Renal Replacement Therapy

CASE REPORT

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Case series showing the safety and changes in lipid profiles of hemodialysis patients with hypertriglyceridemia after pemafibrate administration

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Abstract

Background Cardiovascular disease is a major cause of morbidity and mortality in patients with chronic kidney disease and end-stage renal disease (ESRD). Dyslipidemia is a key focus of cardiovascular therapy and is characterized by hypertriglyceridemia mainly caused by lipoprotein lipase-mediated metabolism of ApoC-III in patients with ESRD. Pemafibrate, a selective peroxisome proliferator-activated receptor alpha modulator, can be used regardless of renal function and inhibit ApoC-III expression in the liver.

Case presentation We reported the cases of four patients on hemodialysis who met at least 175 mg/dL of triglycerides on the consecutive three tests between September 2022 and November 2022 and took 0.1 mg pemafibrate twice a day from November 2022 to May 2023. They experienced no adverse events after pemafibrate treatment. Pemafibrate significantly reduced triglyceride (TG) (302 ± 72 to 140 ± 50 mg/dL, $p = 0.048$), total cholesterol (187 ± 34 to 156 ± 48 mg/dL, $p = 0.025$), and Apo C-III (15.9 ± 8.2 to 12.6 ± 7.1, $p = 0.030$) levels. Apo A-II levels significantly increased after treatment (27.0 ± 6.1 to 37.1 ± 5.8, $p = 0.041$).

Conclusions Pemafibrate decreased TG, total cholesterol, and Apo-CIII and increased Apo A-II without adverse events. Further study is needed to examine the favorable effects of pemafibrate on the risk of CVD.

Keywords Hemodialysis, Dyslipidemia, Apolipoprotein, Pemafibrate

Background

Cardiovascular disease is a major cause of morbidity and mortality in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) [1]. Although numerous modifiable risk factors for the development of cardiovascular disease and associated mortality have been identified, dyslipidemia remains an essential focus of cardiovascular therapy [2, 3]. Dyslipidemia associated with ESRD is characterized by hypertriglyceridemia and elevated serum concentrations of triglyceride (TG)-rich lipoproteins such as very low-density lipoprotein

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(VLDL), intermediate-density lipoprotein (IDL), and chylomicron remnants [2]. Hypertriglyceridemia in patients with CKD and ESRD results from increased production and decreased clearance of TG-rich lipoproteins [3]. Although the relationships of the serum total cholesterol level with mortality and cardiovascular events in the long-term dialysis population differ from those in the general population due to chronic inflammation and malnutrition [4], high triglyceride levels are reportedly associated with increased cardiovascular events in patients with CKD or ESRD [5, 6].

Fibrates are known as a treatment for lowering triglycerides, and their efficacy in improving lipid profiles and preventing cardiovascular events has been reported in people with normal kidney function and CKD [7]. However, it is difficult to use the conventional fibrates, such as gemfibrozil and bezafibrate, for people with advanced CKD because they are primarily excreted via the kidneys, and their plasma concentrations increase in patients with impaired renal function [8–10].

Pemafibrate is designed as a selective peroxisome proliferator-activated receptor alpha (PPARα) modulator. Pemafibrate is excreted via not the kidney but the liver and can be used regardless of renal function. It has been approved for treating hyperlipidemia in patients undergoing hemodialysis in Japan since October 2022 [11]. We reported four cases of safety and changes in the lipid profile after pemafibrate administration in patients undergoing hemodialysis.

Case presentation

Clinical characteristics of the participants

We recruited outpatients who were on hemodialysis at a dialysis hospital and took 0.1 mg pemafibrate twice a day in the morning and evening after meals from November 2022 to May 2023. Of the 104 patients, we administered pemafibrate to 4 patients (Supplementary figure). All patients had triglycerides of 175 or more mg/dL at three consecutive three non-fasting tests between September 2022 and November 2022 before pemafibrate administration, meeting the Japanese diagnostic criteria for hypertriglyceridemia [12]. The patients' characteristics are shown in Table 1. The mean age of the patients was 72.3 ± 9.0 years, and 75% were men. The mean duration of dialysis was 5.5 ± 2.0 years. The causes of ESRD were nephrosclerosis in two patients, diabetic nephropathy in one patient, and drug-induced renal failure in one patient. Their body mass index (BMI) was 23.1 ± 1.3 kg/m^2. Two patients had type 2 diabetes mellitus, two had cardiovascular or cerebrovascular disease (one had cerebral hemorrhage sequelae, and one had old brain infarction). Two patients had liver disease. Case 2 had a living liver transplant 21 years ago due to liver cirrhosis caused by chronic co-infection with hepatitis B virus (HBV) and hepatitis C virus. The patient had resolved HBV infection at the transplant. Five years prior, after the initiation of dialysis, the patient underwent direct-acting antiviral therapy (DAA; elbasvir and grazoprevir) and got a sustained viral response (SVR). Case 3 had an alcoholic liver disease and chronic hepatitis C and was treated with DAA 5 years ago, achieving SVR. In case 3 only, AST and ALT were in the range of 20–60 IU/mL before administration of pemafibrate, but in the other three cases they were in the normal range. One patient received statin treatment but not with *n*−3 polyunsaturated fatty acids or nicotinic acid. The patient's dry weight on hemodialysis was 62.5 ± 8.9 kg, and their predialysis blood pressure was 143 ± 8/77 ± 5 mmHg. None of the patients had evidence of chronic inflammation or undernutrition. Three patients took 0.2 mg pemafibrate daily for 24 weeks; only one patient occasionally forgot to take the medication for the first 2 weeks. After 2 weeks, every patient could continue taking the drug.

Safety profiles

After pemafibrate administration, CK, D-dimer, and liver injury indices such as AST and γ-GTP were not elevated (Fig. 1, Table 2). ALT and ALP significantly decreased from the levels before the administration of pemafibrate. No serious adverse events, such as rhabdomyolysis or occlusion of the dialysis access, were observed.

Effects of pemafibrate on lipid metabolism

Lipid profiles were measured in all patients at baseline and 24 weeks after administration of pemafibrate (appendix). As shown in Table 2, pemafibrate significantly reduced TG (302 ± 72 to 140 ± 50 mg/dL, $p = 0.048$), total cholesterol (187 ± 34 to 156 ± 48 mg/dL, $p = 0.025$), and Apo C-III (15.9 ± 8.2 to 12.6 ± 7.1 mg/dL, $p = 0.030$) levels. Small dense LDL tended to be lower (40.3 ± 18.4 to 23.9 ± 15.8 mg/dL, $p = 0.069$). ApoA-II levels significantly increased after treatment (27.0 ± 7.1 to 37.1 ± 6.7 mg/dL, $p = 0.041$). On the other hand, there was no change in HDL-C or LPL.

Discussion and conclusions

We reported four hemodialysis patients treated with pemafibrate, suggesting its safety and beneficial effects on the lipid profile. Twenty-four weeks of treatment with pemafibrate may decrease triglyceride, total cholesterol, and Apo C-III levels and increase Apo A-II without adverse events in hemodialysis patients.

Hypertriglyceridemia is common in patients with CKD and ESRD and is attributed to increased production and decreased clearance of TG-rich lipoproteins [3]. ESRD is associated with lipoprotein lipase (LPL) deficiency and

Table 1 Clinical features of four patients

Case	Age, years	Gender	Duration of dialysis, years	DW, kg	BMI, kg/m^2	Causes of kidney diseases	Diabetes mellitus	Previous stroke	Previous liver disease	Kt/V	Albumin, g/dL	hsCRP, mg/dL	Use of statins	Use of pemafibrate
1	77	Male	2.3	61.1	23.6	Nephrosclerosis	No	Yes	No	1.61	3.8	0.112	No	0.1 mg bid
2	72	Male	7.8	60.3	22.4	drug-induced TIN	No	No	Yes	1.68	4.1	0.187	No	0.1 mg bid
3	58	Male	6.5	76.5	25.0	Nephrosclerosis	Yes	Yes	Yes	1.08	3.8	0.275	No	0.1 mg bid
4	82	Female	5.5	51.9	21.6	DKD	Yes	No	No	1.57	3.6	0.395	YES	0.1 mg bid

The values are expressed as the means ± SDs or *n* (%). DW, dry weight; BMI, body mass index; DKD, diabetic kidney disease; TIN, tubulointerstitial nephritis; hs CRP, High-sensitive C-reactive protein; bid, bis in die (twice a day)

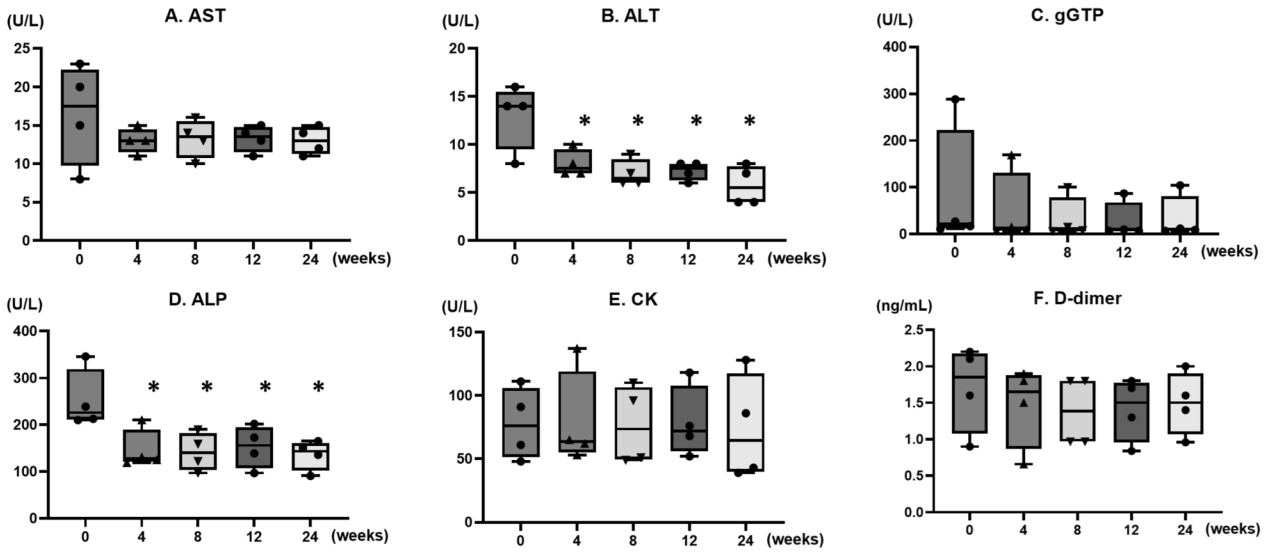

Fig. 1 Box plots showing the changes in **A** AST, **B** ALT, **C** γ-GTP, **D** ALP, **E** CK, and **F** D-dimer before and after the administration of pemafibrate. We performed repeated-measures analysis of variance (ANOVA) and Tukey–Kramer post hoc tests. *p* values less than 0.05 were considered to indicate statistical significance. The figure shows the findings of safety analyses, which revealed no significant elevation. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; CK, creatine kinase

dysfunction, which mediates hydrolysis of the triglycerides of TG-rich lipoproteins. Apo C-III is located on the surface of TG-rich lipoproteins, which inhibits LPL activity and delays hepatic clearance of TG-rich lipoprotein remnants, leading to an increase in triglyceride levels [13]. The level of ApoC-III reportedly increases in CKD and hemodialysis patients [14–16]. ApoC-III is produced in the liver and is controlled by PPARα. The activation of PPARα decreases Apo C-III and triglyceride levels [11]. In the general population, high triglyceride and ApoC-III levels are associated with increased cardiovascular events [17]. Apo C-III-rich VLDL increased the adhesion of human monocytes to vascular endothelial cells (ECs) and activated vascular ECs through the activation of NF-kappaB. Furthermore, Apo C-III induces insulin resistance in vascular endothelial cells, leading to endothelial dysfunction and atherosclerosis [17]. However, it is controversial in patients with CKD and ESRD [3]. In a previous cohort study of hemodialysis patients, elevated TG was not associated with worsened cardiovascular disease (CVD) or all-cause survival after adjustment [18]. On the other hand, in the 2004 Japan Renal Data Registry (JRDR), a significant increase in the risk of myocardial infarction and cerebral infarction was found in patients with triglycerides of 200 mg/dL or more [6]. A secondary analysis of the Heart and Renal Protection (SHARP) trial revealed that higher TG and TRL levels were associated with an increased risk of atherosclerotic vascular events in patients with CKD [5]. The PROMINENT study showed that in patients with type 2 diabetes and mild-to-moderate hypertriglyceridemia, pemafibrate significantly lowered triglyceride and apolipoprotein C-III levels [19], which was confirmed in our dialysis patients. The results are awaited to determine how these results will affect the risk of CVD in the future. Statins, which are LDL-C-lowering agents, had no favorable effect on cardiovascular events or mortality in patients with ESRD [20–22], so the results for patients with CKD might differ from those for the general population.

These cases revealed no significant changes in HDL-C but detected an increase in Apo A-II. HDL plays a major role in reverse cholesterol transport and prevents atherosclerosis [23]. In hemodialysis patients, HDL dysfunction has been observed [24], and HDL-C is inversely associated with the incidence of cardiovascular disease [25]. The TG/HDL-C ratio was reported to predict cardiovascular (CV) events and mortality in hemodialysis patients [26]. Conversely, HDL-C was not associated with survival in a cohort of US dialysis clinics, and the relationship between HDL-C and mortality/CV outcomes in dialysis patients is controversial [18]. The levels of ApoA-I and apoA-II, the main components of HDL, decrease in patients with ESRD [27]. In the 4D study, high apoA-II tended to be associated with a decreased risk of death from all causes, including CVD [28]. Therefore, further study is needed to explore whether changes in Apo A-II after pemafibrate administration could benefit hemodialysis patients.

The adverse events associated with fibrates include liver dysfunction, thrombosis such as deep vein thrombosis,

Table 2 Changes in the lipid profile and safety parameters during the 24-week treatment period

	Baseline	After 24 weeks	*p* value
Total cholesterol, mg/dL	187 ± 34	156 ± 48	0.025
Triglycerides, mg/dL	302 ± 72	140 ± 50	0.048
LDL-C, mg/dL	105 ± 27	92 ± 35	0.178
HDL-C, mg/dL	40 ± 16	46 ± 9	0.591
Non-HDL-C, mg/dL	147 ± 26	110 ± 42	0.055
Apo A-I, mg/dL	129 ± 27	141 ± 17	0.404
Apo A-II, mg/dL	27.0 ± 7.1	37.1 ± 6.7	0.041
Apo B, mg/dL	92 ± 18	77 ± 29	0.276
Apo C-II, mg/dL	5.1 ± 3.5	4.9 ± 3.9	0.627
Apo C-III, mg/dL	15.9 ± 8.2	12.6 ± 7.1	0.030
Apo E, mg/dL	3.2 ± 0.9	3.8 ± 0.9	0.126
RLP-C, mg/dL	10.0 ± 2.9	7.3 ± 7.9	0.580
LPL, ng/mL	285 ± 107	457 ± 197	0.105
Lp(a), mg/dL	18.2 ± 23.7	17.2 ± 20.7	0.572
Small dense LDL, mg/dL	40.3 ± 18.4	23.9 ± 15.8	0.069
VLDL-PAGE, %	17.0 ± 6.7	13.3 ± 6.5	0.507
IDL-PAGE, %	7.1 ± 1.4	6.7 ± 0.7	0.745
LDL-PAGE, %	52.1 ± 7.8	50.2 ± 8.5	0.376
AST, U/L	17 ± 7	13 ± 2	0.256
ALT, U/L	13 ± 3	6 ± 2	0.013
γ-GTP, U/L	86 ± 135	33 ± 47	0.315
ALP, U/L	252 ± 64	136 ± 32	0.031
CK, U/L	78 ± 29	74 ± 42	0.671
D-dimer, μg/mL	1.70 ± 0.59	1.49 ± 0.43	0.494

The data are presented as the means ± SDs before and 6 months after pemafibrate administration. Continuous variables before and six months after pemafibrate administration were compared using paired *t*-tests. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Apo, apolipoprotein; RLP-C, remnant-like particle cholesterol; LPL, lipoprotein lipase; Lp(a), lipoprotein(a); PAGE, polyacrylamide gel electrophoresis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma glutamyl transpeptidase; ALP, alkaline phosphatase; CK, creatine kinase

and rhabdomyolysis [19, 29]. The combination of lovastatin and gemfibrozil, a fibrate excreted by the kidney, induced acute kidney injury and rhabdomyolysis in a patient with moderate renal impairment [8]. On the other hand, clinofibrate, a fibrate excreted by the liver, was reported to be safe for 24 weeks in 12 patients with peritoneal dialysis [30]. Although this is a small number of case reports, no fibrate-related adverse events were observed in any of the patients. A problematic thrombosis in hemodialysis patients is occlusion of the access to dialysis. These patients have experienced no symptoms of thrombosis or rhabdomyolysis and no liver dysfunction, consistent with previous reports in patients with advanced CKD [9, 10]. Pemafibrate has been reported to be beneficial for liver function by modulating lipid turnover and energy metabolism, and in these patients, ALT and ALP were also reduced.

These findings have several limitations. First, this was a relatively small single-center case series, which may have led to favorable results. Second, this case series did not include a placebo control group, so the reduction in lipid profiles, such as triglyceride levels, was partly attributable to the placebo effect or factors beyond the drug treatment, including regression to the mean. Third, the use of statins in these cases were limited to one out of four patients, so lipid profiles and safety results may differ when pemafibrate and statins are combined. Fourth, the patients did not have malnutrition and chronic inflammation. How these factors affect TG levels, cardiovascular disease (CVD) outcome, and prognosis is unknown and will be the subject of further study.

In conclusion, 0.2 mg per day of pemafibrate showed potential safety and efficacy in treating hypertriglyceridemia in hemodialysis patients.

Appendix

Variables and data sources

Blood samples were collected just before the initiation of dialysis. The samples for the measurement of LPL were collected 15 min after the injection of U/kg heparin. Sera were separated immediately after blood collection by centrifugation at 3000 rpm for 15 min at 4 °C. Total cholesterol, TG, and creatinine levels were measured by an enzymatic method; LDL-C and HDL-C levels were measured by a direct method; aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (γ-GT), and creatine kinase (CK) levels were measured by the Japan Society of Clinical Chemistry Transferable Method; alkaline phosphatase (ALP) levels were measured by the International Federation of Clinical Chemistry and Laboratory Medicine Method; albumin levels were measured by a modified bromocresol purple method; blood urea nitrogen (BUN) levels were measured by an ultraviolet method; and D-dimer levels were measured by immunochromatography. Other lipid profiles were measured by Okayama Medical Laboratory Center (Kurashiki city, Okayama, Japan). Lipoprotein fractions were measured by high-performance liquid chromatography; apolipoprotein A-I (Apo A-I), apolipoprotein A-II (Apo A-II), apolipoprotein B (Apo B), apolipoprotein C-II (Apo C-II), apolipoprotein C-III (Apo C-III), and lipoprotein(a) [Lp(a)] levels were measured by a turbidimetric immunoassay; free fatty acid (FFA), remnant-like particle cholesterol (RLP-C), and small dense LDL-C levels were measured by an enzymatic method; and lipoprotein lipase (LPL) levels were measured by an enzyme immunoassay.

Statistical analysis

The data are summarized as percentages, means ± SDs, or medians [interquartile ranges; IQRs], as appropriate. Continuous variables before and 6 months after pemafibrate administration were compared using paired *t*-tests. For repeated measures of safety endpoints, we performed repeated-measures analysis of variance (ANOVA) and Tukey–Kramer post hoc tests. p values less than 0.05 were considered to indicate statistical significance. All the statistical analyses were performed using Stata software (version 17.0; Stata Corporation, College Station, TX, USA).

Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Apo	Apolipoprotein
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CK	Creatine kinase
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DAA	Direct-acting antiviral therapy
ECs	Endothelial cells
ESRD	End-stage renal disease
FFA	Free fatty acid
γ-GTP	Gamma glutamyl transpeptidase
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HPLC	High-performance liquid chromatography
IDL	Intermediate-density lipoprotein
IQR	Interquartile range
JRDR	Japan Renal Data Registry
Lp(a)	Lipoprotein(a)
LDL-C	Low-density lipoprotein cholesterol
LPL	Lipoprotein lipase
PAGE	Polyacrylamide gel electrophoresis
PPARα	Peroxisome proliferator-activated receptor alpha
RLP-C	Remnant-like particle cholesterol
SD	Standard deviation
SVR	Sustained viral response
TG	Triglyceride
VLDL	Very low-density lipoprotein

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41100-024-00590-8.

Additional file 1.

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Author contributions

Conceptualization, Y.O.; methodology, R.O. and Y.O.; formal analysis, R.O. and Y.O.; investigation, R.O. and Y.O.; resources, all the authors; data curation, Y.O.; writing—original draft preparation, R.O. and Y.O.; writing—review and editing, all the authors; supervision, N.K. and J.W.; funding acquisition, Y.O., H.M., and N.K. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The data underlying this article will be shared upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki, and the protocol was approved by the ethics committee of Okayama University Hospital (authorization number: K2309-039). All study participants had the opportunity to opt out of this study by visiting the website or the outpatient clinic.

Consent for publication

All patients provided written consent for publication.

Competing interest

Jun Wada receives speaker honoraria from Astra Zeneca, Daiichi Sankyo, Novartis, Novo Nordisk Pharma, and Tanabe Mitsubishi and receives grant support from Astellas, Baxter, Bayer, Chugai, Dainippon Sumitomo, Kyowa Kirin, Novo Nordisk Pharma, Ono, Otsuka, Tanabe Mitsubishi, and Teijin. The other authors declare no conflicts of interest.

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