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22

Fenofibrate: Panacea for Aging-Related Conditions?

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1. Introduction

Fenofibrate, a selective peroxisome proliferator-activated receptors alpha (PPAR-α) activator, has been primarily developed to treat human dyslipidemia. PPAR modulate the expression of genes involved in lipid metabolism through peroxisome proliferator response elements (Willson et al., 2000). Although fenofibrate became commercially available in 1974 (Fournier, Inc., France), its lipid-lowering action mechanism has not been clarified until the late 1990's, contributing to open new research doors. With respect to the mechanisms of action, the drug with pleiotropic activity may be regarded as a "21st-century agent" (Staels et al., 1995).

Fenofibrate as a ligand of PPAR-α exhibits lipid-lowering effects by activating PPAR-α.

PPAR-α activators stimulate the β-oxidation of fatty acids in the liver resulting in a decreased availability of fatty acids for triglyceride (TG) synthesis (Schoonjans et al., 1995, 1996a, 1996b). In addition, fenofibrate enhances the production of apo-AI and apo-AII: the major component of HDL by activating PPAR-α and increases plasma level of HDL-C directly (Vu-Dac, 1994, 1995). Thus, the lipid-lowering action mechanism of fenofibrate involves potent TG-reducing and HDL-C-increasing actions. Statins, another type of lipid-lowering agent do not show such actions, though statins can inhibit hydroxymethylglutaryl (HMG)-CoA reductase (Endo A, 1992).

Furthermore, fenofibrate decreased the level of low-density lipoprotein cholesterol (LDL-C), especially "small dense LDL", which may be a powerful metabolic contributor to arteriosclerosis (Superko, 2000).

PPAR-α regulates the transcription of lipid-associated genes and various genes involved in homeostasis, suggesting the PPAR-α-mediated pleiotropic activities of fenofibrate. The reports on the pleiotropic activities of fenofibrate has been accumulated in a variety of large-scale, randomized, controlled trials (RCTs).

The studies presumably associated with the anti-aging actions of fenofibrate are reviewed in this article.

2. Clinical efficacy

The pleiotropic activities other than the lipid-lowering actions reported in clinical practice: the anti-inflammatory, antioxidant, and serum uric acid-reducing actions of fenofibrate are

reviewed in this section. These activities may be tightly associated with anti-aging actions of fenofibrate. Three large-scale, randomized, comparative clinical studies of fenofibrate ("DAIS", "FIELD" and "ACCORD"), in which intervention was performed in patients with type II diabetes mellitus (DM), were published since 2000.

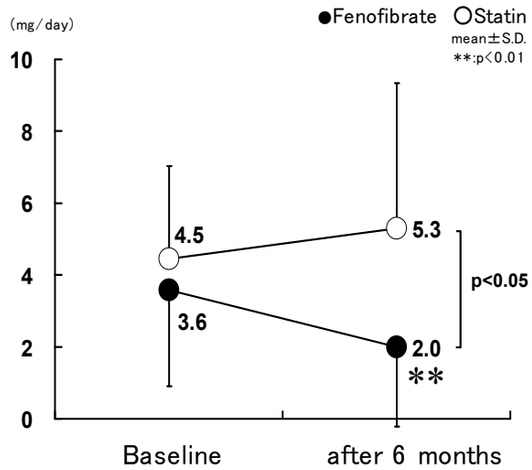
2.1 Anti-aging activities

Previous studies reported the involvement of various clinical parameters in anti-aging actions of fenofibrate (Schlesinger et al., 2009). In particular, chronic, systemic, silent, low-grade inflammation, named inflammaging is the target for intensive research in aging study (Goto, 2008b). Ross et al. defined arteriosclerosis as "chronic vascular inflammation" resulting from an interaction between oxidized lipid and macrophages (Ross, 1999). Inflammation is involved in the onset of arteriosclerotic disorders and acute coronary syndrome. Furthermore, oxidative stress that can induce a vicious cycle of chronic inflammation has been believed to be the major driving force to promote aging (Yu & Chung, 2001; Romano et al., 2010).

Uric acid has recently been considered to be a prognostic factor for the onset of DM and dementia that may accelerate aging (Hikita et al., 2007; Abate et al., 2004; Martinon et al., 2006), although an excess level of uric acid is the primary incite for gouty attack (Schlesinger et al., 2009).

2.1.1 Anti-inflammatory actions

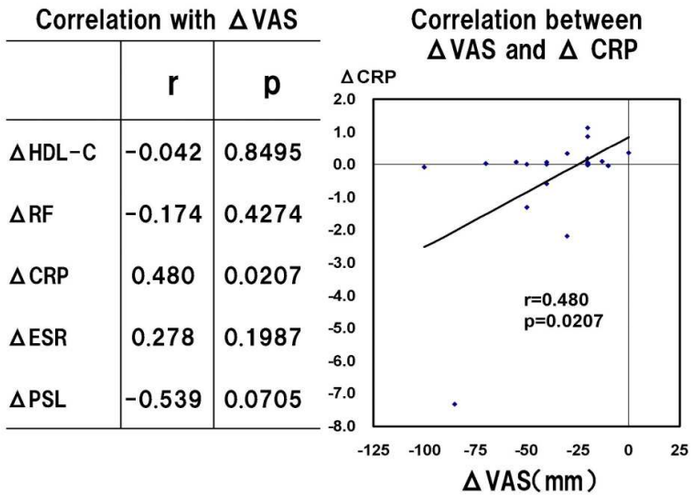
The anti-inflammatory actions of fenofibrate were reported in Nature in 1998 (Staels et al., 1998). PPAR-α ligand: fenofibrate inhibited cyclooxygenase-2 (COX-2) expression and prostaglandin production by suppressing the transcription of COX-2 genes through the inhibition of nuclear factor κB (NF-κB: transcription factor) signals. Fenofibrate administration decreased the inflammatory parameters including serum levels of IL-6, fibrinogen, and C-reactive protein (CRP) in coronary disease patients and the patients with hypertriglyceridemia (Tsimihodimos et al., 2004; Muhlestein et al., 2006).



Closed circles represent fenofibrate; open circles represent statins. mean ± S.D.
Wilcoxon signed rank test versus baseline, ** P <0.01, Mann-Whitney U test versus group

Fig. 1. Changes in prednisolone (PSL) dosage.

We compared the anti-inflammatory effects of fenofibrate and statins in 44 patients with a chronic inflammatory disorder: rheumatoid arthritis (RA) (Goto, 2010). Japanese patients with RA and dyslipidemia were randomly divided into 2 groups: fenofibrate (Lipidil, Kaken Pharmaceutical Co., Ltd., micronized fenofibrate at 200 mg/day, n=23) and statins (n=21) groups. After 6-month administration, the laboratory data were compared, and pain was evaluated using the visual analogue scale (VAS) and dose change of prednisolone (PSL) was monitored. The VAS scores significantly decreased in the fenofibrate (from 49.1 to 14.7 mm, $p<0.0001$) and statin (from 47.4 to 20.2 mm, $p<0.001$) groups. The dose of PSL significantly reduced only in the fenofibrate group (from 3.58 to 2.00 mg/day, $p<0.01$). The reduction rate was also significantly better than in the statin group (Fig. 1).
In the fenofibrate group, a significant correlation was between the rate of change in the ΔVAS score and that in the ΔCRP level (Fig.2. $p<0.05$). The results suggest that, in patients with RA, fenofibrate exhibits more potent anti-inflammatory effects compared to statins.



Spearman rank correlation coefficient
VAS visual analogue scale; HDL-C high-density lipoprotein-cholesterol; RF rheumatoid factor; CRP C-reactive protein; ESR erythrocyte sedimentation rate; PSL prednisolone

Fig. 2. Fenofibrate administration group: correlation between anti-inflammatory markers and ΔVAS.

2.1.2 Antioxidant actions

Oxidative stress has been considered to promote aging (Harman, 1978; Yu & Chung, 2001; Romano et al., 2010). As for oxidative stress markers that can be measured on clinical examination, serum lipids, MDA-LDL and Ox-LDL, and urinary lipids, 8-OHdG and 15-isoprostane F2t: 8-epi-PGF2α/8-isoPGF2α, are employed (Harman, 1978; Yu& Chung, 2001). Coenzyme Q10 (CoQ10), also known as ubiquinone shows antioxidant actions and has been monitored as an in vivo marker of oxidative stress.
CoQ10 is biosynthesized from mevalonic acid in the liver. As the pathway of CoQ10 biosynthesis is partially overlapped with that of cholesterol synthesis, the administration of an HMG-CoA reductase inhibitor, statins, reduces the production of CoQ10. Therefore,

statins, represented by atorvastatin, also inhibit CoQ10 biosynthesis in vivo, leading to the increase in oxidative stress (Mabuchi et al., 2005).

The administration of standard fenofibrate at 150 mg/day to 18 Japanese type II DM with dyslipidemia for 12 weeks significantly decreased the triglyceride (TG) level (from 232±109 to 145±74 mg/dL, -37%, $p<0.01$), and significantly improved the HDL-C level (from 45±8.7 to 52±9.8 mg/dL, +14%, $p<0.01$) (Asano et al., 2006).

The plasma ubiquinol-10 level in fenofibrate group increased significantly after 8 weeks (from 768±265 to 886±310 nM, $p<0.05$) and after 12 weeks (from 768±265 to 894±336 nM, $p<0.05$). However, total plasma CoQ10 level (ubiquinol-10 plus ubiquinone-10) as an oxidative stress marker, decreased in statin group, elevated in fenofibrate group after 12 weeks administration (from 1010±296 to 1070±285 nM, +6%). In addition, plasma ubiquinone-10 in fenofibrate group decreased insignificantly. Fenofibrate treatment elevates plasma CoQ10, especially plasma ubiquinol-10 level.

In the wild-type mice administered by diethylhexylphthalate (DEHP: PPAR-α activator), elevation of plasma ubiquinone was significant, but the elevation was not observed in the PPAR-α-null mice (Turunen et al., 2000). In addition, the expression of PPAR-α gene was regulated in the liver of SAMP1 (senescence accelerated mouse prone 1) mice given ubiquinol for long term (Schmelzer et al., 2010a, 2010b). Although the antioxidant action mechanisms of fenofibrate remained unclear in human, mice studies suggested the direct interaction between CoQ10 and PPAR-α.

Fenofibrate not only restores the serum lipid profiles, but also suppresses oxidative stress. Fenofibrate with a variety of pleiotropic activities may protect the pathogenesis and progression of aging-associated atherosclerosis.

2.1.3 Serum uric acid-reducing actions

Hyperuricemia, a common co-morbidity in the patients with metabolic syndrome and dyslipidemia has recently been emphasized as an independent risk factor for cardiovascular disease (Lippi et al., 2008).

Kodama et al. performed a meta-analysis of 11 clinical studies, and reported that a 1-mg/dL increase in the serum uric acid level significantly elevated the relative risk of type II DM by 1.17-fold (Kodama et al., 2009). Schretlen et al. investigated 96 persons aged 60 to 92 years, and indicated that the information-processing capacity and memory were reduced in persons with high uric acid level, suggesting that the serum uric acid level may be a prognostic factor for dementia (Schretlen et al., 2007). Thus, hyperuricemia may play a role not only in the onset of cardiovascular disease but also in the promotion of dementia and aging.

Fenofibrate has been known to reduce the serum levels of lipids and also uric acid (Schlesinger et al., 2009). The serum uric acid-reducing action mechanism of fenofibrate, independent of lipid-profile changes, involves the promotion of uric-acid excretion (Liamis et al., 1999).

Urate Transporter 1 (URAT1), the target molecule of uric acid-reducing agents such as benzbromarone was identified which is responsible for the reabsorption of uric acid in the proximal uriniferous tubule (Enomoto et al., 2002). Furthermore, URAT1 inhibition was involved in the serum uric acid-reducing action mechanism of fenofibrate (Uetake et al., 2010). According to their study, the single-dose administration of standard fenofibrate at 300

mg to healthy adults decreased the serum uric acid level by approximately 1.5 mg/dL. In Japan, fenofibrate has been administered to metabolic syndrome patients with hyperuricemia, leading to the decrease in the serum uric acid level by approximately 2 mg/dL.

2.2 Randomized controlled trial (RCT)

Large-scale, randomized, controlled clinical trials of fenofibrate involving type II DM, that is, high-risk patients for arteriosclerosis, were conducted. The representative 3 studies were reviewed in this section: "DAIS" study, regarding coronary arteriosclerosis retraction, "FIELD" study, in which the inhibitory effects on cardiovascular events were examined, and "ACCORD" study, in which the inhibitory effects of lipid-intensified therapy with statins on cardiovascular events were investigated.

2.2.1 Diabetes Atherosclerosis Intervention Study (DAIS)

The DAIS is a placebo-controlled, double-blind, comparative study to verify whether the deterioration of coronary arteriosclerosis can be prevented by restoring abnormal lipid metabolism with fenofibrate in type II diabetics employing quantitative coronary angiography (DAIS investigators, 2001). This international, interventional study was conducted based on the World Health Organization (WHO)'s request and cooperation. This study is the first interventional study in which it was prospectively evaluated whether the correction of disturbance of lipid metabolism in type II DM prevents the deterioration of arteriosclerosis. It was carried out in Canada, Finland, Sweden, and France. Four-hundred and eighteen patients with type II diabetes in whom blood sugar control was favourable were randomly divided into fenofibrate (micronized fenofibrate, 200 mg/day, n=207) and placebo (n=211) groups to evaluate the deterioration of coronary arteriosclerosis using quantitative coronary angiography after 38-month (mean duration) administration.

In the fenofibrate group, a decrease in the minimum lumen diameter and an increase in the percent stenosiswere significantly suppressed in comparison with the placebo group (by 40%), confirming the inhibitory effects of fenofibrate on the deterioration of coronary arteriosclerosis in type II DM.

In the continuing study of DAIS, fenofibrate reduced the small dense LDL level, leading to the inhibition of the deterioration of diabetic nephropathy (DAIS investigators, 2003, 2005), confirming that fenofibrate inhibited the deterioration of macro- and micro-angiopathy in type II DM.

2.2.2 Fenofibrate Intervention and Event Lowering in Diabetes Study (FIELD)

The FIELD is a study to verify the inhibitory effects of fenofibrate on cardiovascular events involving approximately 10,000 patients with type II DM (FIELD investigators, 2005). It was conducted in Finland, Australia, and New Zealand. The subjects were 9,795 type II diabetics with mild dyslipidemia. They were randomly divided into fenofibrate (micronized fenofibrate, 200 mg/day, n=4,895) and placebo (n=4,900) groups. Each agent was administered for 5 years.

In the fenofibrate group, this agent inhibited the incidence of coronary events by 11% in comparison with the placebo group. Unfortunately, there was no significant difference between two groups. This was possibly because statins were combined with the

placebo/fenofibrate in 32% of patients receiving the placebo and in 16% of patients receiving fenofibrate, reducing the effects of fenofibrate alone. Fenofibrate decreased the incidence of non-fatal myocardial infarction by 24% ($p<0.05$) and that of total cardiovascular events by 11% ($p<0.05$), confirming its efficacy.

In primary prevention patients without a history of cardiovascular disease, accounting for approximately 80%, fenofibrate significantly inhibited the incidences of coronary (by 25%) and total cardiovascular (by 19%) events in comparison with the placebo group. Furthermore, in the FIELD, fenofibrate inhibited the onset of diabetic nephropathy, deterioration of diabetic retinopathy, proportion of patients undergoing lower-limb amputation, and deterioration of diabetic neuropathy (FIELD investigators, 2005, 2007, 2009, 2010, 2011). As fenofibrate reduced DM-associated 3 major complications (retinopathy, nephropathy and neuropathy), this agent may be useful for treating diabetic complications.

Study name	Micro/macro-angiopathy	Rate of decrease in the relative risk	p value	Reference
DAIS	Diabetic nephropathy	progression in albumin excretion fenofibrate 8%, Placebo 18%	$p<0.05$	DAIS investigators, 2005
FIELD	Diabetic nephropathy	-14%	$p=0.002$	FIELD investigators, 2005, 2011
	Diabetic retinopathy	-31%	$p<0.001$	FIELD investigators, 2007
	Lower-limb amputation	-36%	$p=0.02$	FIELD investigators, 2009
	Diabetic neuropathy	-40%	$p=0.009$	FIELD investigators, 2010
ACCORD-Lipid	Diabetic nephropathy	incidence of microalbuminuria fenofibrate 38.2%, Placebo 41.6%	$p=0.01$	ACCORD Study Group, 2010
		incidence of macroalbuminuria fenofibrate 10.5%, Placebo 12.3%	$p=0.04$	
ACCORD-EYE	Diabetic retinopathy	-40%	$p=0.006$	ACCORD Study Group; ACCORD Eye Study Group, 2010

Table 1. Inhibitory effects of fenofibrate on diabetic angiopathy in a large-scale clinical study involving type II DM

2.2.3 ACCORD-Lipid & ACCORD-EYE study

In the ACCORD-Lipid study, the inhibitory effects of 3 intensified/standard medicinal therapies (blood sugar, blood pressure, lipids) on compound cardiovascular events were investigated in approximately 10,000 type II diabetics with mild dyslipidemia and the high risk of cardiovascular disease (CVD) under the auspices of the National Institutes of Health (NIH). Lipid intervention was performed in 5,518 patients: intensified (simvastatin 20mg + micronized fenofibrate 200mg) and standard (simvastatin 20mg + placebo) therapies. The mean follow-up was 4.7 years. In the fenofibrate-combined group, the incidence of cardiovascular events was inhibited by 8%, although there was no significant difference. In patients with a pre-treatment TG level of 204 mg/dL or more and HDL-C level of 34 mg/dL or less, significant inhibitory effects on events were confirmed (-31% ($p<0.05$), NNT=20) (ACCORD Study Group et al., 2010).

In the ACCORD–EYE study, the deterioration of diabetic retinopathy was evaluated in 2,856 patients from whom informed consent was obtained (lipid intervention: 1,593 patients) among type II DM who participated in the ACCORD-Lipid study (ACCORD Study Group; ACCORD Eye Study Group et al., 2010). In the fenofibrate-combined group, intensified therapy significantly inhibited the deterioration of diabetic retinopathy (by 40%) in comparison with the simvastatin group ($p=0.006$). The ACCORD–EYE study, the second large-scale clinical study following the FIELD, demonstrated the inhibitory effects of fenofibrate on the deterioration of diabetic retinopathy, supporting its efficacy for diabetic retinopathy.

The inhibitory effects of fenofibrate on diabetic microangiopathy are summarized below (Table 1). In a large-scale clinical study of lipid-lowering agents, no statin exhibited any inhibitory effects on diabetic microangiopathy. Only fenofibrate inhibited the complication. Thus, fenofibrate should be recognized as a "prophylactic drug for diabetic complications", and not solely as a lipid-lowering agent.

3. Conclusion

Fenofibrate is a generalized, PPAR-α-mediated, serum lipid-lowering agent. In this chapter, the pleiotropic effects of fenofibrate other than serum lipid-lowering actions were primarily reviewed. Concerning to the anti-inflammatory actions, we examined the effects of fenofibrate in patients with a representative inflammatory disorder, RA. Although there were no significant changes in inflammation parameters including CRP and ESR, improvement in the ΔVAS and PSL dose was achieved in patients receiving fenofibrate. In particular, improvement in the ΔVAS was significantly correlated with a reduction in the ΔCRP level, suggesting that the anti-inflammatory effects of fenofibrate may contribute the improvement in the patient's quality of life (QOL).

In Japan, infectious diseases have been the major causes of death in patients with RA (Souen, 2007; Shinomiya et al., 2008). However, the proportion of cardiovascular events represented by cerebral/myocardial infarction has been increasing, probably because of the changes in life-style (Goto et al., 2008a). So, fenofibrate with lipid-lowering, anti-inflammatory and anti-oxidant actions may be appropriate for reducing disturbances of lipid metabolism and also homeostasis in Japanese patients with RA.

With respect to antioxidant actions, fenofibrate, but not statin increased the plasma level of ubiquinol-10: a family of CoQ10. As fenofibrate exhibits antioxidant actions, combination

therapy with fenofibrate and statins may be useful for achieving anti-aging effects and reducing oxidative stress. However, the evaluation methods for antioxidant activity in human should be strictly reviewed in the near future.

The serum uric acid-reducing actions of fenofibrate are regarded as one of its characteristic pleiotropic effects. The action mechanism may be mediated by a uric acid transporter, URAT1, but not by PPAR-α. This may suggest that among fibrate preparations fenofibrate may be favorably administered to the patients with high serum TG and high uric acid levels, as no other fibrate preparations can reduce the serum level of uric acid.

The large-scale clinical study of fenofibrate (FIELD) showed that early administration to "primary prevention" diabetics without a history of cardiovascular events inhibited the onset of cardiovascular events. Furthermore, the DAIS, FIELD, and ACCORD-EYE studies suggested that early fenofibrate administration to all diabetics with dyslipidemia should inhibit the deterioration of diabetic complications regardless of the duration of disease or risk of events.

Fenofibrate shows pleiotropic actions, especially a variety of clinical effects that may not be achieved by statins. This agent may be useful for inhibiting the deterioration of arteriosclerosis, and may play a role as an anti-aging panacea if properly used.

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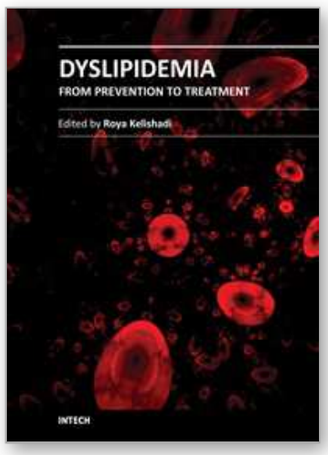

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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

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