Clinical and Experimental HEPATOLOGY

Clin Exp HEPATOL 2023; 9, 2: 172–178
DOI: https://doi.org/10.5114/ceh.2023.127813
Received: 06.02.2023, **Accepted:** 14.05.2023, **Published:** 23.06.2023

Original paper

Effects of body composition and liver function after long-term pemafibrate treatment on dyslipidemia-associated non-alcoholic fatty liver disease

Toru Ishikawa[1*], Nanako Terai[2*], Takanori Igarashi[1], Shun Yamazaki[1], Takamasa Kobayashi[1], Toshifumi Sato[1], Akito Iwanaga[1], Tomoe Sano[1], Junji Yokoyama[1], Terasu Honma[1]

[1]Department of Gastroenterology, Saiseikai Niigata Hospital, Niigata, Japan
[2]Department of Radiography, Saiseikai Niigata Hospital, Niigata, Japan

*These two authors are equal contributors to this work and designated as co-first authors.

Abstract

Aim of the study: Owing to the association between non-alcoholic fatty liver disease (NAFLD) and dyslipidemia, there is a need for new treatment strategies to manage both conditions concomitantly. Our aim in this study was to evaluate the effectiveness of pemafibrate in alleviating dyslipidemia-associated NAFLD, including the evaluation of its effects on liver function and body composition.

Material and methods: The study sample included 67 patients with dyslipidemia-associated NAFLD (29 males, mean age 65.7 years [range, 58.4-73.7]) who were administered pemafibrate continuously for a period of at least 12 months, between June 2019 and January 2022. Outcomes were the change in body composition indices (visceral adipose tissue index – VATI, subcutaneous adipose tissue index – SATI, and skeletal muscle index – SMI), lipid biochemistry, and liver function, reserve, and fibrosis score, from baseline to the 12-month time point of pemafibrate treatment.

Results: Pemafibrate treatment improved liver function (alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase, and alkaline phosphatase), and lipid biochemistry (triglycerides and total cholesterol). Improvements in ferritin and hepatic reserve (Mac-2 binding protein, albumin-to-bilirubin score, and NAFLD fibrosis score) were also observed, as well as a decrease in SATI.

Conclusions: Pemafibrate improved dyslipidemia, liver function, and hepatic reserve. The positive effects of pemafibrate on body composition likely contributed to the improvements in liver function. Longer-term treatment may be necessary to influence VATI and thus to further evaluate the relationship between improved body composition and NAFLD with pemafibrate treatment.

Key words: non-alcoholic fatty liver disease, pemafibrate, liver function, liver fibrosis, body composition.

Address for correspondence:

Toru Ishikawa, MD, PhD, Director, Department of Gastroenterology, Saiseikai Niigata Hospital, Teraji 280-7, Niigata 950-1104, Japan, phone: +81-25-233-6161, fax: +81-25-233-8880, e-mail: toruishi@ngt.saiseikai.or.jp

Introduction

There is an urgent need to establish a new treatment modality for non-alcoholic fatty liver disease (NAFLD), a hepatic phenotype of metabolic syndrome with a high incidence among patients with underlying dyslipidemia. Accordingly, the revised 2020 guidelines for the treatment of NAFLD recommend the use of statins for dyslipidemia-associated NAFLD [1]. Recently, pemafibrate (K-877, Parmodia tablet, Kowa Company, Ltd., Nagoya, Japan), a selective peroxisome proliferator-activated receptor α modulator (SPPARMα), was approved in July 2017 and released in June 2018 in Japan for the treatment of dyslipidemia [2, 3]. Pemafibrate ame-

liorates lipid abnormalities in patients with dyslipidemia by lowering serum triglycerides (TG) and raising high-density lipoprotein (HDL) cholesterol. Of clinical importance, pemafibrate was developed to reduce the adverse effects associated with fenofibrate, another PPARα agonist, and to reduce restrictions on the use of PPARα agonists in patients with renal disease or in combination with statins. Our aim in this study was to evaluate the effectiveness of pemafibrate in improving dyslipidemia among patients with NAFLD and to evaluate the effects on liver function and body composition.

Material and methods

Study population

Patients with a diagnosis of dyslipidemia-associated NAFLD, confirmed by histological findings, and treated for hypertriglyceridemia with pemafibrate continuously for a period ≥ 12 months at our hospital, between June 2019 and January 2022, were eligible for inclusion in the study. Pemafibrate was administered to all patients at 0.1 mg twice per day. The inclusion criteria were as follows: negative hepatitis B surface antigen and hepatitis C virus antibody tests, normal serum immunoglobulin G level, and alcohol consumption < 30 g/day in males and < 20 g/day in females. The exclusion criteria were as follows: severe chronic kidney disease, defined by serum creatinine > 2.5 mg/dl, prior history of pemafibrate treatment, cessation of pemafibrate treatment within the first 3 months, past cardiovascular events, and treatment for diabetes mellitus and other carbohydrate disorders – prediabetes, insulin resistance. Furthermore, patients with chronic hepatitis due to other causes such as autoimmune hepatitis and primary sclerosing cholangitis were excluded. None of the patients changed their exercise or dietary regimens during the entire study period. After selection, 67 patients were included in the study sample.

Measured outcomes

The following indices of body composition and lipid biochemistry were evaluated before and after 12 months of the first administration of pemafibrate treatment [4-6]: visceral adipose tissue index (VATI), subcutaneous adipose tissue index (SATI), and skeletal muscle index (SMI). These indices were quantified from cross-sectional unenhanced computed tomography (CT) images obtained, using an Aquilion 4/16/64, ONE system (Toshiba, Tokyo, Japan), solely for the purpose of diagnosing and staging of hepatocellular carcinoma. The skeletal muscle and abdominal adipose tissue area was quantified on cross-sectional CT images at the level of the third lumbar vertebra (L3), using the Slice-O-Matic software (version 5.0; Tomovision, Montreal, Canada). The muscle area included the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis muscles. Skeletal muscle and adipose tissue were differentiated by the following tissue Hounsfield unit (HU) thresholds: -29 to 150 HU for skeletal muscle; –190 to –30 for subcutaneous adipose tissue; and –150 to –50 for visceral adipose tissue. Body composition indices were normalized to height (m^2) and thus expressed as cm^2/m^2. With regard to lipid biochemistry, the following outcomes were calculated: FIB-4 (age (years) × AST (U/l)/platelet count ($\times 10^9$/l) × [ALT (U/l)] 1/2) [7]; NAFLD fibrosis score (–1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST (U/l)/ALT (U/l) ratio – 0.013 × platelets (10^9/l) – 0.66 × albumin (g/dl)) [8]; and the albumin-bilirubin (ALBI) score (log10 bilirubin [μmol/l] × 0.66) + (albumin [g/l] × –0.085) [9].

Statement of ethics

The methods for our retrospective study were approved by the Institutional Review Board of Saiseikai Niigata Hospital (No. E18-18). The study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013). Before participating in this study, written informed consent was provided by all patients.

Statistical analysis

Normally distributed continuous variables were reported as the mean and standard deviation, with non-normally distributed continuous variables reported as the median and range. Categorical variables were expressed as whole numbers. The change from baseline to 12 months was evaluated using the two-tailed unpaired *t*-test for normally distributed continuous variables and the Mann-Whitney *U*-test for non-normally distributed variables. The change in categorical variables was evaluated using Pearson's χ^2 test or Fisher's exact test, as appropriate. Statistical significance was defined by a p-value < 0.05 for all tests. All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) [10].

Results

Description of study sample

The study sample of 67 patients included 29 males and 38 females, with a mean age of 65.7 years (range, 58.4-73.7). Demographics and lipid biochemistry and body compositions indices at baseline are reported in Tables 1 and 2. Body weight and body mass index (BMI) were not significantly altered by pemafibrate treatment during the followup period. No significant differences in creatine kinase or creatinine values before and after treatment were noted.

Effects on liver function and reserve capacity

Changes in liver function and reserve capacity, from baseline to 12 months of pemafibrate treatment, are reported in Table 3. The following lipid biochemistry levels were significantly improved: alanine aminotransferase (ALT) 42.0 to 18.0 IU/l; alkaline phosphatase (ALP) 251.5 to 159.4 IU/l; γ-glutamyl transpeptidase (GGTP) 31.0 to 18.0 IU/l; platelets 21.5 to 24.40; TG 168.5 to 130.8 mg/dl; total cholesterol 207.5 to 185.5 mg/dl; total bilirubin 0.60 to 0.53 mg/dl; and albumin 4.35 to 4.41 mg/dl. With regard to hepatic reserve capacity, improvements were observed in the M2BPGi (0.73 to 0.61), ALBI score (–3.02 to –3.20), and NAFLD fibrosis score (1.33 to 1.45).

Table 1. Demographic and clinical characteristics at baseline

Characteristics	Mean (IQR)
Sex (male/female)	29/38
Age (years)	65.7 (58.4-73.7)
BMI (kg/m^2)	24.2 (22.5-26.9)
AST (IU/l)	29.5 (23.0-36.8)
ALT (IU/l)	42.0 (34.5-55.0)
ALP (IU/l)	251.5 (194.3-339.8)
GGTP (IU/l)	31.0 (17.0-49.5)
Platelets (10^4/μl)	21.5 (17.2-25.9)
TG (mg/dl)	168.5 (127.5-213.0)
Total cholesterol (mg/dl)	207.5 (166.3-216.5)
LDL cholesterol (mg/dl)	128.0 (94.0-140.8)
HDL cholesterol (mg/dl)	50.5 (39.5-56.8)
eGFR (ml/min/1.73 m^2)	76.4 (62.9-90.5)
Total bilirubin (mg/dl)	0.60 (0.46-0.76)
Albumin (mg/dl)	4.35 (4.23-4.40)
UA (mg/dl)	5.90 (4.50-6.58)
Ferritin (ng/ml)	124.6 (61.6-153.1)
HbA_{1c} (%)	5.90 (5.80-6.28)
BS (mg/dl)	101.5 (94.3-130.5)
M2BPGi	0.73 (0.46-1.02)
Fib-4 index	1.42 (1.14-2.33)
NAFLD fibrosis score	1.33 (0.60-2.18)
ALBI score	−3.02 (−3.13–−2.88)

BMI – body mass index, AST – aspartate aminotransferase, ALT – alanine aminotransferase, ALP – alkaline phosphatase, GGTP – γ-glutamyl transpeptidase, TG – triglyceride, LDL – low-density lipoprotein, HDL – high-density lipoprotein, eGRF – estimated glomerular filtration rate, UA – uric acid, HbA_{1c} – hemoglobin A_{1c}, BS – blood sugar, M2BPGi – Mac-2 binding protein, Fib-4 index – fibrosis-4 index, ALBI – albumin-bilirubin

Effects on body composition

The changes in body composition indices are reported in Table 4. From baseline to 12 months of pemafibrate treatment, there was a significant decrease in SATI (62.20 to 60.96) and a slight decrease in SMI (16.38 to 15.94), with no change in VATI (52.16 to 53.49).

Adverse effects

No serious adverse effects were noted. There were no cases of impairment in hepatic and renal function. Mild itching was reported in 3/67 patients and constipation in 1.

Discussion

In this study, we found that a 12-month course of pemafibrate significantly ameliorated ALT, ALP, platelet count, GGTP, serum albumin, and NAFLD score among patients with a diagnosis of dyslipidemia-associated NAFLD. Pemafibrate also improved hepatic function, indexed by M2BPGi and the ALBI score, as well as having positive effects on body composition, with an improvement in SATI and maintenance of SMI. To our knowledge, this is the first report regarding the biological effects of pemafibrate.

The prevalence of metabolic syndrome, caused by visceral fat accumulation, has been increasing in recent years due to a general population trend of ex-

Table 2. Body composition indices at baseline

Index	Mean (IQR)
VATI	52.16 (40.17-61.72)
SATI	62.20 (46.75-90.24)
SMI	16.38 (14.50-18.10)

VATI – visceral adipose tissue index, SATI – subcutaneous adipose tissue index, SMI – skeletal muscle index

Table 3. Changes in lipid biochemistry and liver function scores from baseline to 12 months of pemafibrate treatment

Markers	Baseline	12 months	*P*-value
AST (IU/l)	29.5 (23.0-36.8)	25.5 (21.7-32.3)	0.235
ALT (IU/l)	42.0 (34.5-55.0)	18.0 (14.5-24.0)	**< 0.001**
ALP (IU/l)	251.5 (194.3-339.8)	159.4 (123.6-218.1)	**< 0.001**
GGTP (IU/l)	31.0 (17.0-49.5)	18.0 (12.5-29.0)	**< 0.001**
Platelets (10^4/µl)	21.5 (17.05-25.90)	24.4 (20.35-28.50)	**< 0.001**
TG (mg/dl)	168.5 (127.5-213.0)	130.8 (94.3-170.2)	**0.007**
Total cholesterol (mg/dl)	207.5 (166.3-216.5)	185.5 (154.6-199.1)	**0.017**
LDL cholesterol (mg/dl)	128.0 (94.0-140.8)	112.1 (83.2-129.7)	**0.007**
HDL cholesterol (mg/dl)	50.5 (39.5-56.8)	53.5 (38.9-62.9)	0.791
eGFR (ml/min/1.73 m^2)	76.4 (62.9-90.5)	73.7 (64.0-87.3)	0.463
Total bilirubin (mg/dl)	0.60 (0.46-0.76)	0.53 (0.44-0.69)	**0.035**
Albumin (mg/dl)	4.35 (4.23-4.40)	4.41 (4.28-4.64)	**0.029**
UA (mg/dl)	5.90 (4.50-6.58)	5.72 (4.93-6.64)	0.313
Ferritin (ng/ml)	124.6 (61.6-153.1)	108.2 (89.9-173.5)	0.176
HbA_{1c} (%)	5.90 (5.80-6.28)	5.97 (5.72-6.19)	0.862
BS (mg/dl)	101.5 (94.3-130.5)	97.6 (92.5-107.9)	0.824
M2BPGi	0.73 (0.46-1.02)	0.61 (0.44-0.86)	**0.010**
Fib-4 index	1.42 (1.14-2.33)	1.34 (0.90-2.28)	0.222
ALBI score	−3.02 (−3.13–−2.88)	−3.20 (−3.34–−3.02)	**< 0.001**
NAFLD fibrosis score	1.33 (0.60-2.05)	1.45 (0.78-2.26)	**0.049**

Data are presented as the mean (IQR), P-values indicated in bold are significant; AST – aspartate aminotransferase, ALT – alanine aminotransferase, ALP – alkaline phosphatase, GGTP – γ-glutamyl transpeptidase, TG – triglyceride, LDL – low-density lipoprotein, HDL – high-density lipoprotein, eGFR – estimated glomerular filtration rate, UA – uric acid, HbA_{1c} – hemoglobin A_{1c}, BS – blood sugar, M2BPGi – Mac-2 binding protein, Fib-4 index – fibrosis-4 index, ALBI – albumin-bilirubin

Table 4. Change in body composition indices from baseline to 12 months of pemafibrate treatment

Index	Baseline	12-months	*P*-value
VATI	52.16 (40.17-61.72)	53.39 (40.45-70.21)	0.295
SATI	62.20 (46.75-90.24)	60.96 (41.13-89.14)	**< 0.001**
SMI	16.38 (14.50-18.10)	15.94 (14.47-18.42)	0.561

Data are presented as the mean (IQR), P-values in bold are significant; VATI – visceral adipose tissue index, SATI – subcutaneous adipose tissue index, SMI – skeletal muscle index

cessive caloric intake and decreased physical activity. Visceral fat accumulation increases insulin resistance, resulting in diabetes mellitus and glucose intolerance, as well as in hypertension and lipid metabolic disorders [11]. Of the effects of increased insulin resistance, hypertriglyceridemia and hypo-high-density lipoproteinemia are thought to be involved in the development of NAFLD [12]. Specifically, the two main mechanisms of NAFLD development consist of increased fatty acid influx and increased synthesis of new fatty acid. Increased fatty acid influx results from increased lipolysis and an excessive intake of lipids, while continued excessive intake of carbohydrates and fructose, especially in a state of hyperinsulinemia, leads to increased new fatty acid synthesis. Therefore, NAFLD treatment includes both diet modification and exercise to achieve weight loss in patients with obesity, with drug therapy indicated for underlying health conditions, such as high TG and low-density lipoprotein (LDL) cholesterol levels, as well as dyslipidemia-related cardiovascular disease. This is important as among patients with NAFLD, cardiovascular events are the most common cause of death [13]. In Japan, 65.7% of patients with NAFLD have dyslipidemia, with a particularly high rate of hypertriglyceridemia (45.3%) [14]. Hence, concomitant treatment of both dyslipidemia and NAFLD would be beneficial.

PPARα is a nuclear receptor that forms heterodimers with retinoid X receptors (RXR) and binds to genes with PPAR response elements (PPREs) in their

promoter regions to regulate their transcriptional activities [15]. Pemafibrate binds to the nuclear receptor PPARα, inducing a ligand-specific conformational change in PPARα, resulting in selective regulation of the expression of genes involved in lipid metabolism, mainly in the liver, thereby improving lipid metabolism [16].

Pemafibrate was developed as a selective PPARα modulator, with higher selectivity, a stronger TG-lowering effect, and a higher safety profile, including fewer adverse effects such as hepatic dysfunction and elevation of creatine kinase, than conventional fibrate formulations [15-18]. In addition to being highly effective in improving hypertriglyceridemia, a sub-analysis of clinical trials revealed that pemafibrate improves liver function. Moreover, pemafibrate treatment has been associated with improvement in liver stiffness, measured by magnetic resonance elastography, although a domestic phase II trial for NAFLD did not show a significant decrease in liver steatosis with pemafibrate treatment [19]. Hence, pemafibrate can improve the pathogenesis of NASH by modulation of lipid turnover and energy metabolism in the liver in a diet-induced rodent model of NASH compared with fenofibrate [20].

A postulated mechanism for the decrease in liver stiffness is that pemafibrate decreases the production of very low-density lipoproteins in the liver, thus reducing fat deposition in the liver due to its TG-degrading effect associated with the promotion of lipoprotein lipase activity [21].

In addition to suppressing fat deposition with pemafibrate, suppression of inflammation is also considered with respect to suppression of fibrosis. The effect on NASH by suppressing inflammation with fibrates is considered [22-25].

Recently, fibroblast growth factor 21 (FGF-21) has been attracting attention as a regulator of glucose and lipid metabolism [26]. FGF-21 is a multifunctional intercellular signaling factor that exerts a variety of effects, such as proliferative activity and differentiation induction, on various cells, including fibroblasts. There are 23 types of FGFs, with FGF-21 considered to be an endocrine FGF that can act as an endocrine factor and is expressed mainly in the liver, with blood levels of FGF-21 being derived from the liver [27]. Physiologically, FGF-21 is involved in metabolic homeostasis and thus is expected to be developed as a therapeutic agent for the treatment of obesity and obesity-related complications [28]. Studies have shown that the nuclear receptor PPARα is involved in the regulation of FGF-21 expression [29, 30]. With regards to pemafibrate, which exerts a specific effect on PPARα receptors, it has been shown to increase FGF-21 expression in hepatocytes in high-fat-diet loaded mice; accordingly, there is growing clinical interest in the use of pemafibrate in improving lipids, as well as in its physiological effects in lowering blood glucose, maintaining pancreatic beta cell function, and improving obesity and fatty liver [31, 32].

Moreover, the potent PPARα activating effect of pemafibrate enhances catabolism in the liver and in brown adipose tissue and muscle, suggesting that it may be a useful drug for patients with NAFLD and metabolic syndrome. Our study findings suggest that the lipid-lowering effect of pemafibrate not only improves liver function and dyslipidemia, but also exerts a positive effect on hepatic reserve and body composition. Pemafibrate improved serum ALT, ALP, GGTP, TG, and Alb levels, as well as improving liver fibrosis-related factors, such as M2BPGi, while decreasing subcutaneous fat (SATI) and maintaining the SMI. As women are more likely to accumulate subcutaneous fat then men [33], a previous study identified female sex as a mediating factor for improvements in ALT with pemafibrate treatment [34]. In a rodent model, it was found that pemafibrate activates a wider range of genes in females than males [35]. The positive effect of pemafibrate that we report in our study might reflect the higher prevalence of women than men (38 of the 67 patients included) in our study sample. Studies are warranted to comprehensively evaluate the effects of pemafibrate on subcutaneous fat. Moreover, longer-term studies are needed to evaluate the effects of pemafibrate, including CT body composition, with treatment of > 12-month duration.

The limitations of our study need to be acknowledged. First, this was a small observational study, with a sample size of only 67 patients and a period of observation of 12 months. Selection bias could not be avoided as patients were enrolled retrospectively, with only those with clinically confirmed NAFLD being considered. Moreover, there were missing data that needed to be compensated by using median values. Accordingly, a causative effect between pemafibrate treatment and measured improvement cannot be established.

We do note, however, that our data are consistent with prior experimental and trial data [2, 20]. Therefore, our data do provide support for the use of pemafibrate in the treatment of dyslipidemia-associated NAFLD, with the positive effects of pemafibrate on body composition likely to contribute to the noted improvements in NAFLD pathophysiology.

Conclusions

Pemafibrate, a new selective PPARα modulator, improved dyslipidemia, liver function, and hepatic

reserve in patients with dyslipidemia-associated NAFLD. Pemafibrate has the potential to be the first standard medication of dyslipidemia-associated NAFLD. The positive effects of pemafibrate on body composition likely contributed to the improvements in liver function. Longer-term treatment may be necessary to fully evaluate the effects of pemafibrate on body composition, including visceral adipose tissue (VATI), and thus to further evaluate the relationship between improved body composition and NAFLD with pemafibrate treatment.

Acknowledgments

We would like to thank Editage (www.editage.com) for their assistance with English language editing.

Disclosure

The authors declare no conflict of interest.

References

1. Tokushige K, Ikejima K, Ono M, et al. Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis 2020. J Gastroenterol 2021; 56: 951-963.
2. Ishibashi S, Yamashita S, Arai H, et al. Effects of K-877, a novel selective PPARα modulator (SPPARMα), in dyslipidaemic patients: A randomized, double blind, active and placebo-controlled, phase 2 trial. Atherosclerosis 2016; 249: 36-43.
3. Araki E, Yamashita S, Arai H, et al. Effects of pemafibrate, a novel selective PPARa modulator, on lipid and glucose metabolism in patients with type 2 diabetes and hypertriglyceridemia: A randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2018; 41: 538-546.
4. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, et al. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol 1998; 85: 115-122.
5. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013; 31: 1539-1547.
6. Goodpaster BH, Carlson CL, Visser M, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. J Appl Physiol 2001; 90: 2157-2165.
7. Sumida Y, Yoneda M, Hyogo H, et al. Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population. BMC Gastroenterol 2012; 12: 2.
8. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007; 45: 846-854.
9. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence based approach-the ALBI grade. J Clin Oncol 2015; 33: 550-558.
10. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013; 48: 452-458.
11. Tylutka A, Morawin B, Walas Ł, et al. Assessment of metabolic syndrome predictors in relation to inflammation and visceral fat tissue in older adults. Sci Rep 2023; 13: 89.
12. Chen Z, Yang L, Liu Y, et al. The potential function and clinical application of FGF21 in metabolic diseases. Front Pharmacol 2022; 13: 1089214.
13. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015; 149: 389-397.
14. Nakahara T, Hyogo H, Yoneda M, et al. Type 2 diabetes mellitus is associated with the fibrosis severity in patients with nonalcoholic fatty liver disease in a large retrospective cohort of Japanese patients. J Gastroenterol 2014; 49: 1477-1484.
15. Fruchart JC. Pemafibrate (K-877), a novel selective peroxisome proliferator-activated receptor alpha modulator for management of atherogenic dyslipidaemia. Cardiovasc Diabetol 2017; 16: 124.
16. Yamashita S, Masuda D, Matsuzawa Y. Pemafibrate, a new selective PPARα modulator: Drug concept and its clinical applications for dyslipidemia and metabolic diseases. Curr Atheroscler Rep 2020; 22: 5.
17. Sahebkar A, Chew GT, Watts GF. New peroxisome proliferator-activated receptor agonists: potential treatments for atherogenic dyslipidemia and non-alcoholic fatty liver disease. Expert Opin Pharmacother 2014; 15: 493-503.
18. Pawlak M, Lefebvre P, Staels B. Molecular mechanism of PPARα action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. J Hepatol 2015; 62: 720-733.
19. Nakajima A, Eguchi Y, Yoneda M, et al. Randomised clinical trial: Pemafibrate, a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα), versus placebo in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2021; 54: 1263-1277.
20. Honda Y, Kessoku T, Ogawa Y, et al. Pemafibrate, a novel selective peroxisome proliferator-activated receptor alpha modulator, improves the pathogenesis in a rodent model of nonalcoholic steatohepatitis. Sci Rep 2017; 7: 42477.
21. Staels B, Dallongeville J, Auwerx J, et al. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation 1998; 98: 2088-2093.
22. Shiri-Sverdlov R, Wouters K, van Gorp PJ, et al. Early diet-induced non-alcoholic steatohepatitis in APOE2 knock-in mice and its prevention by fibrates. J Hepatol 2006; 44: 732-741.
23. Ip E, Farrell G, Hall P, et al. Administration of the potent PPARalpha agonist, Wy-14,643, reverses nutritional fibrosis and steatohepatitis in mice. Hepatology 2004; 39: 1286-1296.
24. Larter CZ, Yeh MM, Van Rooyen DM, et al. Peroxisome proliferator-activated receptor-alpha agonist, Wy 14,643, improves metabolic indices, steatosis and ballooning in diabetic mice with non-alcoholic steatohepatitis. J Gastroenterol Hepatol 2012; 27: 341-350.
25. Takei K, Han SI, Murayama Y, et al. Selective peroxisome proliferator-activated receptor-α modulator K-877 efficiently activates the peroxisome proliferator-activated receptor-α pathway and improves lipid metabolism in mice J Diabetes Investig 2017; 8: 446-452.
26. Fisher FM, Maratos-Flier E. Understanding the physiology of FGF21 Annu Rev Physiol 2016; 78: 223-241.
27. Markan KR, Naber MC, Ameka MK, et al. Circulating FGF21 is liver derived and enhances glucose uptake during refeeding and overfeeding. Diabetes 2014; 63: 4057-4063.

28. Kliewer SA, Mangelsdorf DJ. A dozen years of discovery: Insights into the physiology and pharmacology of FGF21. Cell Metab 2019; 29: 246-253.
29. Lundåsen T, Hunt MC, Nilsson LM, et al. PPARalpha is a key regulator of hepatic FGF21. Biochem Biophys Res Commun 2007; 360: 437-440.
30. Badman MK, Pissios P, Kennedy AR, et al. Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic state. Cell Metab 2007; 5: 426-437.
31. Yokote K, Yamashita S, Arai H, et al. A pooled analysis of pemafibrate phase II/III clinical trials indicated significant improvement in glycemic and liver function-related parameters. Atherosclerosis Supplements 2018; 32: 154-155.
32. Araki M, Nakagawa Y, Oishi A, et al. The peroxisome proliferator-activated receptor α (PPARα) agonist pemafibrate protects against diet-induced obesity in mice. Int J Mol Sci 2018; 19: 2148.
33. Palmer BF, Clegg DJ. The sexual dimorphism of obesity. Mol Cell Endocrinol 2015; 402: 113-119.
34. Iwadare T, Kimura T, Kunimoto H, et al. Higher responsiveness for women, high transaminase levels, and fat percentage to pemafibrate treatment for NAFLD. Biomedicines 2022; 10: 2806.
35. Smati S, Polizzi A, Fougerat A, et al. Integrative study of diet-induced mouse models of NAFLD identifies PPARα as a sexually dimorphic drug target. Gut 2022; 71: 807-821.