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FIBRATES THE BEST MODIFYING STRATEGY FOR DYSLIPIDEMIAS : A REVIEW

Gurfeth Singh^{1*},

Ankur Rohilla², Seema Rohilla², Ashok Kumar¹, Masih Uzzaman Khan Khan³, Razia Khanam²

¹Onkar College of Pharmacy, Sunam-148026, Punjab, India

² Department of Pharmaceutical Sciences, Shri Gopi Chand Group of Institutions, Baghpat-250609, UP, India

³ Sri Sai College of Pharmacy, Badhani, Pathankot-145001, Punjab, India

ABSTRACT

Fibrates, the synthetic agonists of the peroxisome proliferator activated receptor- α (PPAR- α), are known to be conventional, effective and well-tolerated agents in the management of dyslipidemias. At the molecular level, fibrates bind to PPAR- α and increase the expression of genes that are involved in fatty acid uptake (fatty acid binding protein, FABP), β -oxidation (acyl-CoA oxidase, ACOX) and ω -oxidation (cytochrome P450). The key actions of fibrates include reduction in elevated triglyceride (TG) and low-density lipoprotein (LDL) levels and consequent rise in high density lipoprotein (HDL) cholesterol concentrations. Moreover, the shifting of dense LDL to larger more buoyant particles is encouraged by fibrates which makes them less susceptible to oxidation and possess higher binding affinity for removal by the non-atherogenic LDL receptor pathway. The present review article highlights about the mechanism of action of fibrates in the management of dyslipidemias. Moreover, the pleiotropic effects of fibrates have also been discussed.

Correspondence to Author

Gurfeth Singh

Onkar College of Pharmacy,
Sunam-148026, Punjab, India

Email

gurfatehsingh1980@rediffmail.com

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INTRODUCTION

Coronary heart disease (CHD) is the leading cause of morbidity and mortality and its prevalence is continuously increasing worldwide [1]. Epidemiological studies have shown that dyslipidemia is associated with an increased risk of CHD and is recognized as an independent risk factor for the same. Fibrates are effective and well-tolerated in long-term management of dyslipidemia in individuals at high CHD risk. Fibrates are synthetic agonists of PPAR- α , a subfamily of the nuclear receptor superfamily naturally activated by ligands such as free fatty acids and eicosanoids [2-4]. PPAR- α is expressed in tissues with highly active fatty acid metabolism such as liver, heart, kidney, endothelium and vascular smooth muscle [4,5]. Fibrates have been widely used in the treatment of hypercholesterolemia, hypertriglyceridemia and to reduce elevated total cholesterol, LDL cholesterol, serum TGs and apolipoprotein-B (apo-B), and to increase HDL cholesterol in patients with primary hypercholesterolemia and mixed dyslipidemia [2,6]. In addition, fibrates have been reported to possess various pleiotropic effects such as anti-inflammatory, antioxidant and antithrombotic effects along with improvement of endothelial function [7-10]. In this review, the pharmacology of the fibrates is discussed along with evaluating their role in primary and secondary prevention of CHD. Moreover, various pleiotropic effects exhibited by fibrates have delineated.

MECHANISM OF ACTION OF FIBRATES

The PPARs (i.e., PPAR-alpha, -beta, -delta and -gamma) form a subfamily of the nuclear receptor gene family that are activated by fatty acids and derivatives to differing extents. The primary mechanism of action of fibrates is via activation of the nuclear transcription factor PPAR- α which is predominantly expressed in tissues metabolising fatty acids such as the liver, kidney and heart [2,5,11]. PPAR- α activators increase hepatic uptake and esterification of free fatty acids causing increased mitochondrial free fatty acid uptake and the resulting free fatty acid oxidation. On activation by binding of hypolipidemic fibrates, PPAR- α binds as heterodimers with retinoid X receptor (RXR), which

subsequently recognizes and binds to specific PPAR- α response elements leading to modulation of expression of the target genes [2,5]. In addition, the activity of lipoprotein lipase is increased and synthesis of apoC-III is decreased which collectively enhance the clearance of circulating TG-rich lipoproteins. Hepatic fatty acid oxidation is also increased leading to reduced production of TG-rich very low-density lipoproteins (VLDL) [4,6]. Moreover, the increase in plasma HDL-cholesterol is due to overexpression of apoA-I and apoA-II [12]. In addition, fibrates encourage shifting of density of LDL particles towards larger and more buoyant particles that are less susceptible to oxidation and possess increased affinity for LDL receptor [13-14]. Further, the PPAR- α activation regulates gene expression involved in metabolic pathways including lipid metabolism thereby reducing TG concentrations and increasing HDL concentrations.

EFFECTS ON LIPIDS AND LIPOPROTEINS

Fibrates such as clofibrate, gemfibrozil, bezafibrate and fenofibrate have been reported to possess modulatory effects on lipids and lipoproteins [15]. Fibrates reduce plasma levels of TGs by 30-50%, reduce LDL cholesterol levels by 15-20% and increase HDL cholesterol levels by 5-15% depending on the underlying lipid abnormality and baseline lipid phenotype [2,6,16-17]. Clofibrate has been noted to decrease TG, VLDL and LDL levels by increasing the catabolism of VLDL to LDL and decreasing the synthesis of VLDL by the liver. Moreover, cholesterol formation is found to be inhibited early in the biosynthetic chain and the excretion of neutral steroids is increased [18]. Moreover, fibrates have been noted to stimulate reverse cholesterol transport by modulating macrophage cholesterol efflux, cholesterol transport and bile acid synthesis resulting in reduced TG and LDL levels and substantially enhancing HDL concentrations. Recently, gemfibrozil has been shown to stimulate cholesterol efflux via upregulation of ATP-binding cassette transporter or ABCA-1 transporter protein [19]. Moreover, gemfibrozil has been reported to inhibit the intracellular storage of excess esterified cholesterol molecules. Bezafibrate showed significant lipid-modifying profile which is characterised by marked

decrease in elevated TG levels, increases in HDL cholesterol levels and decreases in total and LDL cholesterol levels [20]. Moreover, bezafibrate is found to be effective in most types of primary and secondary dyslipidemia and in conditions featuring hypertriglyceridemia and HDL cholesterol deficiency. It has been noted that low-dose bezafibrate decreased serum and liver TG levels in mice by attenuating hepatic lipogenesis and TG secretion that involve down-regulation of sterol regulatory element-binding protein (SREBP)-1c. Whereas, the high-dose bezafibrate decreased serum and liver TG levels by enhancement of hepatic fatty acid uptake and β -oxidation via PPAR- α activation [11]. Fenofibrate, an activator of PPAR- α , is a well known hypolipidemic agent and is generally used to treat hypertriglyceridemia, hypercholesterolemia and mixed dyslipidemia [3,7].

Apo A-1 is the cofactor of the enzyme lecithin cholesterolacyltransferase (LCAT), which plays a key role

on the efflux of cholesterol from extrahepatic tissue to liver for excretion. The decreased level of Apo-AI is associated with increased risk of CHD. Gemfibrozil has been noted to stimulate the production of HDL by upregulating the expression of apo A-I and A-II [21-22]. Moreover, PPAR- α activation by bezafibrate has been noted to suppress the transcriptional expression of apo-CIII, an endogenous inhibitor of lipoprotein lipase and hepatic TG lipase ultimately leading to an enhancement of lipoprotein lipolysis. In addition, apoAV gene is found to be implicated in triglyceride metabolism, the deficiency of which results in an increase of plasma triglycerides, whereas its overexpression leads to a reduction of triglycerides in mice [23-24]. Similarly, human apoAV deficiency contributes to severe hypertriglyceridemia in the affected subjects [25]. Additionally, numbers of published data have shown that fibrates induce apoAV expression by activating the PPAR- α expression [26-27].

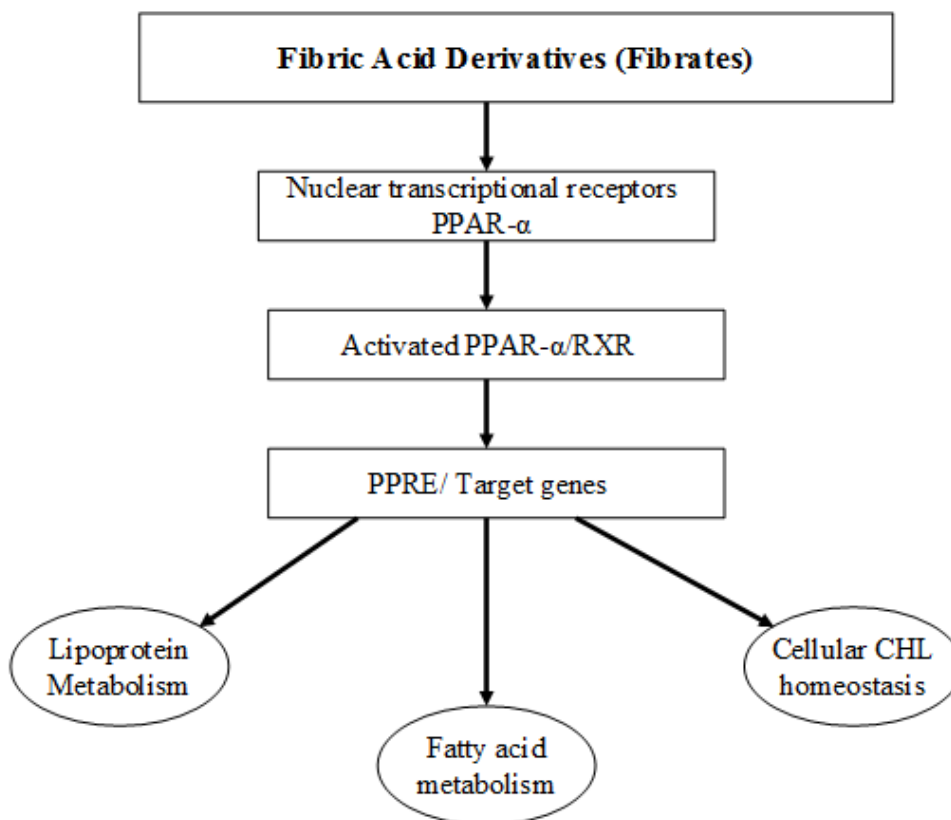


Fig 1. Schematic representation of mechanism of action of fibrates
 PPAR- α , peroxisome proliferator activated receptor- α ; RXR, retinoid X receptor;
 PPRE, peroxisome proliferator response elements; CHL, cholesterol

PLEIOTROPIC EFFECTS OF FIBRATES

Apart from lipid modifying effects, fibrates also exert numerous pleiotropic effects such as their anti-inflammatory, antioxidant and antithrombotic effects along with their ability to improve endothelial function. PPAR- α activation by fibrates is found to be involved in the control of the anti-inflammatory responses via inhibition of the transcriptional factor nuclear factor kappa-B (NF- κ B) [2]. The expression of many adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular CAM-1 (ICAM-1) is regulated by NF- κ B. Moreover, the activation of NF- κ B also increases synthesis and release of proinflammatory cytokines such as interleukin (IL)-1, IL-2 and IL-6, which activate inflammatory cells and enhance their attachment to the vessel wall [28-29]. The activation of NF- κ B is inhibited by PPAR- α agonists and thus inhibited translocation of the active component of NF- κ B into the nucleus. Additionally, fibrates attenuated the production of pro-inflammatory stimuli such as interleukin-6 (IL-6) and various prostaglandins as well as the acute phase proteins including fibrinogen and C-reactive protein (CRP) levels [30-31]. In addition, three month therapy with the PPAR- α agonist fenofibrate decreased the circulating levels of VCAM-1 and ICAM-1 in the fasting state of patients with hypertriglyceridemia [32]. Fenofibrate lowered the plasma concentrations of adhesion molecules E-selectin, MCP-1 and VCAM-1 in patients with type 2 diabetes mellitus and mixed hyperlipoproteinemia [33]. Additionally in cultured human umbilical vein endothelial cells, fenofibrate significantly diminished the expression of proinflammatory mediators such as CD40, CD40L and gelatinase activities induced by CRP that further evidenced its potential effect as anti-inflammatory agent [34-35].

Moreover, fibrates have been reported to possess favourable effects on coagulation and fibrinolysis. Fenofibrate and bezafibrate have been noted to reduce levels of fibrinogen by up to 20% [9]. Moreover, fenofibrate have been shown to increase fibrinolysis and attenuate platelet hyperaggregability in hypercholesterolemic subjects that further accounts for its pleiotropic effects [36]. Fibrates have been

significantly noted to decrease plasma fibrinogen levels and inhibit tissue factor expression in human monocytes and macrophages. Interestingly, gemfibrozil, bezafibrate and fenofibrate has been noted to reduce plasminogen activator inhibitor type 1 (PAI-1) and fibrinogen levels in hypercholesterolemic subjects [35,37]. It has been observed that fenofibrate significantly reduced fibrinogen and PAI-1 antigen levels [7-8].

It has been widely accepted that PPAR- α activation by fibrates is involved in affording cardioprotection. PPAR- α activation by clofibrate afforded cardioprotection by a mechanism that involves increased eNOS and NO production along with inhibition of NADPH oxidase activity [38]. Treatment with clofibrate has been shown to inhibit superoxide dismutase and glutathione peroxidase activities accounting for its antioxidant effect. Furthermore, clofibrate showed cardioprotection in a model of hypertension by increasing the release of NO. Administration of fenofibrate markedly attenuated the development of oxidative stress and vascular inflammation [34,39]. Fenofibrate has been shown to improve the integrity of vascular endothelium by activation of eNOS and generation of NO in the vessels and consequent reduction in oxidative stress evidencing its potential in cardioprotection [10]. Moreover, treatment with bezafibrate reduced the elevated levels of lipoprotein-A and fibrinogen, which are independent cardiovascular risk factors). In addition, bezafibrate afforded cardioprotection in patients with diabetes which showed that bezafibrate users had a lower hazard for incident diabetes that account for its antidiabetic cardioprotective properties [40]. Furthermore fenofibrate significantly improved flow-mediated dilation in patients with hypertriglyceridemia. It has also been observed that fenofibrate significantly improved percent flow-mediated dilator response to hyperemia in these patients further accounting for its cardioprotective potential [7-8].

Moreover, fibrates improved carbohydrate metabolism in patients with dyslipidemia including diabetic patients. Fenofibrate have been reported to significantly decrease serum uric acid levels, increase serum creatinine and homocysteine levels. Moreover,

reduction in serum alkaline phosphatase and gamma glutamyltranspeptidase activity has been well-documented by fibrates treatment [41]. Additionally, the PPAR- α ligands improved insulin sensitivity and reduced adiposity in rodent models [42]. Experiment studies have revealed that AdipoR1 and AdipoR2, the receptors for adiponectin, are induced by activation of PPAR- α . The expression of adiponectin mRNA in visceral fat deposits has been found to be elevated by fenofibrate treatment when compared to untreated rats, whereas TNF- α mRNA is down-regulated by fenofibrate which suggest that fenofibrate has a beneficial role in the treatment of type 2 diabetes by regulating adiponectin and TNF- α levels [35,43]. Further, treatment with bezafibrate significantly reduced serum TG and free fatty acid levels and improved insulin resistance in rodent model [44]. In addition, it has been observed that fenofibrate therapy significantly increased plasma adiponectin levels and insulin sensitivity in primary hypertriglyceridemic patients [8,35,45].

CONCLUSIONS

Fibrates, the PPAR- α agonists are the most effective and well-tolerated agents in the management of patients with dyslipidemias. Fibrates have been known to possess various pleiotropic effects such as anti-inflammatory, antioxidant and antithrombotic affects. Moreover, improvement of endothelial function and carbohydrate metabolism in patients with dyslipidemia has also been obtained with fibrates therapy. However, the interesting results of fibrates alongwith their pleiotropic effects potentially suggest a new recommendation for fibrate therapy. Further studies are awaited concerning the potential beneficial effects of fibrate therapy in more profound clinical and non-clinical manifestations which would translate into improved quality of life for patients presented with cardiovascular risk associated with dyslipidemias.

REFERENCES

1. Schwartz JS. Primary Prevention of Coronary Heart Disease With Statins: It's Not About the Money. *Circulation*, 124, 2011, 130-132.

2. Chapman MJ. Fibrates in 2003: therapeutic action in atherogenic dyslipidaemia and future perspectives. *Atherosclerosis*, 171, 2003, 1-13.
3. Zambon A, Gervois P, Pauletto P, Fruchart JC, Staels B. Modulation of hepatic inflammatory risk markers of cardiovascular diseases by PPAR-alpha activators: clinical and experimental evidence. *Arterioscler Thromb Vasc Biol*, 26, 2006, 977-986.
4. Chapman MJ, Redfern JS, McGovern ME, Giral P. Niacin and fibrates in atherogenic dyslipidemia: Pharmacotherapy to reduce cardiovascular risk. *Pharmacol Therap*, 126, 2010, 314-345.
5. Fazio S, Linton MF. The role of fibrates in managing hyperlipidemia: mechanism of action and clinical efficacy. *Curr Atherosclerosis Rep*, 6, 2004, 148-157.
6. Chapman MJ. Fibrates: therapeutic review. *Br J Diabetes Vasc Dis*, 6, 2006, 11-18.
7. Koh KK, Ahn JY, Han SH. Effects of fenofibrate on lipoproteins, vasomotor function, and serological markers of inflammation, plaque stabilization, and hemostasis. *Atherosclerosis*, 174, 2004, 379-383.
8. Koh KK, Han SH, Quon MJ, Ahn JY, Shin EK. Beneficial effects of fenofibrate to improve endothelial dysfunction and raise adiponectin levels in patients with primary hypertriglyceridemia. *Diabetes Care*, 28, 2005a, 419-424.
9. Turpin G, Bruckert E. Efficacy and safety of ciprofibrate in hyperlipoproteinaemias. *Atherosclerosis*, 124, 1996, S83-S87.
10. Balakumar P, Rohilla A, Mahadevan N. Pleiotropic actions of fenofibrate on the heart. *Pharmacol Res*, 63, 2011, 8-12.
11. Nakajima T, Tanaka N, Kanbe H, Hara A, Kamijo Y, Zhang X, et al. Bezafibrate at Clinically Relevant Doses Decreases Serum/Liver Triglycerides via Down-Regulation of Sterol Regulatory Element-Binding Protein-1c in Mice: A Novel

- Peroxisome Proliferator-Activated Receptor alpha-Independent Mechanism. *Mol Pharmacol*, 75, 2009, 782-792.
12. Fruchart JC, Duriez P. Mode of action of fibrates in the regulation of triglyceride and HDL-cholesterol metabolism. *Drugs Today*, 42, 2006, 39-64.
 13. Vakkilainen J, Steiner G, Ansquer JC. Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease. *Circulation*, 107, 2003, 1733-1737.
 14. Backes J, Gibson CA. Effect of lipid-lowering drug therapy on small dense low-density lipoprotein. *Ann Pharmacother*, 39, 2005, 523-526.
 15. Chapman MJ. Pharmacology of fenofibrate. *Am J Med*, 83, 1987, 21-25.
 16. Belalcazar LM, Ballantyne CM. Defining specific goals of therapy in treating dyslipidemia in the patient with low high-density lipoprotein cholesterol. *Prog Cardiovasc Dis*, 41, 1998, 151-174.
 17. Steiner G. Fibrates and coronary risk reduction. *Atherosclerosis*, 182, 2005, 199-207.
 18. Luci S, Giemsa B, Kluge H, Eder K. Clofibrate causes an upregulation of PPAR- α target genes but does not alter expression of SREBP target genes in liver and adipose tissue of pigs. *AJP - Regu Physiol*, 293, 2007, R70-R77.
 19. Hossain MA, Tsujita M, Gonzalez FJ, Yokoyama S. Effects of fibrate drugs on expression of ABCA1 and HDL biogenesis in hepatocytes. *J Cardiovasc Pharmacol*, 51, 2008, 258-266.
 20. Goa KL, Barradell LB, Plosker GL. Bezafibrate. An update of its pharmacology and use in the management of dyslipidaemia. *Drugs*, 52, 1996, 725-753.
 21. Saku K, Gartside PS, Hynd BA, Kashyap ML. Mechanism of action of gemfibrozil on lipoprotein metabolism. *J Clin Invest*, 75, 1985, 1702-1712.
 22. Avik Roy and Kalipada Pahan. Gemfibrozil, stretching arms beyond lipid lowering. *Immunopharmacol Immunotoxicol*, 31, 2009, 339-351.
 23. Pennacchio LA, Olivier M, Hubacek JA, Cohen JC, Cox DR, Fruchart JC et al. An apolipoprotein influencing triglycerides in humans and mice revealed by comparative sequencing. *Science* 294, 2001, 169-173.
 24. Peters JM, Aoyama T, Burns AM, Gonzalez FJ. Bezafibrate is a dual ligand for PPAR-alpha and PPAR-beta: studies using null mice. *Biochim Biophys Acta* 1632, 2003, 80-89.
 25. Priore Oliva C, Pisciotta L, Li Volti G, Sambataro MP, Cantafora A, Bellocchio A et al. Inherited apolipoprotein A-V deficiency in severe hypertriglyceridemia. *Arterioscler Thromb Vasc Biol*, 25, 2005, 411-417.
 26. Prieur X, Coste H, Rodriguez JC. The human apolipoprotein AV gene is regulated by peroxisome proliferator-activated receptor alpha and contains a novel farnesoid X-activated receptor response element. *J Biol Chem*, 278, 2003, 25468-25480.
 27. Vu-Dac N, Gervois P, Jakel H, Nowak M, Bauge E, Dehondt H et al. Apolipoprotein A5, a crucial determinant of plasma triglyceride levels, is highly responsive to peroxisome proliferator-activated receptor alpha activators. *J Biol Chem*, 278, 2003, 17982-17985.
 28. Koh KK. Effects of statins on vascular wall: vasomotor function, inflammation, and plaque stability. *Cardiovasc Res*, 47, 2000, 648-657.
 29. Koh KK, Han SH, Quon MJ. Role of inflammatory markers and the metabolic syndrome: insights from therapeutic interventions. *J Am Coll Cardiol*, 46, 2005b, 1978-1985.
 30. Marx N, Sukhova GK, Collins T, Libby P, Plutzky J. PPARalpha activators inhibit cytokine-induced vascular cell adhesion

- molecule-1 expression in human endothelial cells. *Circulation*, 99, 1999, 3125-3131.
31. Zambon A, Gervois P, Pauletto P, Fruchart JC, Staels B. Modulation of hepatic inflammatory risk markers of cardiovascular diseases by PPAR-alpha activators: clinical and experimental evidence. *Arterioscler Thromb Vasc Biol*, 26, 2006, 977-986.
 32. Marchesi S, Lupattelli G, Lombardini R. Effects of fenofibrate on endothelial function and cell adhesion molecules during post-prandial lipemia in hypertriglyceridemia. *J Clin Pharm Ther*, 28, 2003, 419-424.
 33. Empen K, Frost RJ, Geiss HC, Otto C, Parhofer KG. Differential effects of fenofibrate versus atorvastatin on the concentrations of E-selectin and vascular cellular adhesion molecule-1 in patients with type 2 diabetes mellitus and mixed hyperlipoproteinemia: a randomized cross-over trial. *Cardiovasc Diabetol*, 2, 2003, 17.
 34. Koh KK, Quon MJ, Han SH. Additive beneficial effects of fenofibrate combined with candesartan in the treatment of hypertriglyceridemic hypertensive patients. *Diabetes Care*, 29, 2006, 195-201.
 35. Koh KK, Quon MJ, Rosenson RS, Chung WJ, Han SH. Vascular and metabolic effects of treatment of combined hyperlipidemia: Focus on statins and fibrates. *Int J Cardiol*, 124, 2008, 149-159.
 36. Simpson IA, Lorimer AR, Walker ID, Davidson JF. Effect of ciprofibrate on platelet aggregation and fibrinolysis in patients with hypercholesterolaemia. *Thromb Haemostat*, 54, 1989, 442-444.
 37. Zambrana JL, Velasco F, Castro P, et al. Comparison of bezafibrate versus lovastatin for lowering plasma insulin, fibrinogen, and plasminogen activator inhibitor-1 concentrations in hyperlipemic heart transplant patients. *Am J Cardiol*, 80, 1997, 836-840.
 38. Diep QN, Amiri F, Touyz RM, et al. PPARalpha activator effects on Ang II-induced vascular oxidative stress and inflammation. *Hypertension*, 40, 2002, 866-871.
 39. Goya K, Sumitani S, Xu X. Peroxisome proliferator-activated receptor alpha agonists increase nitric oxide synthase expression in vascular endothelial cells. *Arterioscler Thromb Vasc Biol*, 24, 2004, 658-663.
 40. Flory JH, Ellenberg S, Szapary PO, Strom BL, Hennessy S. Antidiabetic Action of Bezafibrate in a Large Observational Database. *Diabetes Care*, 32, 2009, 547-551.
 41. Despres JP, Lemieux I, Robins SJ. Role of fibric acid derivatives in the management of risk factors for coronary heart disease. *Drugs*, 64, 2004, 2177-2198.
 42. Guerre-Millo M, Gervois P, Raspe E. Peroxisome proliferator-activated receptor alpha activators improve insulin sensitivity and reduce adiposity. *J Biol Chem*, 275, 2000, 16638-16642.
 43. Choi KC, Ryu OH, Lee KW. Effect of PPAR-alpha and-gamma agonist on the expression of visfatin, adiponectin, and TNF-alpha in visceral fat of OLETF rats. *Biochem Biophys Res Commun*, 336, 2005, 747-753.
 44. Jia D, Yamamoto M, Otani M, Otsuki M. Bezafibrate on lipids and glucose metabolism in obese diabetic Otsuka Long-Evans Tokushima fatty rats. *Metabolism*, 53, 2004, 405-413.
 45. Idzior-Walus B, Sieradzki J, Rostworowski W, et al. Effects of comiconised fenofibrate on lipid and insulin sensitivity in patients with polymetabolic syndrome X. *Eur J Clin Invest*, 30, 2000, 871-878.
