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Effect and safety of pemafibrate for patients with type 2 diabetes mellitus and hypertriglyceridemia: a retrospective analysis of clinical data

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Abstract

Objectives Fibrates are suitable for the treatment of patients with high triglyceride (TG) levels. Although pemafibrate (PEMA) has been reported to have beneficial and pleiotropic actions, clinical examinations of the efficacy of PEMA for Japanese patients with hypertriglyceridemia are still limited in actual clinical settings. The aim was to evaluate the efficacy of PEMA by analyzing data from diabetic patients treated with PEMA in clinical practice.

Methods Patients with type 2 diabetes mellitus and hypertriglyceridemia who were started on PEMA for at least 3 months were included in the analysis. Changes in lipid metabolism, liver function, renal function, and blood tests from before to after 3 months of PEMA treatment were evaluated.

Results A total of 100 eligible patients were included in the analysis (72 males, mean age 52.9 years). TG levels decreased significantly, and high-density lipoprotein cholesterol levels increased significantly after 3 months of therapy. Low-density lipoprotein cholesterol levels were not significantly changed. Liver-related parameters showed a significant decrease. In addition, a significant decrease in creatinine levels was found in patients switching from other fibrates. There were no severe adverse events.

Conclusion PEMA showed beneficial effects on lipid metabolism and liver function. The improvement of lipid metabolism was found in patients switching from other fibrates. It is possible that PEMA may improve lipid metabolism in patients with hypertriglyceridemia.

Clinical trial number Not applicable.

Keywords Pemafibrate, Hypertriglyceridemia, Type 2 diabetes mellitus, Triglyceride, Liver function

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Introduction

Low-density lipoprotein cholesterol (LDL-C) is one of the most important risk factors for atherosclerotic cardiovascular disease (ASCVD) [1], and primary and secondary prevention of ASCVD with statins has been investigated in numerous studies [2]. Because the goal of lipid-lowering therapy is to prevent the onset of ASCVD, and lower LDL-C levels substantially decrease the risk of ASCVD [3], statins are widely used as first-line agents for strict control of LDL-C levels.

Epidemiological studies and clinical trials have also shown that hypertriglyceridemia, in addition to high LDL-C levels, is an independent risk factor for ASCVD [4, 5]. Triglycerides (TGs) are an energy source in heart or skeletal muscle and are stored as energy in adipose tissue [6]. Although TG levels themselves are unlikely to be a risk factor for ASCVD compared to LDL-C level, TG-rich lipoproteins may be involved in plaque formation [7]. High TG and low high-density lipoprotein cholesterol (HDL-C) levels are often associated with metabolic syndrome or type 2 diabetes mellitus. Even when LDL-C levels are well controlled by statin treatment, elevated TG levels are considered a residual risk factor for ASCVD [8, 9].

There are three subtypes (α, γ, and β/δ) of peroxisome proliferator-related receptors (PPARs), and fibrates have been reported to lower TG levels by activating PPARα, thus reducing the incidence of ASCVD with monotherapy [10, 11]. However, with bezafibrate and fenofibrate, the risks in patients with rhabdomyolysis or reduced renal function limit their use in combination with statins, or their off-target effects are clinical issues. Pemafibrate (PEMA) was approved for clinical use in Japan in 2018. PEMA showed more selective and potent activation of PPARα compared with other fibrates [12] and was shown to be as effective as fenofibrate in lowering TG levels [13]. In addition, there have been many reports that PEMA improves liver function because of its characteristics, and it has also been reported that, unlike other existing fibrates, the route of excretion has little adverse effect on renal function [14]. However, clinical examinations of the efficacy of PEMA for Japanese patients with hypertriglyceridemia are still limited in actual clinical settings.

The aim of this study was to explore the clinical characteristics of PEMA treatment by analyzing data from patients who were treated with PEMA in clinical practice. The effects of PEMA on hepatic and renal function, as well in treatment-emergent type 2 diabetes mellitus with hypertriglyceridemia, were examined.

Methods

Study design

This was a retrospective, observational study that analyzed clinical data from a single clinical institution in Japan. Data for all patients who received PEMA were retrospectively extracted from the electronic medical records of patients regularly attending the Okamoto Internal Medicine Clinic, Tokyo Japan, between July 2018 and March 2023. PEMA-treated patients fulfilling the following criteria were eligible: (1) age 20 years or older at the time of PEMA administration; (2) TG ≥ 150 mg/dL at the time of PEMA administration; and (3) treated for type 2 diabetes mellitus with stable HbA1c (Hemoglobin A1c) and BMI (Body mass index) levels. The allowance for changes in body weight and HbA1c was ± 10%. The exclusion criteria were as follows: (1) a history of hypersensitivity to any of the ingredients of the PEMA formulation; (2) serious liver injury, Child-Pugh class B or C cirrhosis, or biliary obstruction; (3) gallstones; (4) pregnant or potentially pregnant women; and (5) cyclosporine or rifampicin treatment.

Patients were switched from other fibrates to PEMA or newly prescribed PEMA with or without statins; PEMA 0.1 mg was taken orally twice daily in the morning and evening. The maximum dose was 0.2 mg twice daily. In addition, the dosage and administration of hypoglycemic drugs or lipid metabolism-improving drugs administered prior to the start of PEMA were not changed in principle.

Data handling

The baseline of the study was the time of the first PEMA prescription, and clinical data recorded at baseline and 3 months (± 2 weeks) after the start of PEMA were used in the analysis. From the clinical data, the following were extracted at baseline and 3 months after the start of PEMA administration: body weight, HbA1c, lipid profile [LDL-C, HDL-C, TG], liver-related parameters [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyltransferase (γGTP), albumin, lactate dehydrogenase (LDH)], renal function parameters [creatinine, estimated glomerular filtration rate (eGFR), uric acid, urea nitrogen (BUN)], and blood tests [white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, creatine kinase (CK)]. ALT measured by the JSCC method was converted to the IFCC method.

Evaluation items

The primary evaluation for the clinical efficacy of PEMA was the changes in TG and HDL-C levels from baseline to 3 months. Secondary evaluations were changes in LDL-C levels, liver function, and renal function. These assessments were also performed in patients who switched from other fibrates to PEMA.

Statistical analysis

Sample size estimation was not performed because this was an analysis of data used in clinical practice. However,

Table 1 Participants' baseline characteristics (*N* = 100)

	***N* (%) or mean (SD)**	
Sex (male)	72.0	(72.0)
Age (y)	59.2	(9.9)
BMI (kg/m^2)	26.3	(4.1)
Weight (kg)	73.6	(14.4)
HbA1c (%)	6.61	(0.77)
Triglycerides (mg/dL)	278.9	(136.4)
HDL-C (mg/dL)	49.2	(9.9)
LDL-C (mg/dL)	93.2	(19.9)
Serum creatinine (mg/dL)	0.78	(0.19)
eGFR (mL/min/1.73 m^2)	77.5	(16.8)

Data are n (%) or mean (SD; standard deviation) values

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate

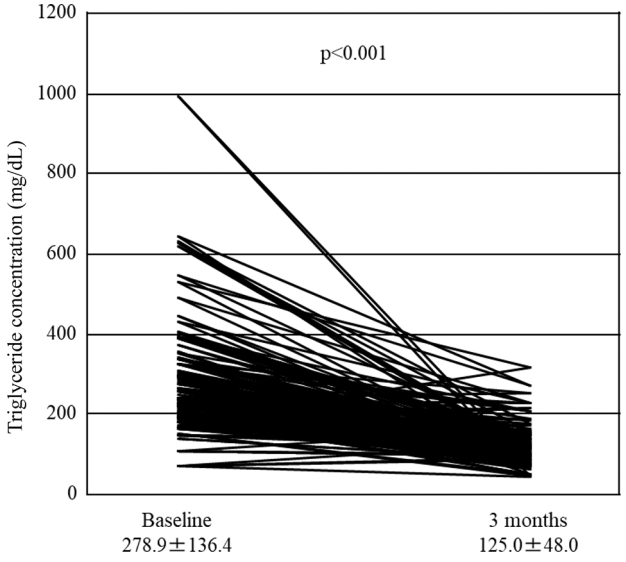

Fig. 1 Changes in triglyceride levels from before to after 3 months of pemafibrate treatment. Baseline and 3-month comparisons of continuous variables were performed using the paired t-test or Wilcoxon's rank-sum test

the sample size of 100 patients used in this analysis could detect at least a 25 mg/dL reduction in the TG level with 90% statistical power (β), using a significance level (α) of 0.05. Continuous variables are expressed as mean and standard deviation values, and categorical variables are expressed as frequencies and percentages. Baseline and 3-month comparisons of continuous variables were performed using the paired *t*-test or Wilcoxon's rank-sum test. The significance level was at less than 5%.

The study plan was approved by the Okamoto Internal Medicine Clinic Committee and complied with the Declaration of Helsinki and the "Ethical Guidelines for Medical Research Involving Human Subjects". The research protocol was reviewed and approved by the Ethics Committee of Juntendo University (no. E22-0436), and written, informed consent was obtained from all participants.

Table 2 Comparisons of parameters of lipid metabolism and liver and renal function between baseline and 3 months (*N* = 100)

	Baseline		**3 months**		***p* value**
Triglycerides (mg/dL)	278.9	(136.4)	125.0	(48.0)	< 0.001
HDL-C (mg/dL)	49.2	(9.9)	56.2	(12.4)	< 0.001
Triglyceride/HDL-C ratio	5.99	(3.27)	2.43	(1.34)	< 0.001
LDL-C (mg/dL)	93.2	(19.9)	91.9	(23.3)	0.557
AST (IU/L)	28.0	(17.7)	24.5	(13.6)	< 0.001
ALT (IU/L)	35.2	(29.0)	23.9	(15.9)	< 0.001
ALP (IU/L)*	119.9	(85.2)	82.1	(59.4)	< 0.001
γGTP (IU/L)	64.8	(100.6)	36.5	(40.4)	< 0.001
Uric acid (mg/dL)	5.21	(1.22)	5.18	(1.22)	0.678
Serum creatinine (mg/dL)	0.78	(0.19)	0.78	(0.17)	0.196
eGFR (mL/min/1.73 m^2)	77.5	(16.8)	75.3	(15.9)	0.037

Data are mean (standard deviation) values. P values are for comparisons between baseline and 3 months after the start of pemafibrate

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphate; γGTP, γ-glutamyl transpeptidase; eGFR, estimated glomerular filtration rate

* The value of ALP measured by the JSCC method was converted to the value of the IFCC method

Results

A total of 322 patients were prescribed PEMA; of them, 100 (72 males) met the eligibility criteria. Table 1 shows the background information of the 100 patients included in this analysis. The patients' mean age was 58.2 ± 9.9 years, and their mean BMI was 26.3 ± 4.1 kg/m^2; their mean body weight and mean HbA1c levels were 73.6 ± 1.4. kg and 6.61 ± 0.77% at baseline and 73.6 ± 14.1 kg and 6.54 ± 0.52% at 3-month follow-up, respectively. There were no significant changes between baseline and 3-month follow-up ($p = 0.771$ and $p = 0.791$, respectively).

Primary evaluation

The TG level was significantly decreased, from 278.9 ± 136.4 mg/dL at baseline to 125.0 ± 48.0 mg/dL at 3-month follow-up ($p < 0.001$, Fig. 1; Table 2), and the change in the TG level was 153.9 ± 130.1 mg/dL. The HDL-C level increased significantly, from 49.2 ± 9.9 mg/dL at baseline to 56.2 ± 12.4 mg/dL at 3-month follow-up ($p < 0.001$, Fig. 2; Table 2). The TG/HDL-C ratio decreased significantly, from 5.99 ± 3.27 to 2.43 ± 1.34 after 3 months ($p < 0.001$).

Secondary evaluation

Table 2 shows the comparisons of the parameters between baseline and 3 months. AST, ALT, ALP, and γGTP levels were significantly lower, and the albumin level was significantly higher. Of the renal function parameters, creatinine was not significantly changed, but eGFR showed a significant, but slight, decrease (Table 2). Uric acid and BUN were not significantly changed (Table 2).

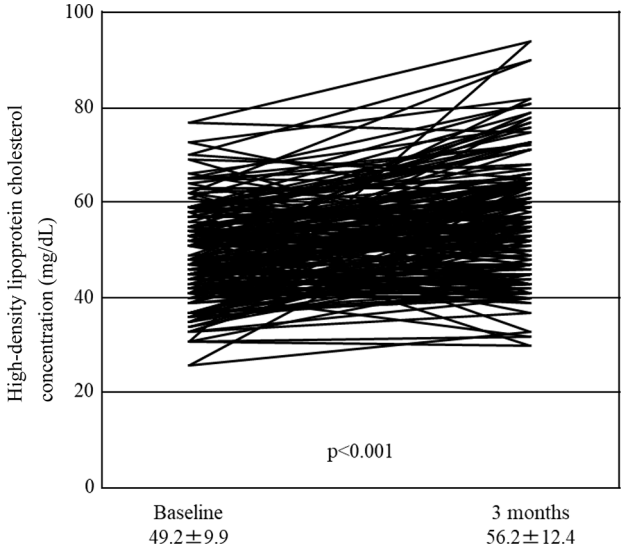

Fig. 2 Changes in high-density lipoprotein cholesterol levels from before to after 3 months of pemafibrate treatment. Baseline and 3-month comparisons of continuous variables were performed using the paired t-test or Wilcoxon's rank-sum test

Table 3 Comparisons of parameters of lipid metabolism and liver and renal function in patients switched from other fibrates between baseline and 3 months (*N* = 14)

	Baseline		3 months		*p* value
Triglycerides (mg/dL)	207.7	(95.8)	130.8	(49.6)	0.004
HDL-C (mg/dL)	50.4	(6.4)	53.2	(9.8)	0.135
Triglyceride/HDL-C ratio	4.30	(2.28)	2.62	(1.23)	0.003
AST (IU/L)	32.3	(16.0)	26.4	(8.5)	0.074
ALT (IU/L)	35.4	(23.4)	25.3	(11.8)	0.044
ALP (IU/L)*	65.1	(19.8)	59.5	(20.5)	0.184
γGTP (IU/L)	61.4	(37.8)	40.3	(15.9)	0.034
Serum creatinine (mg/dL)	0.91	(2.00)	0.78	(0.13)	0.001
eGFR (mL/min/1.73 m^2)	65.5	(13.5)	75.4	(9.6)	< 0.001

Data are mean (standard deviation) values. P values are for comparisons between baseline and 3 months after the start of pemafibrate

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphate; γGTP, γ-glutamyl transpeptidase; eGFR, estimated glomerular filtration rate

* The value of ALP measured by the JSCC method was converted to the value of the IFCC method

Switching from other fibrates

Table 3 shows changes in evaluation parameters in the 14 patients switched from other fibrates to PEMA. Of them, 9 patients had received bezafibrate, and 5 patients had received fenofibrate. In these 14 patients, TG, ALT, and γGTP levels were significantly decreased, and renal function parameters (creatinine and eGFR) were also significantly improved.

Safety

Table 4 shows changes in the safety parameters. No serious adverse events and no adverse drug reactions due to PEMA administration were observed. A significant decrease in hemoglobin and a significant increase in the platelet count were observed, but these changes were minimal. The CK level was not significantly changed.

Table 4 Changes in the safety parameters (*N* = 100)

	Baseline		3 months		*p* value
White blood cell count (/μL)	6914	(1753.7)	6747	(1941.1)	0.210
Red blood cell count (10^4/μL)	490.9	(52.4)	486.8	(51.3)	0.076
Hemoglobin (g/dL)	14.8	(1.6)	14.6	(1.5)	< 0.001
Hematocrit (%)	45.7	(4.5)	45.1	(4.3)	0.005
Platelet count (10^4/μL)	24.8	(6.0)	26.2	(6.4)	< 0.001
Serum albumin (g/dL)	4.46	(0.3)	4.54	(0.3)	0.001
LDH (U/L)	172.9	(35.2)	169.8	(36.8)	0.292
BUN (mg/dL)	15.1	(3.5)	15.2	(3.3)	0.760
CK (U/L)	106.5	(82.0)	112.2	(92.9)	0.249

Data are mean (standard deviation) values. P values are for comparisons between baseline and 3 months after the start of pemafibrate

LDH, lactate dehydrogenase; BUN, urea nitrogen; CK, creatine kinase

Discussion

This retrospective, observational study showed that TG levels were significantly decreased, and HDL-C levels were increased after the start of PEMA, with unchanged body weight and HbA1c levels. Together with these changes, liver function parameters (AST, ALT, ALP, and γGTP) improved.

PEMA is a compound with strong PPARα activation and very high PPARα selectivity, synthesized from analyses of the conformation and ligand-binding mode of PPARα protein, and it is positioned as a selective PPARα modulator (SPPARαM) [15]. A multicenter, placebo-controlled, double-blind, randomized trial reported that PEMA 0.4 mg/day showed almost the same TG-lowering effect as micronized fenofibrate 200 mg/day (equivalent to a 160-mg tablet), and the adverse event rate was similar to that of placebo and lower than that of fenofibrate [16]. In addition, another clinical study in high-TG patients with treated type 2 diabetes mellitus showed that PEMA 0.4 mg reduced TG levels and increased HDL-C levels [17]. In these studies, TG levels before PEMA treatment were different, but PEMA 0.4 mg/day resulted in a 51.9% or 45.1% reduction in TG levels. In the present analysis, the reduction in TG levels was 55.2% (from 278.9 mg/dL to 125.0 mg/dL), similar to the previous clinical studies. The increase in HDL-C levels after the start of PEMA was also confirmed in the present analysis. In addition to the present results, the PEMA-induced TG-lowering effect was comparable with or without statins in the pooled data analysis of clinical trials [18]. Thus, PEMA may have efficacy for hypertriglyceridemia treatment in clinical practice.

Compared with existing fibrates, PEMA has more pleiotropic effects and is also likely to be useful in improving blood glucose levels and preventing the progression of renal function decline by improving insulin resistance in type 2 diabetes mellitus [18]. In cases of high TG levels associated with type 2 diabetes mellitus, PEMA should be used more aggressively than other fibrates.

The present findings showed the improvement of liver-related parameters in addition to that of the lipid profile after the start of PEMA. The number of non-alcoholic fatty liver disease (NAFLD) cases has increased due to the increased prevalence of obesity and metabolic syndrome [19]. Patients with NAFLD are likely to have high TG, low HDL-C, and high LDL-C levels, along with abnormal liver function. It is possible that PEMA may contribute to liver function improvement through an increase in fibroblast growth factor 21 (FGF21), which is also a lifestyle-related disease-improving factor [20], although FGF21 levels were not evaluated in the present study. In studies involving patients with NAFLD, it was confirmed that PEMA significantly improved liver function parameter[s] [21, 22]. Further evaluations of liver function including liver fibrosis are needed to confirm the role of PEMA in the treatment of NAFLD.

Limitations

This study has several limitations worth noting. First, there may have been selection bias given the small sample size and the fact that patients were from one medical institution that specializes in diabetes treatment. Therefore, application to actual clinical settings could be limited. A large-scale, multicenter, controlled study will be needed. Second, the study lacked a control group, and participants were receiving a heterogeneous group of concomitant glucose-lowering drugs. These may lead to less novelty. Additional study, which includes a control/comparator group, is required. Third, important factors such as health behavior were not evaluated. Such factors should also be evaluated in future studies. Finally, the follow-up period of 6 months was relatively short. As a next step, cohort studies with longer follow-up periods should be conducted to assess long-term outcomes, including glycemic control.

Conclusion

PEMA showed beneficial effects on lipid metabolism and liver function, with no deterioration of renal function. Improvement of lipid metabolism was found in patients switching from other fibrates. It is possible that PEMA may improve lipid metabolism in patients with hypertriglyceridemia.

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Author contributions
All authers contributed to study conception and design. Material preparation, datacollection, and analysis were performed by AO and TN. The first draft of the manuscript was written by AO and HY, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasetes generated and/or analyzed during the current study are bot publicly avaiable due to private and ethical considerations but can be avaiable from the corresponding author on reasonable request. Yhe datasets that support the conclusion in the article.

Declarations

Ethics approval and informed consent
The study plan was approved by the Okamoto Internal Medicine Clinic Committee and complied with the Declaration of Helsinki and the Ethical Guidelines for Medical Research Involving Human Subjects. The research protocol was reviewed and approved by the Ethics Committee of Juntendo University (no. E22-0436), and written, informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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