limitation is that during the study period of more than 20 years, there have been changes in the use of the drug for lowering serum uric acid level because febuxostat was introduced in 2012 in the subject hospital. However, there was no significant difference in the ratio of the prescription count of allopurinol and febuxostat between two the treatment groups (group without fenofibrate vs. with fenofibrate) as shown in Supplementary Table 2. Finally, our analysis did not contain a confirmation for patient adherence to medication. It is a well-known and inevitable limitation of retrospective data. However, the level of adherence would be randomly distributed in both treatment groups, and there are no indications or factors that adherence was higher in a certain group as compared to that in the other group.

In conclusion, this data shows that the addition of fenofibrate reduced uric acid levels in patients with gout who were taking allopurinol or febuxostat, and they showed no significant change in renal or hepatic functions. Therefore, cotreatment of fenofibrate with xanthine oxidase inhibitors might be a favorable therapeutic strategy in patients with gout who have hypertriglyceridemia.

**Methods**

**Data source and study participants.** We used the data from the electronic medical record (EMR) system of the Ajou University Hospital, which has been operating as a tertiary teaching hospital in Korea since 1994. The EMR system collects information based on unique, de-identified numbers for patients combined with their age and sex, the diagnostic codes based on the International Classification of Diseases (ICD-10), admission and discharge dates, laboratory test results, and prescribed medications/treatments from about 2.9 million...
patients (including 543,617 inpatients). The information about diagnostic codes including combined diseases was obtained from the EMR and validated by manual chart review (H.-A.K. and J.-Y.J).

To investigate the effect of allopurinol or febuxostat with fenofibrate on uric acid levels, we selected 3,608 patients with gout (ICD-10 code: M10.x) between 1995 and 31 February 2018. Among the 3,608 patients, we first selected patients treated for at least 30 consecutive days with allopurinol or febuxostat (n = 2,299). We excluded those who did not have a uric acid test within 2 months before taking allopurinol or febuxostat (n = 710) and within 2 months after taking allopurinol or febuxostat for 30 days (n = 566).

We excluded 160 patients with uric acid levels < 6.0 before medication use. Finally, this study included the 863 patients with gout. The flowchart for selecting the study participants is displayed in Fig. 2. In addition, we

| Variables | b  | S.E. | 95% CI | p-value |
|-----------|----|------|--------|---------|
| Treatment groups |    |      |        |         |
| allopurinol or febuxostat | Ref. |      |        |         |
| allopurinol or febuxostat + fenofibrate | -0.879 | 0.300 | -1.468 | -0.290 | 0.003 |
| Sex |    |      |        |         |
| Men | Ref. |      |        |         |
| Women | 0.456 | 0.285 | -0.103 | 1.015 | 0.110 |
| Age |    |      |        |         |
| < 29 | Ref. |      |        |         |
| 30–39 | 0.353 | 0.353 | -0.338 | 1.044 | 0.317 |
| 40–49 | 0.213 | 0.345 | -0.464 | 0.890 | 0.538 |
| 50–59 | 0.052 | 0.352 | -0.637 | 0.741 | 0.883 |
| 60–69 | -0.105 | 0.374 | -0.837 | 0.628 | 0.779 |
| 70– | -0.364 | 0.387 | -1.122 | 0.394 | 0.346 |
| Hypertension |    |      |        |         |
| No | Ref. |      |        |         |
| Yes | -0.330 | 0.176 | -0.675 | 0.015 | 0.061 |
| Hyperlipidemia |    |      |        |         |
| No | Ref. |      |        |         |
| Yes | 0.024 | 0.180 | -0.329 | 0.376 | 0.896 |
| Diabetes mellitus |    |      |        |         |
| No | Ref. |      |        |         |
| Yes | -0.048 | 0.230 | -0.499 | 0.404 | 0.836 |
| Colchicine |    |      |        |         |
| No | Ref. |      |        |         |
| Yes | 0.158 | 0.188 | -0.211 | 0.527 | 0.400 |
| Steroid |    |      |        |         |
| No | Ref. |      |        |         |
| Yes | -1.098 | 0.182 | -1.454 | -0.742 | <0.0001 |
| NSAID |    |      |        |         |
| No | Ref. |      |        |         |
| Yes | 0.127 | 0.177 | -0.220 | 0.475 | 0.472 |
| HMG-CoA reductase inhibitor |    |      |        |         |
| No | Ref. |      |        |         |
| Yes | -0.405 | 0.388 | -1.167 | 0.356 | 0.297 |
| Angiotensin receptor |    |      |        |         |
| No | Ref. |      |        |         |
| Yes | 0.466 | 0.360 | -0.240 | 1.172 | 0.195 |
| Year of diagnosis |    |      |        |         |
| 1995–2000 | Ref. |      |        |         |
| 2001–2005 | 0.843 | 0.701 | -0.531 | 2.218 | 0.229 |
| 2006–2010 | 1.489 | 0.692 | 0.133 | 2.846 | 0.031 |
| 2011–2015 | 0.505 | 0.688 | -0.843 | 1.852 | 0.463 |
| 2016–2018 | 0.128 | 0.697 | -1.238 | 1.495 | 0.854 |

Table 2. Association between treatment groups (with and without fenofibrate) and change in serum acid level. SD: standard deviation; NSAIDs: nonsteroidal anti-inflammatory drugs; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA. Outcome variable was change in serum uric acid level (‘after drug administration’ minus ‘before drug administration’). The negative estimation means decreased average serum uric acid level compared with the reference group.
eliminated 98 patients who did not have renal and liver function tests within 2 months before taking allopurinol or febuxostat and within 2 months after taking allopurinol or febuxostat for 30 days, to examine whether patients taking additional fenofibrate had adverse drug effects on the liver or kidneys.

**Outcomes.** The primary outcome was serum uric acid (mg/dL), which was measured within 2 months before the date of prescription of hypouricemic agents and within 2 months after a consecutive 30-days of prescription of hypouricemic agents. Renal (creatinine and BUN) and liver (AST and ALT) function tests were performed within the same period.

**Exposure.** The patients were classified into two treatment groups using prescribed medication based on data extracted from the EMR of Ajou University: (1) the group administered allopurinol or febuxostat for 30 consecutive days, and (2) the group co-administered fenofibrate during 30-days of allopurinol or febuxostat treatment.

**Confounders.** Data on demographics, comorbidities, and use of other medication were included in this study. All confounders were assessed during the period of exposure. The demographic factors were sex and age. Comorbidities (hypertension, hyperlipidemia, and diabetes mellitus) were included by reviewing the patients’ prescriptions in the medical records. Medication for the treatment of patients with gout were included: NSAIDs,

|                     | Total N | No treatment | With treatment |
|---------------------|---------|--------------|---------------|
|                     | Mean/n  | SD/Row%      | Mean/n        | SD/Row%      |
| Creatinine (mg/dL)  |         |              |               |              |
| allopurinol or febuxostat | 762     | 1.81         | 2.01          | 1.84         | 2.18         |
| allopurinol or febuxostat plus fenofibrate | 68      | 1.21         | 0.29          | 1.26         | 0.27         |
| BUN (mg/dL)         |         |              |               |              |
| allopurinol or febuxostat | 760     | 22.23        | 17.22         | 23.07        | 18.6         |
| allopurinol or febuxostat plus fenofibrate | 68      | 15.54        | 8.04          | 15.24        | 5.07         |
| AST (IU/L)          |         |              |               |              |
| allopurinol or febuxostat | 760     | 28.89        | 22.33         | 30.15        | 21.31        |
| allopurinol or febuxostat plus fenofibrate | 69      | 33.58        | 22.14         | 33.09        | 17.6         |
| ALT (IU/L)          |         |              |               |              |
| allopurinol or febuxostat | 759     | 35.79        | 44.0          | 35.72        | 30.15        |
| allopurinol or febuxostat plus fenofibrate | 67      | 46.16        | 39.86         | 40.09        | 27.23        |
| AST*                |         |              |               |              |
| allopurinol or febuxostat | 698     | 11           | 1.6           | 16           | 2.3          |
| allopurinol or febuxostat plus fenofibrate | 67      | 3            | 4.5           | 1            | 1.5          |
| ALT*                |         |              |               |              |
| allopurinol or febuxostat | 698     | 26           | 3.7           | 31           | 4.4          |
| allopurinol or febuxostat plus fenofibrate | 67      | 6            | 9.0           | 3            | 4.5          |
| Bilirubin           |         |              |               |              |
| allopurinol or febuxostat | 755     | 0.73         | 0.37          | 0.76         | 0.41         |
| allopurinol or febuxostat plus fenofibrate | 68      | 0.71         | 0.35          | 0.68         | 0.25         |
| Total cholesterol   |         |              |               |              |
| allopurinol or febuxostat | 758     | 181.0        | 42.0          | 180.96       | 39.83        |
| allopurinol or febuxostat plus fenofibrate | 68      | 203.2        | 43.7          | 190.81       | 38.15        |
| HDL cholesterol     |         |              |               |              |
| allopurinol or febuxostat | 430     | 42.91        | 12.18         | 42.91        | 12.18        |
| allopurinol or febuxostat plus fenofibrate | 56      | 39.13        | 9.99          | 39.13        | 9.99         |
| LDL cholesterol     |         |              |               |              |
| allopurinol or febuxostat | 187     | 113.71       | 38.41         | 109.49       | 34.26        |
| allopurinol or febuxostat plus fenofibrate | 23      | 120.04       | 39.71         | 102.27       | 42.5         |
| Triglyceride        |         |              |               |              |
| allopurinol or febuxostat | 469     | 196.41       | 106.76        | 187.71       | 109.39       |
| allopurinol or febuxostat plus fenofibrate | 62      | 418.42       | 190.01        | 316.17       | 185.15       |
| Glucose             |         |              |               |              |
| allopurinol or febuxostat | 754     | 110.41       | 33.86         | 106.55       | 28.27        |
| allopurinol or febuxostat plus fenofibrate | 68      | 106.68       | 27.09         | 105.39       | 27.03        |

**Table 3.** Results of laboratory tests before and after medication use according to medication treatment groups. SD: standard deviation; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; HDL: high density lipoprotein; LDL: low density lipoprotein. *The number and proportion of patients who exceed three times of the maximum normal range before and after medication.
glucocorticoids (methylprednisolone, prednisolone, deflazacort, triamcinolone, and hydrocortisone), and colchicine. This study also included drugs that could affect serum uric acid level, viz., statin and angiotensin receptors.

**Statistical analysis.** We compared the characteristics of the allopurinol or febuxostat and allopurinol plus fenofibrate or febuxostat plus fenofibrate groups using chi-square and independent *t*-test. We used the independent *t*-test to compare the difference in serum uric acid levels between the two groups (allopurinol or febuxostat vs. allopurinol plus fenofibrate or febuxostat plus fenofibrate). Two-way ANOVA was used for testing the interaction effect between two the treatment groups and time. Multiple linear regression was conducted to determine the effect of fenofibrate on the difference (‘after drug administration’ minus ‘before drug administration’) in serum uric acid levels in patients with gout. To examine whether patients coadministered fenofibrate had adverse drug reactions, we calculated the average creatinine, BUN, AST, and ALT values before and after medication based on the groups. For the liver function test, we calculated the number and proportion of patients who exceed three times of the maximum normal range before and after medication. A *p* < 0.05 was considered statistically significant. Data were managed using the Microsoft SQL Server (Microsoft Corp), and all statistical analyses were conducted using the SAS software package (ver. 9.4; SAS Institute, Cary, NC, USA).

**Ethics statement.** This study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-OBS-18-102), which waived the requirement for informed consent because the anonymized data were analyzed retrospectively.

**Data Availability Statement**
The datasets analyzed during the current study are not publicly available due to legal restrictions imposed by the government of South Korea in relation to the Personal Information Protection Act, but are available from the corresponding author on reasonable request.

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