Effect of Long-term Fenofibrate Therapy on Serum Creatinine and Its Reversibility in Hypertriglyceridemic Patients with Hypertension

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Objective: Previous studies have shown that fenofibrate therapy increases serum creatinine level and that there is a return of serum creatinine to baseline level after the discontinuation of the drug. We evaluated the effect of long-term fenofibrate therapy on creatinine levels and its reversibility in patients with hypertension and hypertriglyceridemia.

Methods: This retrospective study enrolled 54 hypertensive and hypertriglyceridemic patients taking fenofibrate for 3-6 years (Fenofibrate group) and 30 control patients with similar age, sex, follow-up duration, and creatinine levels (Control group). In 23 patients taking fenofibrate with low triglyceride level and/or with high creatinine levels, fenofibrate was discontinued, and creatinine levels were measured after 2 months.

Results: Creatinine levels increased in both the fenofibrate group (from 0.91±0.18 mg/dL to 1.09±0.23 mg/dL, p<0.001) and the control group (from 0.94±0.16 mg/dL to 0.98±0.16 mg/dL, p=0.04) compared to baseline. However, the elevation was more pronounced in the fenofibrate group than in the control group (21.1±15.4% vs. 4.5±11.3%, p<0.001). The discontinuation of fenofibrate lowered creatinine levels (from 1.39±0.32 mg/dL to 1.15±0.24 mg/dL, p<0.001) which were still higher than pre-treatment levels (p=0.013).

Conclusion: Long-term fenofibrate therapy significantly increased creatinine levels in hypertensive and hypertriglyceridemic patients. The effect of fenofibrate on creatinine level was partially reversible. This finding suggests that follow-up creatinine level is necessary with fenofibrate therapy. (J Lipid Atheroscler 2017 December;6(2):89-96)

Key Words: Fenofibrate, Creatinine, Hypertension, Hypertriglyceridemia, Nephrotoxicity

INTRODUCTION

Fibrate, a peroxisome proliferator-activated receptor α agonist, is effective in raising high-density lipoprotein-cholesterol (HDL-C) levels and to lower triglyceride levels.1,2 Fibrate is generally well tolerated although it is associated with a slightly increased risk for hepatotoxicity, myopathy, cholelithiasis, and venous thrombosis.3 In addition, previous studies have shown that fenofibrate increases the creatinine level, although it is not associated with an increased risk for both acute and chronic renal failure.4-9

Recent large-scale studies have investigated the effect of fenofibrate on the prevention of cardiovascular events in patients with diabetes with various types of dyslipidemias.7-9 However, the results were uncertain and
fenofibrate was effective only in hypertriglyceridemic patients with or without low HDL-C.

Hypertension is a major risk for cardiovascular morbidity and mortality, and is frequently associated with other risk factors including dyslipidemia. Fenofibrate is often prescribed in these patients.10,11

We observed the effect of long-term fenofibrate therapy on creatinine levels and its reversibility in hypertensive and hypertriglyceridemic patients.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board of Chung-Ang University Hospital. This retrospective study enrolled 54 patients with hypertension and hypertriglyceridemia (≥ 200 mg/dL) who were taking fenofibrate (200 mg of fenofibrate or 160 mg of micronized fenofibrate) for 3 to 6 years and in whom pre- and post-treatment creatinine levels were available (Fenofibrate group). Patients with abnormal renal function (baseline creatinine >1.3 mg/dL) were excluded. Pre-treatment creatinine levels were measured within 6 months before starting the medication. Among these patients, creatinine levels after treatment for 1 to 3 years were also available in 40 patients. As a control group, 30 patients who had similar age, sex, follow-up duration, creatinine levels, and lipid profiles compared with the fenofibrate group (Control group) were selected. These patients preferred lifestyle modifications and did not want the medications. Patients with additional lipid-lowering drugs other than fibrates during follow-up period were not excluded.

In 23 patients with ongoing fenofibrate therapy, fenofibrate was discontinued because triglyceride levels were low enough to discontinue the drug and/or because creatinine levels were over upper normal limit. And, creatinine levels were measured after 2 months.

After overnight fasting, blood samples were obtained. Concentrations of total cholesterol (Olympus Diagnostica, Hamburg, Germany) and triglyceride (Wako Pure Chemical Industries, Ltd, Osaka, Japan) were determined by the enzymatic method using an automatic analyzer (AU5400, Olympus Corporation, Tokyo, Japan). The concentration of HDL-C was measured by selective elimination method (Wako Pure Chemical Industries, Ltd, Osaka, Japan) using an automatic analyzer. The concentration of creatinine was measured by the Jaffe reaction (Olympus Life and Material Science, Hamburg, Germany) on an automatic analyzer, using calibrators supplied by the manufacturer.

Data are expressed as mean±standard deviation. Statistical analysis was performed using the Social Package for Social Science (SPSS version 23, SPSS Inc., Chicago, IL, USA). For non-normally distributed variables, the Wilcoxon signed-rank test was used to compare concentrations before and after therapy, and the Mann-Whitney U test was used to evaluate differences between groups. For other variables, the paired t-test was used to compare the concentrations before and after medication, and the Student’s t-test was used to evaluate differences between groups. The distribution of discrete variables was analyzed using the χ² test. The relations between parameters were analyzed using the Pearson correlation method. Non-normally distributed variables were transformed logarithmically if necessary. The stepwise linear regression method was used to obtain independent variables. The simple and forward logistic regression tests were used to obtain independent parameters between two groups. Two-tailed p value <0.05 was considered statistically significant.

RESULTS

Baseline demographic, clinical, and laboratory characteristics were similar between the fenofibrate and control groups (Table 1) except aspartate aminotransferase levels
Table 1. Comparisons of Baseline Demographic and Clinical Characteristics between the Control and Fenofibrate Groups

|                         | Control (n=30) | Fenofibrate (n=54) | p value |
|-------------------------|---------------|-------------------|---------|
| Men/women               | 16/14         | 34/20             | 0.49    |
| Age (years)             | 59.0±9.5      | 56.1±10.0         | 0.21    |
| Body mass index (kg/m²)| 25.7±2.79     | 25.8±2.98         | 0.90    |
| Hypertension            | 100%          | 100%              | 1.00    |
| Ischemic heart disease  | 20%           | 15%               | 0.56    |
| Diabetes mellitus       | 20%           | 19%               | 1.00    |
| Alcohol                 | 40%           | 50%               | 0.49    |
| Smoking                 | 17%           | 28%               | 0.30    |
| Medications             |               |                   |         |
| Aspirin                 |               |                   |         |
| Ca channel blocker      | 47%           | 30%               | 0.16    |
| Diuretics               | 57%           | 65%               | 0.49    |
| Beta blocker            | 53%           | 59%               | 0.65    |
| ACEI or ARB             | 33%           | 52%               | 0.12    |
| Statin                  | 23%           | 15%               | 0.38    |
| Metformin               | 3%            | 11%               | 0.41    |
| Sulfonylurea            | 10%           | 13%               | 1.00    |
| Nitrate                 | 13%           | 9%                | 0.72    |
| Follow-up duration (years) | 4.08±0.58   | 4.22±0.85         | 0.43    |
| Creatinine (mg/dL)      | 0.94±0.16     | 0.91±0.18         | 0.38    |
| BUN (mg/dL)             | 14.8±3.66     | 15.5±5.12         | 0.49    |
| Cholesterol (mg/dL)     | 203±39.0      | 208±33.8          | 0.56    |
| HDL-C (mg/dL)           | 43.3±7.59     | 40.4±7.78         | 0.10    |
| nHDL-C (mg/dL)          | 160±35.5      | 168±32.1          | 0.28    |
| LDL-C (mg/dL)           | 97.5±36.3     | 99.6±25.4         | 0.79    |
| Triglyceride (mg/dL)    | 334±127       | 369±163           | 0.14    |
| AST (IU/L)              | 31.3±12.9     | 25.6±7.92         | 0.033   |
| ALT (IU/L)              | 33.0±17.8     | 30.2±13.4         | 0.41    |
| Creatine kinase (IU/L)  | 91±33.6       | 100±47.3          | 0.37    |

ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, BUN: blood urea nitrogen, HDL-C: high density lipoprotein cholesterol, nHDL-C: non-high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, AST: aspartate aminotransferase, ALT: alanine aminotransferase

Table 2. Comparisons of percent changes in renal functions and lipid profiles between the control and fenofibrate groups

|                         | Fenofibrate (n=54) | Control (n=30) | p value* |
|-------------------------|-------------------|---------------|----------|
| Percent change          | p value**         | Percent change | p value** | p value* |
| Creatinine              | 21.1±15.4         | 0.000         | 4.5±11.3 | 0.04     | 0.000    |
| BUN                     | 19.0±37.1         | 0.025         | 25.4±28.0| 0.000    | 0.30     |
| Cholesterol             | -6.9±17.7         | 0.001         | -6.2±18.3| 0.021    | 0.93     |
| HDL-C                   | 18.6±21.5         | 0.000         | 8.4±22.4 | 0.12     | 0.024    |
| nHDL-C                  | -12.5±21.4        | 0.000         | -9.1±23.1| 0.006    | 0.52     |
| LDL-C***                | 25.3±34.6         | 0.000         | 22.7±53.0| 0.39     | 0.40     |
| Triglyceride            | -56.1±24.7        | 0.000         | -16.8±58.3| 0.003   | 0.000    |

BUN: blood urea nitrogen, HDL-C: high density lipoprotein cholesterol, nHDL-C: non-high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol

*; control versus fenofibrate groups, **; baseline versus follow-up, ***; in patients with TG<400 mg/dL

<0.033).

Creatinine levels increased in both the fenofibrate group (from 0.91±0.18 mg/dL to 1.09±0.23 mg/dL, <0.001) and the control group (from 0.94±0.16 mg/dL to
Fig. 1. Changes in creatinine levels of patients in the fenofibrate group with available levels after medication for 1–3 years (solid) and in the control group (dotted). *; p<0.05 versus baseline levels.

Fig. 2. Comparisons of creatinine levels at baseline, fenofibrate therapy for 5.4 years, and withdrawal of fenofibrate for 2 months. *; p<0.05 versus baseline levels, **; p<0.05 versus levels after fenofibrate therapy.

Table 3. Parameters associated with percent changes of creatinine levels

|                        | Total     |                          |                                      |                          |                          |
|------------------------|-----------|--------------------------|-------------------------------------|--------------------------|--------------------------|
|                        | r        | p value                 | r                                   | p value                 | r                          |
| Sex                    | 0.20     | 0.063                    | 0.10                                | 0.60                    | 0.29                      | 0.031                    |
| Age                    | -0.08    | 0.45                     | -0.04                               | 0.84                    | 0.01                      | 0.94                     |
| Body mass index        | 0.14     | 0.22                     | 0.20                                | 0.29                    | 0.13                      | 0.34                     |
| Alcohol                | 0.12     | 0.29                     | 0.20                                | 0.29                    | 0.18                      | 0.19                     |
| Smoking                | 0.22     | 0.045                    | 0.14                                | 0.46                    | 0.28                      | 0.040                    |
| Diabetes mellitus      | 0.25     | 0.023                    | 0.15                                | 0.44                    | 0.36                      | 0.007                    |
| IHD                    | 0.02     | 0.82                     | 0.35                                | 0.060                   | 0.12                      | 0.40                     |
| Cholesterol            | -0.08    | 0.49                     | 0.17                                | 0.36                    | -0.26                     | 0.061                    |
| HDL-C                  | -0.10    | 0.36                     | 0.25                                | 0.18                    | -0.11                     | 0.43                     |
| nHDL-C                 | -0.05    | 0.67                     | 0.13                                | 0.49                    | -0.24                     | 0.076                    |
| LDL-C                  | -0.10    | 0.45                     | 0.20                                | 0.32                    | -0.34                     | 0.037                    |
| Triglyceride           | 0.03     | 0.77                     | -0.04                               | 0.84                    | -0.02                     | 0.87                     |
| AST                    | -0.10    | 0.36                     | -0.03                               | 0.88                    | 0.09                      | 0.54                     |
| ALT                    | 0.05     | 0.65                     | 0.05                                | 0.81                    | 0.15                      | 0.27                     |
| BUN                    | 0.12     | 0.29                     | -0.27                               | 0.15                    | 0.19                      | 0.18                     |
| Creatinine             | -0.06    | 0.62                     | -0.24                               | 0.21                    | 0.06                      | 0.64                     |
| Follow-up duration     | 0.10     | 0.39                     | 0.23                                | 0.22                    | 0.01                      | 0.96                     |
| Fenofibrate therapy    | 0.50     | 0.000                    | -                                   | -                       | -                         | -                        |

IHD: Ischemic heart disease, HDL-C: high density lipoprotein cholesterol, nHDL-C: non-high density lipoprotein cholesterol, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, FU: follow-up.

0.98±0.16 mg/dL, p=0.04). However, the elevation was more pronounced in the fenofibrate group than in the control group (21.1±15.4% vs. 4.5±11.3%, p<0.001, Table 2).

In patients with available creatinine levels after the medication for 1 to 3 years in the fenofibrate group (n=40, mean follow-up 1.90±0.58 years), creatinine levels increased from 0.91±0.19 mg/dL to 1.05±0.22 mg/dL (p<0.001). After then, creatinine levels showed the trend to rise slightly to 1.08±0.24 mg/dL after 4.27±0.82 years although it didn’t reach statistical significance (p=0.14, Fig. 1).
Table 4. Comparisons of parameter according to change of creatinine levels

| Parameter                        | <0.2 mg/dL (n=52) | ≥0.2 mg/dL (n=32) | p value |
|----------------------------------|-------------------|-------------------|---------|
| Men/women                        | 30/22             | 20/12             | 0.82    |
| Age (years)                      | 57.0±10.4         | 57.4±9.1          | 0.85    |
| Body mass index (kg/m²)          | 25.4±2.94         | 26.5±2.74         | 0.09    |
| Ischemic heart disease           | 19%               | 13%               | 0.55    |
| Diabetes mellitus                | 14%               | 28%               | 0.10    |
| Alcohol                          | 46%               | 47%               | 1.00    |
| Smoking                          | 17%               | 34%               | 0.11    |
| Follow-up duration (years)       | 4.02±0.78         | 4.21±0.77         | 0.31    |
| Creatinine (mg/dL)               | 0.94±0.04         | 0.88±0.09         | 0.10    |
| BUN (mg/dL)                      | 14.9±5.14         | 15.9±3.68         | 0.33    |
| Cholesterol (mg/dL)              | 204±43.5          | 211±35.8          | 0.41    |
| HDL-C (mg/dL)                    | 41.4±6.95         | 41.5±9.12         | 0.95    |
| nHDL-C (mg/dL)                   | 163±34.4          | 169±32.6          | 0.40    |
| LDL-C (mg/dL)                    | 96.7±30.8         | 102±28.9          | 0.48    |
| Triglyceride (mg/dL)             | 357±169           | 357±120           | 0.30    |
| AST (IU/L)                       | 28.3±11.2         | 26.6±8.7          | 0.48    |
| ALT (IU/L)                       | 30.9±16.2         | 31.7±13.2         | 0.82    |
| Fenofibrate therapy             | 46%               | 94%               | 0.000   |

BUN: blood urea nitrogen, HDL-C: high density lipoprotein cholesterol, nHDL-C: non-high density lipoprotein cholesterol, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

The discontinuation of fenofibrate for 2 months lowered creatinine levels from 1.39±0.32 mg/dL to 1.15±0.24 mg/dL (n=23, p<0.001). In patients with available pre-treatment creatinine levels (n=16), creatinine levels increased from 1.06±0.25 mg/dL to 1.42±0.36 mg/dL after fenofibrate therapy for 5.6±4.3 years (p<0.001) and decreased to 1.18±0.27 mg/dL after the discontinuation of fenofibrate (p<0.001), which was significantly still higher than pre-treatment levels (p=0.013, Fig. 2).

In all patients, the elevation of creatinine levels were related to fenofibrate therapy (r=0.50, p<0.001), the presence of diabetes mellitus (r=0.25, p=0.023), and non-smoking status (r=0.22, p=0.045). Among these parameters, fenofibrate therapy and the presence of diabetes mellitus were independent variables (Table 3).

In the fenofibrate group, the elevation of creatinine levels were related to the presence of diabetes mellitus (r=0.36, p=0.007), higher low-density lipoprotein cholesterol level (LDL-C, r=0.34, p=0.037), female gender (r=0.29, p=0.031), and non-smoking status (r=0.28, p=0.040). Among these parameters, only diabetes mellitus was an independent variable. In the control group, none of parameters were associated with changes in creatinine levels.

When all patients were divided into two groups according to changes of creatinine levels (≥0.2 mg/dL versus <0.2 mg/dL), only fenofibrate therapy was related to changes of creatinine levels. The presence of diabetes mellitus didn’t reach statistical significance (p=0.10, Table 4).

**DISCUSSION**

This retrospective study confirmed that fenofibrate therapy increased creatinine levels mainly during the early period of therapy in patients with hypertension and hypertriglyceridemia, and suggested that this phenomenon might be partially reversible.

An increase in creatinine level has been reported with
all kinds of fibrates, such as bezafibrate, ciprofibrate, fenofibrate, and less commonly gemfibrozil,4-6,12 and it has been noted in large scale and long-term follow-up trials with fenofibrate, such as the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.8,9 The present study reconfirmed the findings of previous studies in hypertensive and hypertriglyceridemic patients. To evaluate the clinical significance of the change of serum creatinine by fenofibrate, further studies are necessary.

Most of the previous studies have observed the effect of fenofibrate on renal function in patients with hyperlipidemia, abnormal renal function, or diabetes mellitus.7-9,13-15 Hypertension is one of the most important risk factors for cardiovascular diseases and is frequently associated with low HDL-C and high triglyceride levels.10,11 In subgroup analysis of large scale studies, fenofibrate showed the cardioprotective effects only in hypertriglyceridemic patients with or without low HDL-C.8,9 Therefore, the present study observed the effect of fenofibrate on renal function in patients with both hypertension and hypertriglyceridemia in whom fibrate may be beneficial for the prevention of cardiovascular diseases.

Previous small sized trials with short-term follow-up have reported that fenofibrate elevates creatinine level by 14 to 27% in patients with abnormal renal function13-15 and by 13% in subjects with normal renal function.16 In the present study, creatinine levels increased more by 0.15 mg/dL (17%) in the fenofibrate group than in the control group. Because the present study had long-term follow-up duration in patients with normal renal function, this finding may be consistent with those of previous studies.

Creatinine levels remained an average of 0.11~0.13 mg/dL (12.5%) higher in the fenofibrate group than in the control group in the FIELD study.8 Furthermore, the difference in changes in creatinine levels between the fenofibrate group and the control group was only 0.06 mg/dL (6%) in the ACCORD study.9

This discrepancy of renal effects of fenofibrate among studies can be explained by the study protocols. In the FIELD study, 20% of the fenofibrate group had discontinued the study drug by the end of the trial. However, they were followed up until death or study closure. It may have made the difference in creatinine levels between two groups less. In addition, fenofibrate was stopped when there was a rise in creatinine to >1.8 mg/dL. The number of patients in whom fenofibrate was discontinued due to this criterion is unclear in the paper. However, the incidence of raised creatinine >2.3 mg/dL was 1% (48 patients) in the control group and 2% (73 patients) in the fenofibrate group.8

In the ACCORD study, fenofibrate dose was reduced in patients with baseline eGFR<50 mL/min/1.73m² and fenofibrate was discontinued if an eGFR fell <30 mL/min/1.73m². At the last clinic visit, 440 patients (15.9%) in the fenofibrate group and 194 patients (7.0%) in the placebo group were receiving a reduced dose. Fenofibrate was discontinued by 66 patients (2.4%) in the fenofibrate group and 30 patients (1.1%) in the placebo group.9 Considering the patients in whom the dose was adjusted or in whom the drug was discontinued during follow-up, the effect of fenofibrate on renal function may be underestimated in these studies.

Renal function deteriorates more rapidly in diabetic patients than in patients without diabetes mellitus.17,18 In the present study, creatinine levels increased more in patients with diabetes mellitus than in those without diabetes mellitus. Large scale studies were performed in patients with diabetes mellitus.7,9 However, 19% of patients had diabetes mellitus in the present study. Therefore, the underestimation of fenofibrate effect on renal function in large scale studies may be more than that shown from data.

In the placebo group, creatinine level increased by 0.019
mg/dL (1.7 μmol/L) per year in the FIELD study\textsuperscript{19} and 0.023 mg/dL per year in the ACCORD study.\textsuperscript{9} The elevation is much higher compared to 0.008 mg/dL per year in the present study. The difference may be also explained by the proportion of patients with diabetes mellitus.

Significant elevations of creatinine levels occur during the early period of fenofibrate therapy. Small sized trials with short-term follow-up period have shown significant increases of creatinine levels with fenofibrate therapy.\textsuperscript{13-16} In the FIELD study, creatinine levels were mainly elevated during 6 week run-in period and slightly further till 4 month follow-up.\textsuperscript{19} In the ACCORD study, creatinine levels in the fenofibrate group increased within the first year and remained relatively stable thereafter.\textsuperscript{9} The present study showed similar trend that most elevation of creatinine levels was observed after fenofibrate therapy for 1 to 3 years.

The FIELD study suggested early rise of creatinine levels and subsequent attenuation of the rate of renal function decline with fenofibrate therapy.\textsuperscript{19} After initial rise of creatinine levels till 4 month follow-up, further rise (4 months to close-out) was smaller with fenofibrate than with placebo (0.018 mg/dL/year versus 0.021 mg/dL/year, \(p=0.01\)). In the present study, creatinine levels increased by 0.022 mg/dL/year (1.99 years to 4.27 years) in the fenofibrate group and by 0.008 mg/dL/year in the placebo group (\(p=0.62\)). This difference may be also associated with the cessation of study drug in patients with creatinine levels >1.8 mg/dL in the FIELD study.\textsuperscript{19}

Previous studies have reported that creatinine levels decreased after stopping fenofibrate.\textsuperscript{19,20} However, it is unclear whether the reversibility is complete or partial. A small-sized report in patients with renal dysfunction observed that creatinine levels decreased, however, not to pretreatment levels.\textsuperscript{20} The result of the present study was consistent with that of this study. In the FIELD study, creatinine levels were significantly lower in the fenofibrate group than in the placebo group at 8 weeks after withdrawal of study drugs and it was suggested that fenofibrate had renoprotective effect in conjunction with the effect on albuminuria.\textsuperscript{19} Further studies are needed to establish the degree of reversibility.

It is also controversial about the mechanism for the elevation of creatinine levels with fenofibrate therapy. Several small-sized studies have reported that fenofibrate does not change or showed the trend to decrease glomerular filtration rates without statistical significance.\textsuperscript{13-15} It was reported that fibrates increased creatinine production with no attenuation of the glomerular filtration rate.\textsuperscript{13} Therefore, it has been postulated that the increase in serum creatinine level may reflect an induced elevation of the production rate of creatinine. In contrast, others have reported decreased creatinine clearance,\textsuperscript{16} pathological changes in proximal tubule without damages of the basement membrane or substantial interstitial inflammation of the kidney in renal transplant recipients suggesting a toxic etiology,\textsuperscript{21} and concomitant elevations of blood urea nitrogen (BUN), cystatin C, and homocysteine suggesting decreased glomerular filtration rates.\textsuperscript{22} In the present study, BUN levels increased in both the fenofibrate group and the control group.

There are several limitations of this study. It is a retrospective study and there might be an inhomogeneity between 2 groups. The number of patients is smaller than previous large-scale studies. This study was performed in a single hospital in Asia. The effect of added medications during follow-up period was not evaluated.

In conclusion, fenofibrate therapy significantly increased blood creatinine levels. The elevation occurred in early phase of the medication and might not be completely reversible. Therefore, it is necessary to monitor creatinine levels during the early period of fenofibrate therapy.

**CONFLICTS OF INTEREST**

The authors have no potential conflicts of interest to
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