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Efficacy of Pemafibrate Against Nonalcoholic Fatty Liver Disease: A Prospective Cohort Study

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NAFLD; NASH; HCC; SPPARMα; APRI; cirrhosis; Hyperlipidemia; FIB-4; ferritin; SREBP-1c

1. Abstract

1.1. Background: Nonalcoholic fatty liver disease (NAFLD), one of the most common causes of chronic liver diseases, is characterized by chronic liver inflammation and fibrosis, which consequently promote cirrhosis and liver cancer. Pemafibrate, a selective PPARα modulator is a new lipid-lowering drug that provides better hypertriglyceridemia control compared to greater other fibrates without increasing adverse effects.

1.1. Methods: A total of 32 participants with NAFLD (16 men and 16 women) who received pemafibrate (0.2 mg) were enrolled. Body weight and serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (γ-GTP), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), glycated hemoglobin, uric acid, creatinine, and ferritin, as well as the AST to platelet ratio index (APRI) and fibrosis-4 (FIB-4) index values, were measured at baseline and after 3 and 6 months.

1.3. Results: After 6 months of pemafibrate treatment, serum levels of AST, ALT, γ-GTP, TG, and ferritin, as well as APRI and FIB-4 index values, decreased significantly, whereas serum HDL-C levels increased significantly. Moreover, reduced serum ALT levels at 6 months were significantly correlated with baseline TG and ferritin levels, while decreased serum ALT levels were significantly correlated with decreased serum ferritin at 6 months.

1.4. Conclusions: Pemafibrate significantly reduced serum TG and ferritin levels, as well as APRI and FIB-4 index values, and increased serum HDL-C levels while improving liver function, suggesting its potential as an effective therapeutic modality for improving liver injury in participants with NAFLD.

2. Introduction

Nonalcoholic fatty liver disease (NAFLD) remains one of the most chronic liver diseases, affecting approximately 25% of the worldwide population. In Japan, [1]. This certainly in line with the recent changes in lifestyle, including dietary intake and customs, which have increased the number of individuals with obesity. Considering that NAFLD carries shares several complications with metabolic syndrome, such as impaired glucose intolerance, dyslipidemia, and hypertension, it has been regarded as the hepatic manifestation of metabolic syndrome [2]. Estimates have shown that approximately 20% of patients with NAFLD may develop nonalcoholic steatohepatitis (NASH) with liver injury and fibrosis, with a certain percentage of those with NASH potentially progressing to cirrhosis and hepatocellular carcinoma (HCC). NAFLD has a multifactorial pathology that may promote impaired glucose tolerance and diabetes mellitus. Considering that visceral fat accumulation is closely associated with metabolic syndrome and NAFLD/NASH, obesity has been regarded as the main factor causing NAFLD. Therefore, visceral fat obesity is very associated with metabolic syndrome and NAFLD/NASH [3]. In fact, NAFLD/NASH is based on insulin resistance, which has been shown to promote fat deposition, β-oxidation of fatty acids, free radical production, and oxidative stress [4]. Therefore, NAFLD/

NASH may cause hepatic liver damage and eventually lead to cirrhosis and HCC.

Given the current lack of a specific pharmacotherapy for NAFLD, dietary and exercise therapies have generally been used to control NAFLD. Moreover, pharmacotherapy is usually considered in patients who have difficulty modifying their life style or those at high risk for progression to cirrhosis and liver cancer. Furthermore, pharmacotherapy for comorbidities accompanying NAFLD, including dyslipidemia and type 2 diabetes mellitus, is similarly important. In particular, fibrates, which mainly functions to decrease triglyceride (TG) levels and increase high-density lipoprotein cholesterol (HDL-C) by activating peroxisome proliferate-activated receptor-α (PPARα), have generally been used for the pharmacotherapy of hypertriglyceridemia. However, fibrates are contraindicated for patients with impaired renal function and liver dysfunction given the potential for worsening renal dysfunction and liver injury.

Pemafibrate is a selective PPARα modulator approved for use in July 2017 and released in June 2018. Accordingly, phase 2 and 3 trials in Japan have demonstrated that pemafibrate significantly ameliorated lipid abnormalities in patients with dyslipidemia without increasing adverse effects. Pemafibrate is believed to have decreased TG levels by upregulating PPARα activity [5]. In a rodent model of NASH, pemafibrate promoted greater improvement in liver function compared to several fibrates [6]. The current study aimed to examine the clinical effects of pemafibrate administration for 6 months in participants with NAFLD. We hypothesize that Pemafibrate administration will contribute to the improvement of liver dysfunction, hyperlipidemia, liver fibrosis marker, and hyperferritinemia.

3. Materials and Methods

3.1. Study Design

This prospective, open-label, uncontrolled pilot study was conducted between September 2018 and March 2020. All participants received 0.2 mg/day of pemafibrate for 6 months. Body weight was monitored throughout the study, from which body mass indexes were calculated. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (γ-GTP), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), TG, glycated hemoglobin (HbA1C), uric acid (UA), creatinine (Cre), and ferritin, as well as the AST to platelet ratio index (APRI) and fibrosis-4 (FIB-4) index values, were measured at baseline and after 3 and 6 months. APRI values were calculated according to the following equation: ARPI = {[AST (IU/L) ×100] / [platelet count (10^9/L)]} [7]. FIB-4 index values were calculated according to the following equation: FIB-4 index = {[age (yr) × AST (IU/L)] / [platelet count (10^9/L) × ALT (IU/L)]} [8]. B.M.I(Body Mass index)=BW(Body weight) <Kg>/Height(m).

4. Patients

A total of 32 participants with NAFLD (16 men and 16 women) were enrolled in the present study. All participants underwent abdominal ultrasonography and were screened for metabolic syndrome, diabetes mellitus, dyslipidemia, hypertension, and NAFLD, as well as all current medications being taken. The inclusion criteria required that all participants have a fatty liver; did not have other causes of chronic liver diseases, including alcoholism, drug-induced liver injury, viral hepatitis, hemochromatosis, and auto-immune liver disease; and were older than 20 years. The main exclusion criteria were current or potential pregnancy and baseline serum TG levels of <150 mg/dL. NAFLD was defined according to characteristic ultrasonographic findings, such as increased hepatorenal contrast or enhanced liver brightness [9]. All participants had dyslipidemia, with the clinical background of patients receiving pemafibrate being summarized in Table 1.

Table 1: Clinical background of patients receiving pemafibrate.

Cases	32
Sexuality (male/female)	16/16
Age	65.9 ± 12.4
Complications	
Diabetes mellitus	14
Hypertension	14
Hyperuricemia	2

5. Statistical Analysis

Data are expressed as means ± standard deviation. Changes in parameters were evaluated using the Wilcoxon rank-sum test. Differences between the means of two variables were evaluated using an independent t-test. Spearman's rank correlation coefficient was used to assess association between variables. All statistical tests were performed using StatFlex 7.0 software (Windows ver. 6.0; Artech, Oaska, Japan), with $P < 0.05$ indicating statistical significance. This study was performed in accordance with the ethical standards established in the 1975 Declaration of Helsinki.

6. Results

All participants successfully completed the study protocol. Accordingly, serum AST levels decreased significantly from 35.3 IU/L at baseline to 30.0 and 28.8 IU/L after 3 and 6 months of treatment, respectively ($P < 0.05$). Serum ALT levels decreased significantly from 44.5 IU/L at baseline to 29.5 and 27.1 IU/L after 3 and 6 months of treatment, respectively ($P < 0.05$).

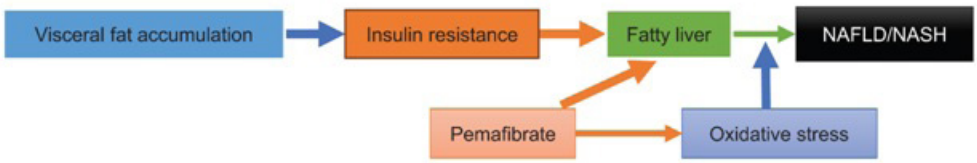
Serum γ-GTP levels decreased significantly from 51.0 IU/L at baseline to 37.8 and 30.2 IU/L after 3 and 6 months of treatment, respectively ($P < 0.05$). Serum TG levels decreased significantly from 260.1 mg/dL at baseline to 158.1 and 169.7 mg/dL after 3 and 6 months of treatment, respectively ($P < 0.05$). Serum HDL-C levels increased significantly from 51.1 mg/dL at baseline to 56.0 and 55.0 mg/dL after 3 and 6 months of treatment, respectively ($P < 0.05$). Serum ferritin levels decreased significantly from 152.4 ng/mL at baseline to 123.4 and 103.8 ng/mL after 3 and 6 months of treatment, respectively ($P < 0.05$). APRI index values decreased significantly from 0.41 at baseline to 0.34 and 0.32 after 3 and 6 months of treatment, respectively ($P < 0.05$). FIB-4 index values decreased slightly from 1.63 at baseline to 1.56 after 3 months but showed a significant decrease to 1.51 ($P < 0.05$) after 6 months of treatment. Serum LDL-C, UA, HbA1C, and Cre levels, body weight and B.M.I remained unchanged throughout the study. The aforementioned data are detailed in Table 2.

The reduction in serum ALT levels after 6 months was negatively correlated with serum TG levels at baseline ($R = -0.342$, $P < 0.05$) (Figure 1). Moreover, the decrease in serum ALT levels after 6 months was positively correlated with serum ferritin levels at baseline ($R = 0.596$, $P < 0.05$) (Figure 2). Furthermore, the reduction in serum ALT levels after 6 months was significantly positively correlated with the decrease in serum ferritin levels after 6 months ($R = 0.684$, $P < 0.05$) (Figure 3).

Table 2: Changes in the examined variables after 3 and 6 months of pemafibrate treatment.

	Pre-treatment	3 Months	6 Months
AST (IU/L)	35.3 ± 21.6	30.0 ± 15.1*	28.8 ± 12.4*
ALT (IU/L)	44.5 ± 36.8	29.5 ± 18.4*	27.1 ± 16.7*
γ-GTP (IU/L)	51.0 ± 41.8	33.8 ± 22.0*	30.2 ± 20.0*
LDL-C (mg/dL)	119.3 ± 26.3	115.6 ± 30.2	114.6 ± 23.7
HDL-C (mg/dL)	51.1 ± 14.5	56.0 ± 14.4*	55.0 ± 13.0*
TG (mg/dL)	260.1 ± 134.3	158.4 ± 82.5*	169.7 ± 95.0*
UA (mg/dL)	5.42 ± 1.50	5.68 ± 1.22	5.62 ± 1.24
Cre (mg/dL)	0.77 ± 0.24	0.77 ± 0.21	0.74 ± 0.19
HbA1C (%)	6.12 ± 0.73	6.08 ± 0.72	6.11 ± 0.71
Body weight (kg)	67.6 ± 14.1	67.9 ± 14.1	67.8 ± 14.0
Ferritin (ng/mL)	152.4 ± 130.0	120.6 ± 83.2*	106.6 ± 75.3*
APRI	0.41 ± 0.34	0.34 ± 0.25*	0.32 ± 0.21*
FIB-4 index	1.63 ± 0.88	1.56 ± 0.93	1.51 ± 0.74*
B.M.I	26.2 ± 3.83	26.4 ± 3.88	26.3 ± 3.84

AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transferase; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid; Cre, creatinine; HbA1C, glycated hemoglobin; APRI, AST to platelet ratio index; FIB-4, fibrosis-4; B.M.I, Body Mass Index Data are presented as mean ± standard deviation. * $P < 0.05$ vs. before treatment.



Concept Diagram/Graphical Abstract

The therapeutic effect of Pemafibrate for NAFLD.

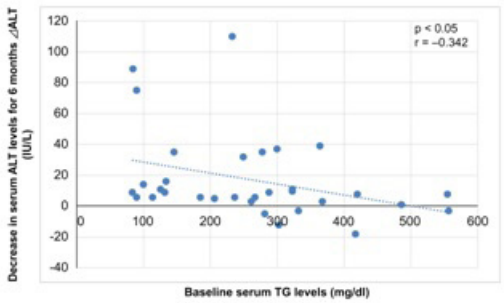


Figure 1: Correlation between decreased serum alanine aminotransferase levels and baseline serum triglyceride levels.

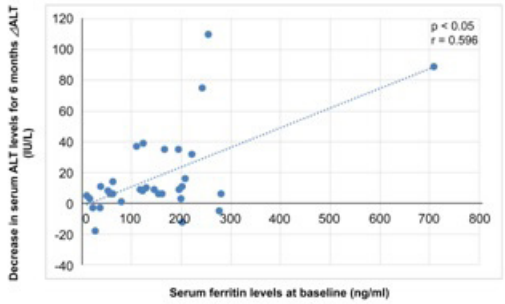


Figure 2: Correlation between decreased serum alanine aminotransferase levels and baseline serum ferritin levels at 6 months

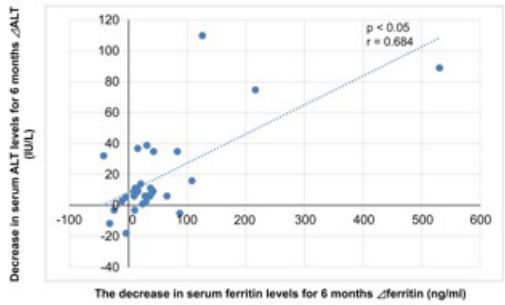


Figure 3: Correlation between decreased serum alanine aminotransferase levels and decreased serum ferritin levels

7. Discussion

The present study aimed to investigate the efficacy of pemafibrate for improving liver enzyme levels in patients with NAFLD. Accordingly, our results showed that pemafibrate was able to improve lipid abnormalities, as well as serum AST, ALT, and γ-GTP levels. Previous studies have reported that patients receiving pemafibrate had approximately 40% lower serum TG levels than those receiving a placebo. In the current study, serum TG levels decreased by approximately 35%, which came close to values reported in previous studies [10]. Pemafibrate treatment has been shown to promote an increase HDL-C level. Indeed, lipoprotein analysis showed that the increase in HDL-C levels with pemafibrate was attributed to significant increases in the three smaller subpopulations of HDL. Moreover, pemafibrate treatment also decrease lipid parameters closely associate with TGs, including VLDL-cholesterol, remnant-cholesterol, apo B, apo B 48, and apo C-III [11]. In the aforementioned study, patients receiving pemafibrate had higher serum HDL levels than those receiving a placebo. These results suggest that pemafibrate treatment may improve lipid abnormality and provide anti-atherogenic effects on lipid metabolism. Studies have shown that co-administration of fibrate and statin increased the incidence of rhabdomyolysis particularly in participants with impaired kidney function [12]. As such, impaired kidney function should be considered when administering fibrates, which may not be a concern with pemafibrate. A phase II study in Europe showed that 12 weeks of pemafibrate treatment had minor effects on changes in serum creatinine that could be consid-

ered clinically negligible or not associated with treatment [13]. Similarly, the current study found almost no change in serum UA and Cre levels partly because pemafibrate is predominantly metabolized not by the liver and not the kidneys [14].

In current study found that pemafibrate treatment significantly decreased serum AST, ALT, and γ-GTP levels. In mouse models of NAFLD/NASH, pemafibrate improved liver function and histology and attenuated fatty liver and ballooning, as well as inflammation and fibrosis [15]. The mechanisms by which pemafibrate improves NAFLD may involve the upregulation of genes for fatty acid oxidation. Studies have suggested that sterol regulatory element-binding protein-1c (SREBP-1c) plays a major role in the regulation of fatty acid synthesis, with its expression being significantly increased in NAFLD. SREBP-1c is positively regulated by insulin signaling pathways, including insulin receptor substrate (IRS)-1, 2. In NAFLD, enhanced IRS-1 expression was positively correlated with SREBP-1c expression [16]. Evidence has shown that NAFLD is often accompanied by insulin resistance [17]. Given that insulin resistance involves dysregulation of the insulin signaling pathways, including IRSs, the decrease in IRS-2 expression might be pertinent to insulin resistance, despite the increase in IRS-1 expression. However, IRS-2 expression decreased and was not correlated with SREBP-1c expression. Studies have shown that the suppression of IRS-2 expression is a compensatory mechanism for the enhanced IRS-1 expression and that the switch from to IRS-1-dependent regulation may cause enhanced fatty acid synthesis via SREBP-1c in NAFLD [18]. Thus, the concept of selective insulin resistance in the liver should be carefully considered given the potential for elevated fatty acids and TGs to worsen the diabetic state [19].

Figure 1 shows that the reduction in serum ALT levels after 6 months was negatively correlated with serum TG levels at baseline wherein lower serum TG levels promoted a greater the decrease in serum ALT levels at 6 months. Although NAFLD is generally controlled through dietary and exercise therapy, the aforementioned results suggest that the early administration of pemafibrate may have a positive influence on NAFLD therapy. Therefore, pemafibrate may improve serum TG levels and liver dysfunction in NAFLD in order to suppress fatty acid synthesis via SREBP-1c. Furthermore, Figures 2 and 3 show that reduced serum ALT levels were significantly correlated with baseline serum ferritin levels and decreased serum ferritin levels at 6 months. Given that serum ferritin is a protein expressed in the acute phase, its levels become elevated in the presence of liver necrosis and inflammation [20]. Some studies have suggested that the increased serum ferritin levels among patients with NAFLD might be associated with insulin resistance and hepatocyte damage [21]. Notably, Valenti. L et al. reported that the accumulation of iron may contribute to the production of inflammatory cytokines, which might lead to the hepatic fibrosis [22].

Mahsa et al. reported that phlebotomy had a positive effect on the biochemical markers of fatty liver and liver histology in patients with NAFLD [23]. Reducing iron liver stores through phlebotomy can decrease oxidative stresses and hepatocellular necrosis, with the associated improvement in insulin resistance also decreasing liver glucose production, which is one of the mechanisms for the development of steatosis in NAFLD [24]. Thus, elevated serum ferritin is related to insulin resistance and hepatocyte damage and plays a role in increasing fibrosis and inflammation during the progression of NAFLD [25].

Indeed, the current study showed that higher serum ferritin levels at baseline were associated with a greater decrease in serum ALT levels at 6 months. The aforementioned results suggest that pemafibrate treatment may largely effective for NAFLD cases having higher serum ferritin levels at baseline or a remarkable decline in serum ferritin levels at 6 months and that improvement in serum ferritin levels following pemafibrate treatment might improve insulin resistance, suppress liver inflammation, and prevent liver cirrhosis and hepatocellular carcinoma. Although liver biopsy is currently the gold standard for diagnosing progressive NASH, several drawbacks do exist, including sampling errors, cost, and the risk of complications [26]. Therefore, non-invasive diagnostic tests for diagnosing NAFLD or NASH are needed. The current study utilized the APRI and FIB-4 indices as non-invasive diagnostic tests for the diagnosis of liver fibrosis in participants with NAFLD. Accordingly, our findings showed a significant decrease in the APRI and FIB-4 indices after pemafibrate treatment. Decreased AST levels have been considered to directly indicate improvement in inflammation-related liver injury. Platelets, which have been reported to play an active role in the process of liver inflammation [27], exert potent inflammatory effects and play a central part in the progression from simple steatosis to NASH [28]. As such, decreased APRI could indicate improvement in hepatic inflammation and liver fibrosis. FIB-4 index has been proposed as a parameter indicating the progression of fibrosis in patients with hepatitis C and NAFLD. The JSG-NAFLD study involving Japanese subjects showed that the FIB-4 index was most useful in differentiating patients with advanced fibrosis [29]. The mechanism of liver carcinogenesis for NAFLD/NASH is obesity, non-infective sterile inflammation with metabolic syndrome, abnormal secretion of adipokine and the like. Also, prevention of obesity is closely connected with the suppression of progression for fatty liver, NAFLD/NASH and liver carcinogenesis for NAFLD/NASH. Pemafibrate may improve hepatic fibrosis and prevent cirrhosis and hepatocellular carcinoma, as well as promote decreased steatosis in patients with NAFLD. We previously reported the efficacy of canagliflozin, a type of SGLT2 inhibitor, in patients with NAFLD [30]. Accordingly, canagliflozin administration improved liver dysfunction and decreased serum HbA1C, BS, TG, UA, and ferritin levels together with the FIB-4 index and body weight. Although pemafibrate administration did not decrease body weight, it did improve liver dysfunction and decrease serum TG and ferritin levels, as well as the FIB-4 index. We believe that the improvement in liver dysfunction following

pemafibrate administration may contribute toward the suppression of fatty acid synthesis via SREBP-1c and improvement in insulin resistance through improved iron metabolism independent of the decrease in body weight.

The present study has some limitations worth noting. First, other lipid-lowering, hypoglycemic, anti-hypertensive, or UA-lowering agents, as well as differences in food intake and/or exercise, may have influenced the study results. Second, the number of participants for this study is small. Although we believe that the sample size is sufficient, more participants would have certainly enhanced the statistical significance of this study. Third, given the relatively short observation period of 6 months, studies examining the efficacy and safety of pemafibrate treatment for more than a year are needed. In conclusion, the current study showed that pemafibrate administration can be an effective pharmacotherapy during the early stages of NAFLD that contributes toward improving liver dysfunction and dyslipidemia and suppressing the progression to insulin resistance, diabetic mellitus, liver fibrosis, liver cirrhosis, and liver cancer. Future studies will be necessary to examine the long-term clinical efficacy of pemafibrate.

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