Beneficial Vascular and Metabolic Effects of Peroxisome Proliferator–Activated Receptor-α Activators

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Abstract—Fibric acid is a synthetic ligand of the nuclear receptor peroxisome proliferator–activated receptor (PPAR)-α that is highly expressed in skeletal muscle and heart, where it promotes β-oxidation of fatty acids to mediate hypolipidemic actions. PPAR-α regulates expression of key proteins involved in atherogenesis, vascular inflammation, plaque instability, and thrombosis. Thus, PPAR-α may exert direct antiatherogenic actions in the vascular wall. Endothelial dysfunction associated with the metabolic syndrome and other insulin-resistant states is characterized by impaired insulin-stimulated nitric oxide production from the endothelium and decreased blood flow to skeletal muscle. Thus, improvement in insulin sensitivity leads to improved endothelial function. This may be an additional mechanism whereby fibrates decrease the incidence of coronary heart disease. Adiponectin is a protein secreted specifically by adipose cells that may couple regulation of insulin sensitivity with energy metabolism and serve to link obesity with insulin resistance. In this review, we discuss the mechanisms underlying the vascular and metabolic effects of fibrates that may act synergistically to prevent or regress atherosclerosis and coronary heart disease. (Hypertension. 2005;46:1086-1092.)

Key Words: fibrates ■ endothelium ■ adipose tissue ■ insulin resistance ■ cardiovascular diseases

Patients with coronary heart disease or its risk factors have impaired vascular endothelial function.1,2 Endothelial dysfunction is characterized by inflammation, smooth muscle proliferation, extracellular matrix deposition, and thrombus formation that contribute to the development of clinically significant atherosclerosis. Nitric oxide (NO) plays a pivotal role in maintaining vascular health and protecting against vascular injury under these pathologic conditions. Plaque disruption and thrombosis are important causes of acute coronary syndromes, even in the absence of angiographically detectable severe stenosis. Acute coronary syndromes usually result from rupture of these vulnerable plaques as a result of an accelerated inflammatory process. Matrix metalloproteinase (MMP), tissue inhibitor of MMP (TIMP), tissue factor (TF), and plasminogen activator inhibitor type-1 (PAI-1) within the plaque are major determinants of plaque instability and thrombogenicity.2,3

Fibric acid is a synthetic ligand of peroxisome proliferator–activated receptor (PPAR)-α, a nuclear receptor activated by fatty acids and its derivatives. PPAR-α mediates the hypolipidemic actions of fibrates and is highly expressed in the heart, where it stimulates β-oxidation of fatty acids. PPAR-α regulates the expression of key proteins involved in all stages of atherogenesis, including vascular inflammation, plaque instability, and thrombosis. PPAR-α exerts direct antiatherogenic actions in the vascular wall.4 Thus, direct vascular effects of fibrates may contribute to a reduction of cardiovascular events and may explain its clinical benefits observed in human trials.5,6

Endothelial dysfunction associated with the metabolic syndrome and other insulin-resistant states is characterized by impaired insulin-stimulated production of NO from the endothelium and decreased blood flow to skeletal muscle.7 Thus, improvement in insulin sensitivity leads to improved endothelial function, and this may be one mechanism by which fibrates decrease the incidence of coronary heart disease. Excess body fat is frequently associated with dyslipidemia, the metabolic syndrome, and atherosclerotic vascular diseases.8 Adiponectin is one of a number of proteins secreted by adipose cells that may couple the regulation of insulin sensitivity with energy metabolism and serve to link obesity with insulin resistance.9 Adiponectin also possesses antiatherogenic properties.10 In this review, we discuss the vascular and metabolic effects of fibrates as plausible mechanisms to prevent or regress atherosclerosis and coronary heart disease.

PPAR-α Activators and Their Receptor Affinity

The PPAR family contains 3 different subtypes, designated PPAR-α, PPAR-γ, and PPAR-δ. Fibrates (synthetic ligands of PPAR-α) that are currently in wide clinical use include...
bezaflibrate, cipofibrate, fenofibrate, and gemfibrozil. Bezaflibrate, cipofibrate, and fenofibrate are related to the parent compound clofibrate by their chemical structures. Gemfibrozil is a nonhalogenated phenoxypentanoic acid and thus, is distinct from other halogenated compounds. A range of potencies for various fibrates to activate human PPAR-α exists. The activity of fenofibrate in a cell-based transactivation assay for PPAR-α is 40% greater than that of either bezafibrate or clofibrate. Both clofibrate and fenofibrate are dual activators of PPAR-α and PPAR-γ, with 10-fold selectivity for PPAR-α, whereas bezafibrate activates all 3 PPAR subtypes at comparable doses.11,12

Vascular Effects of Fibrates

Effects on Lipoproteins and Lipoprotein Particles

When compared with placebo, fenofibrate significantly decreased total cholesterol, non-HDL cholesterol, apolipoprotein B, and triglycerides and increased HDL cholesterol and apolipoprotein A-I in patients with hypertriglyceridemia.13,14

For patients with persistent hypertriglyceridemia, low HDL cholesterol, and low or normal LDL cholesterol who do not respond well to statins, treatment with fibrates instead of statins should be considered.15 Several studies reported that combined therapy with statins and fibrates was more effective at controlling atherogenic dyslipidemia in patients with combined hyperlipidemia than either drug alone.16–19 Combination therapy or cipofibrate alone significantly reduced plasma triglycerides. Combination therapy or simvastatin alone significantly reduced LDL cholesterol when compared with cipofibrate therapy alone. Cipofibrate or combination therapy increased LDL particle size, whereas simvastatin alone had no significant effect on this parameter.17

Unfortunately, the combination of statins and fibrates is more likely to be accompanied by myopathy.20,21 This may be because of the fact that gemfibrozil therapy has significant pharmacokinetic interactions with statins, leading to increased plasma levels of statins.22,23 This limitation has not been observed with fenofibrate, and no significant side effects were observed with combination treatment with statins and fenofibrate.16,18,19,21 In this regard, Grundy et al.24 reported the effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Combination therapy with simvastatin plus fenofibrate was more effective in reducing elevated triglycerides levels when compared with simvastatin monotherapy. This treatment strategy improved the lipoprotein pattern in patients with combined hyperlipidemia, with good safety and tolerability. Jones and Davidson25 examined differences in the rate of myotoxicity when fenofibrate or gemfibrozil was used in combination with statins. Patients taking fenofibrate had fewer reports of rhabdomyolysis than did those taking gemfibrozil when used in combination with any statin. Of the total number of reports of rhabdomyolysis for fibrate and statin therapies, only 2.3% (14 of 606) were associated with fenofibrate/cerivastatin combination therapy, whereas 8% (533 of 606) were associated with gemfibrozil/cerivastatin combination therapy. Combined therapy with atorvastatin and fenofibrate significantly changed lipoproteins when compared with atorvastatin or fenofibrate alone in patients with combined hyperlipidemia.16 Importantly, no patients with combined therapy (atorvastatin and fenofibrate) experienced serious adverse effects.

Effects on Vasomotor Function

Improved flow-mediated dilation after oral fat loading in subjects with type 2 diabetes was observed after 12 weeks of cipofibrate therapy.26 However, similar benefits were not observed in healthy volunteers after 3 weeks of gemfibrozil.27 In patients with coronary artery disease, exercise-induced coronary artery dilation increased after bezafibrate therapy when compared with placebo28; however, gemfibrozil alone or in combination with niacin did not significantly improve flow-mediated dilation.29 We and others found that fenofibrate therapy significantly improved flow-mediated dilation (Figure 1).13,14,30 Plausible mechanisms for this include beneficial changes in lipoprotein levels. In support of this hypothesis, significant correlations between improvement in flow-mediated dilation and changes in total cholesterol, LDL cholesterol, and non-HDL cholesterol levels were observed. Niacin treatment increased HDL cholesterol levels, improved flow-mediated dilation, and increased endothelial NO synthase expression in patients, suggesting that HDL-mediated increases in endothelial NO synthase expression and activity may contribute to enhanced vasorelaxation.31 We also observed that fenofibrate treatment increased HDL cholesterol levels and improved flow-mediated dilation. Furthermore, PPAR-α activators stimulate synthesis of endothelial NO synthase in cell culture and lowered oxidative stress, with a resultant increase in NO bioactivity.32,33 Interestingly, treatment with PPAR-α ligands also decreased the expression and
activity of inducible NO synthase, providing evidence for their anti-inflammatory effects. Hence, suppression of inflammatory signaling pathways by PPAR-α activation provides an additional mechanism whereby PPAR-α ligands may improve endothelial NO synthase activity.34 PPAR-α activators also exerted protective effects against postischemic myocardial15 and cerebral16 injury in mice by an antioxidant mechanism that improved the bioavailability of NO. However, fenofibrate therapy did not change plasma levels of nitrate and malondialdehyde in humans.13 Thus, fenofibrate may not have clinically important antioxidant effects.

Fenofibrate may prevent the development of angiotensin II–dependent hypertension.33,37 Vera et al37 demonstrated that fenofibrate treatment prevented the development of angiotensin II–dependent hypertension in C57BL/6J mice. Upregulation of 20-hydroxyeicosatetraenoic acid production in renal tubules may contribute to the blood pressure–lowering effects of fenofibrate treatment. In addition, fenofibrate improved myocardial inflammation and collagen deposition in rats infused with angiotensin II.38 Fenofibrate treatment of deoxycorticosterone acetate (DOCA)-salt–hypertensive rats prevented myocardial fibrosis and reduced hydroxyproline content and procollagen I and III mRNA levels in vessels.39 Inflammatory gene expression associated with nuclear factor (NF)-κB (typically elevated in DOCA-salt rats) was significantly suppressed by fenofibrate. Finally, activation of NF-κB and expression of I-κB-α in DOCA-salt rats were normalized by fenofibrate treatment.

**Effects on Inflammation**

Transcription of many adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), is regulated by the nuclear transcription factor NF-κB.40 In addition to adhesion molecules, NF-κB also activates transcription of genes encoding chemoattractant factors that attract monocytes into the vessel wall. Importantly, elevated levels of free fatty acids associated with insulin resistance, obesity, diabetes, and the metabolic syndrome cause endothelial dysfunction by activating innate immune inflammatory pathways upstream of NF-κB (Figure 2).41

PPAR-α activators reduced cytokine-induced expression of VCAM-1 and ICAM-1 in human carotid artery endothelial cells in culture.42 Pasceri et al43 reported that fibrates reduced C-reactive protein (CRP)–induced expression of monocyte chemoattractant protein (MCP-1) in human umbilical vein endothelial cells. With regard to clinical studies, Marchesi et al40 observed that 3-month therapy with fenofibrate in hypertriglyceridemic patients decreased VCAM-1 and ICAM-1 levels in the fasting state. Kowalski et al44 reported that fenofibrate reduced both monocyte secretion and plasma levels of MCP-1 in patients with type IIb dyslipidemia.

The effect of PPAR-α activators on human CRP expression has been studied in nonatherosclerotic human CRP-transgenic mice.45 In these studies, treatment with PPAR-α activators decreased interleukin (IL)-1β–induced plasma CRP levels, independent of their cholesterol-lowering effects. These direct anti-inflammatory effects in vivo occurred at the transcriptional level and were confirmed in cultured human liver slices and human hepatoma cells. A molecular rationale for suppression of IL-1–induced CRP transcription is provided by the fact that fenofibrate upregulates I-κB protein expression. This reduces nuclear translocation of p50–NF-κB, resulting in decreased amounts of nuclear p50–NF-κB and CCAAT/enhancer binding protein-β complexes, the major determinants of CRP transcription. These results provide strong evidence for a direct suppressive effect of fenofibrate on CRP expression, independent of cholesterol lowering and atherogenesis. Fenofibrate therapy significantly lowered CRP in hypertriglyceridemic men or those with combined hyperlipidemia.16,47 Fenofibrate therapy also lowered high-sensitivity CRP levels in patients with hypertriglyceridemia.14
Tumor necrosis factor (TNF-α) is a multifunctional circulating cytokine derived from endothelial and smooth muscle cells, as well as macrophages, associated with coronary atherosclerosis. Pretreatment of rat cardiac myocytes with PPAR-α activators inhibited lipopolysaccharide-induced TNF-α mRNA and protein expression in a dose-dependent manner. In clinical studies, fenofibrate significantly lowered plasma levels of TNF-α in patients with hypertriglyceridemia. IL-6 is the principal procoagulant cytokine. In human aortic smooth muscle cells, PPAR-α activators inhibit expression of IL-6. In patients with mild hyperlipidemia, PPAR-α activators decreased circulating levels of IL-6. Elevated levels of IL-6 were also associated with an increased risk of future myocardial infarction in healthy men. With regard to IL-1β, Okopien et al reported that fenofibrate therapy significantly reduced IL-1β mRNA expression in patients with type IIb dyslipidemia, as well as IL-1β release by cultured monocytes.

The proinflammatory mediator CD40 ligand (CD40L) is expressed on CD4+ T cells and activated platelets. Both membrane-bound and soluble forms of CD40L interact with CD40L expressed on vascular cells. CD40L plays an important role in a cascade of inflammatory and proatherothrombotic functions. In cell culture, fenofibrate diminished expression of CD40, CD40L, and gelatinase activities (MMP-2 and MMP-9) induced by CRP in human umbilical vein endothelial cells. In clinical trials, fenofibrate therapy significantly reduced IL-1α and soluble CD40L levels in combined hyperlipidemia.

Effects on Plaque Stability
Lipid-lowering therapies diminished the accumulation of macrophages as well as macrophage expression of MMP-9 in animal studies. Indeed, Xu et al demonstrated that oxidized LDL upregulated MMP-9 expression while reducing TIMP-1 in monocyte-derived macrophages. Furthermore, HDL abrogated oxidized LDL-induced MMP-9 expression. On the other hand, PPAR activators inhibited expression of MMP-9. This PPAR-dependent inhibition may prevent the rupture of atherosclerotic plaques and subsequent thrombosis. TNF-α was found to stimulate the synthesis and secretion of MMP-9. Despite these experimental observations, in clinical studies, fenofibrate did not significantly change serologic markers of plaque stability, and no significant correlations between lipoprotein levels and MMP-9 activity or TIMP-1 levels were observed in humans.

Effects on Hemostasis
PPAR-α inhibited the expression of TF in human monocytes and macrophages. However, fenofibrate treatment did not affect TF activity in patients with hypertriglyceridemia. Several lipid-lowering agents potentiate fibrinogen, independent of alterations in plasma lipoproteins. In this regard, gemfibrozil and fenofibrate reduced plasma levels of PAI-1 and fibrinogen in hypercholesterolemic and hypertriglyceridemic subjects. Fibrates also modulated secretion of the thrombosis inducer PAI-1. These actions of fenofibrate on fibrinogen and PAI-1 antigen levels may decrease the thrombogenic response. Saklamaz et al did not find any significant change in fibrinogen levels during treatment with pravastatin and atorvastatin. However, in the fenofibrate group, fibrinogen levels were significantly decreased in patients with type IIA and type IIB hyperlipidemia. Thus, the beneficial effects of lipid-lowering drugs involve additional mechanisms other than just lipid lowering per se.

Metabolic Effects

Effects of Fibrates on Adiponectin and Insulin Resistance
Therapeutic approaches aimed at increasing plasma adiponectin levels or adiponectin tissue sensitivity may be beneficial in preventing or treating disorders associated with insulin-resistance, including the metabolic syndrome, diabetes mellitus, and atherosclerosis. A number of recent studies have documented beneficial effects of cardiovascular drugs to raise adiponectin levels, which are predicted to promote insulin-sensitizing and antiatherogenic actions.

PPAR-α activators improved insulin sensitivity and reduced adiposity in rodent models of insulin resistance. Chinetti et al performed a DNA array-based global gene expression profiling experiment on human primary macrophages treated with specific PPAR-α and PPAR-γ agonists. They found that expression of AdipoR2, one of the two recently identified receptors for adiponectin, was induced by activation of either PPAR-α or PPAR-γ. In addition, Shimomura et al demonstrated short-term effects of a PPAR-α ligand (fenofibrate) and a PPAR-γ ligand (troglitazone) to increase KATP channel activity and insulin secretion in an insulinoma cell line. Thus, fenofibrate may interact directly with the β-cell membrane to stimulate insulin secretion.

Fenofibrate has been found to improve insulin sensitivity in patients with the metabolic syndrome. Plasma levels of adiponectin are inversely correlated with body mass index, and there are significant correlations between baseline adiponectin levels and baseline HDL cholesterol or triglyceride levels. Fenofibrate lowers triglyceride and increases HDL cholesterol levels. Fenofibrate therapy significantly increased plasma adiponectin levels and insulin sensitivity in patients with primary hypertriglyceridemia (Figure 3). In that study, significant correlations between changes in adiponectin levels and flow-mediated dilation, insulin sensitivity, CRP levels, or insulin levels were observed after fenofibrate therapy. Multivariate regression analysis demonstrated that only changes in adiponectin levels persisted as an independent predictor of changes in flow-mediated dilation.

Fenofibrate therapy for 2 months increased adiponectin levels and improved insulin sensitivity without a change in body weight. This raises the possibility that drug therapy is directly altering adiponectin levels independent of adiposity. Thus, it is possible that increased adiponectin levels are contributing to an improvement in insulin sensitivity rather than simply reflecting a change in adiposity. In another study, fenofibrate alone or combined therapy with atorvastatin and fenofibrate for 2 months in patients with combined hyperlipidemia significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements. However, atorvastatin therapy alone did not.
Clinical Implications and Future Prospects

The metabolic syndrome is associated with atherosclerotic disease. Obesity is one of the most important contributors to cardiovascular disease. Adipose tissue secretes various bioactive molecules that may directly contribute to the development of obesity-related diseases. Dysregulation of adipocyte-derived endocrine factors caused by overnutrition may directly contribute to the development of atherosclerosis. Similar beneficial effects of fenofibrate in a subgroup of 24 patients with the metabolic syndrome were observed when compared with a total cohort of 46 hypertriglyceridemic patients.

Low adiponectin levels and insulin resistance are important in the pathogenesis of atherosclerosis and coronary heart disease. Fenofibrate, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II type I receptor blockers (ARBs), which reduced cardiovascular events in randomized, clinical trials, have important effects on increasing adiponectin levels and reducing insulin resistance. Moreover, these drugs improve endothelium-dependent dilation and reduce vascular inflammation (Figure 2). Patients with the metabolic syndrome are increasing in number and comprise one of the largest groups of individuals with obesity, hyperlipidemia, hypertension, and insulin resistance. The distinct biologic actions of statins, fenofibrate, ACE inhibitors, and ARBs on lipoprotein levels and the angiotensin system may improve endothelium-dependent vascular function and insulin sensitivity by different mechanisms (Figure 2).

PPAR-α activators attenuate the development of hypertension, correct structural abnormalities, and improve endothelial dysfunction induced by angiotensin II. These effects are associated with decreased oxidative stress and inflammation in the vascular wall. Indeed, combination therapy has beneficial additive effects on endothelial function, inflammatory markers, adiponectin levels, and insulin sensitivity. This may be because of the combined effects of the respective monotherapies to improve endothelial function, raise adiponectin levels, and increase insulin sensitivity. However, fenofibrate combined with ACE inhibitor or ARBs therapies have not been investigated compared with either drug alone. The additive beneficial effects of combined therapy are predicted to reduce cardiovascular events, particularly in patients with the metabolic syndrome, more than monotherapy with either drug alone.

In conclusion, fenofibrate therapy significantly improves the percentage of the flow-mediated dilator response to hyperemia, reduces levels of inflammatory markers, increases adiponectin levels, and improves insulin sensitivity in hypertriglyceridemic patients with or without the metabolic syndrome. The effects of fenofibrate treatment to improve endothelial function and insulin sensitivity and suppress inflammatory markers relevant to cardiovascular disease are likely to have important beneficial health consequences in patients with hypertriglyceridemia and/or the metabolic syndrome. Furthermore, the additive beneficial effects of combined therapy are predicted to reduce cardiovascular events, particularly in patients with the metabolic syndrome, more than monotherapy with either drug alone.
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