

# Clinical interest of PPARs ligands

## Particular benefit in type 2 diabetes and metabolic syndrome

B Vergès

### SUMMARY

Cardiovascular disease is significantly increased in patients with metabolic syndrome and type 2 diabetes. Several factors such as chronic hyperglycemia, lipid abnormalities, endothelium dysfunction, inflammation, oxidative stress, increased thrombosis and decreased fibrinolysis are likely to promote cardiovascular events in these patients. Because of positive effects on glucose homeostasis, lipid metabolism, proteins involved in all stages of atherogenesis, endothelium function, inflammation, thrombosis and fibrinolysis, PPARs  $\alpha$  (fibrates) and PPARs  $\gamma$  (glitazones) agonists are good candidates to reduce cardiovascular disease, more precisely in subjects with metabolic syndrome or type 2 diabetes. PPARs  $\alpha$  agonists (fibrates) are potent hypolipidemic agents increasing plasma HDL-cholesterol and reducing free fatty acids, triglycerides, LDL-cholesterol and the number of small dense LDL particles. Moreover, they reduce vascular inflammation and thrombosis, promote fibrinolysis and inhibit the production of the vasoconstrictor factor, endothelin-1, by the endothelium. They have been shown, in clinical trials, to reduce cardiovascular disease, more particularly in patients displaying lipid abnormalities typical of metabolic syndrome and type 2 diabetes (high triglycerides, low HDL-cholesterol). PPARs  $\gamma$  agonists (glitazones) have not only beneficial effects on glucose homeostasis, by increasing insulin sensitivity and reducing blood glucose level but also on lipid metabolism by elevating plasma HDL-cholesterol, decreasing free fatty acids and the number of small dense LDL particles, and for pioglitazone by reducing plasma triglycerides. Furthermore, they diminish vascular inflammation and vasoconstriction, inhibit monocyte chemotaxis, proliferation and migration of smooth muscle cells, in the vascular wall and decrease the production of adhesion molecules and metalloproteinases. PPARs  $\gamma$  agonists (glitazones) have been shown to reduce the development of atherosclerotic lesions in rats. The potential clinical benefit of PPARs  $\gamma$  agonists on the reduction of cardiovascular disease, in type 2 diabetic patients, will be specified by the ongoing intervention studies.

**Key-words:** Diabetes · Metabolic syndrome · PPAR · Fibrate · Glitazone.

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### RÉSUMÉ

#### Intérêt clinique des ligands PPARs. Un bénéfice particulier au cours du diabète de type 2 et du syndrome métabolique

Le risque cardio-vasculaire, particulièrement élevé, au cours du diabète de type 2 est lié à la conjonction de plusieurs facteurs physiopathologiques tels l'hyperglycémie chronique, les anomalies du métabolisme lipidique, la dysfonction endothéliale, l'augmentation du stress oxydatif et le déséquilibre de la balance thrombose-fibrinolyse. En raison de leurs effets bénéfiques sur le métabolisme des lipides et la paroi vasculaire, les agonistes des récepteurs PPARs  $\alpha$  (les fibrates) et PPARs  $\gamma$  (les glitazones) représentent des agents thérapeutiques intéressants dans la réduction du risque cardio-vasculaire chez les patients diabétiques de type 2. Les agonistes des PPARs  $\alpha$  (fibrates) ont un effet marqué sur les lipides : augmentation du HDL-cholestérol et diminution des acides gras libres, des triglycérides, du LDL-cholestérol et du nombre des LDL petites et denses. Par ailleurs, ils réduisent l'inflammation vasculaire, diminuent la production d'endothéline-1, agent vasoconstricteur, et modifient de façon bénéfique la balance thrombose - fibrinolyse. Ils ont fait la preuve de leur efficacité, en clinique, pour réduire le risque cardio-vasculaire en prévention primaire (étude d'Helsinki) et secondaire (étude VAHIT). Les agonistes des PPARs  $\gamma$  (glitazones) présentent, à côté de leur action sur le métabolisme glucidique (augmentation de la sensibilité à l'insuline, diminution de l'hyperglycémie), des effets favorables sur le métabolisme lipidique : augmentation du HDL-cholestérol, réduction des acides gras libres et du nombre des LDL petites et denses et, pour la pioglitazone, diminution de la triglycéridémie. Par ailleurs, ils réduisent l'inflammation vasculaire, diminuent la production de molécules d'adhésion et de métalloprotéinases, favorisent la vasodilatation, inhibent la migration monocytaire dans la paroi artérielle et la multiplication des cellules musculaires lisses. Les agonistes des PPARs  $\gamma$  ont montré leur efficacité pour réduire les lésions d'athérosclérose, chez l'animal. Des études d'intervention sont en cours, chez les patients diabétiques de type 2 afin de préciser leur effet sur la morbi-mortalité cardio-vasculaire.

**Mots-clés :** Diabète · Syndrome métabolique · PPAR · Fibrate · Glitazone.

Address correspondence and reprint requests to:

B Vergès. Service Endocrinologie-Diabétologie et Maladies Métaboliques, hôpital du Bocage, CHU, 21000 Dijon, France.  
bruno.verges@chu-dijon.fr

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Service d'Endocrinologie, Diabétologie et Maladies Métaboliques, hôpital du Bocage, CHU de Dijon.

**P**PARs (Peroxisome Proliferator-Activated receptors) are ligand-activated transcription factors belonging to the nuclear receptor superfamily. Three different PPARs have been identified to date (PPARs  $\alpha$ , PPARs  $\beta$  and PPARs  $\gamma$ ) each displaying distinct tissue distribution pattern [1]. PPARs are activated by natural ligands such as fatty acids and eicosanoids (leukotrienes, prostaglandins) and by pharmacological agonists such as fibrates, binding to PPARs  $\alpha$  and glitazones, binding to PPARs  $\gamma$ . Upon ligand activation, PPARs regulate the transcription of several genes. Activated PPARs heterodimerize with another nuclear receptor, the retinoid X receptor, and modify the transcription of target genes after binding to specific peroxisome proliferator response elements (PPRE) [1, 2]. The genes whose expression is modified by PPARs are numerous and control not only lipid metabolism but also glucose homeostasis, cell cycle control, inflammation and immune response [1, 2]. Interestingly, PPARs take an important part in the control of factors involved in the development of cardiovascular disease, particularly in patients with metabolic syndrome or type 2 diabetes (glucose and lipid metabolism, endothelium function, inflammation, thrombosis and fibrinolysis). Thus, the use of PPARs agonists (fibrates, glitazones), in clinical practice, has the potential not only to improve glucose and lipid metabolism but also to reduce atherosclerosis, more particularly in the metabolic syndrome and type 2 diabetes.

## Clinical interest of PPARs $\alpha$ agonists (fibrates)

### Effects on lipids

PPARs  $\alpha$  agonists modify the expression of several genes involved in lipid metabolism [2-4]. They stimulate cellular uptake, intracellular esterification and mitochondrial  $\beta$ -oxidation of fatty acids by promoting the expression of genes such as FATP (Fatty Acid Transport Protein) gene, Acyl-CoA synthetase gene and Carnitine PalmitoylTransferase I and II genes [2, 5]. Thus, they reduce significantly free fatty acid level in plasma. PPARs  $\alpha$  agonists (fibrates) also increase the expression of the lipoprotein lipase gene and reduce the expression of the gene encoding for apo-C-III, which is a natural inhibitor of lipoprotein lipase [3]. This explains the hypotriglyceridemic effect of fibrates. Moreover, PPARs  $\alpha$  agonists (fibrates) control the expression of several genes involved in HDL-cholesterol metabolism and reverse cholesterol transport. ApoA-I and apoA-II are the major HDL apolipoproteins. PPARs  $\alpha$  agonists increase the transcription of these two genes [3, 4]. ABC-A1 (ATP-Binding Cassette transporter A1) plays a key role in reverse cholesterol transport by exporting unesterified cholesterol and phospholipids from cells to HDL particles [6, 7]. It has been demonstrated that PPARs  $\alpha$  agonists induce ABC-A1

gene expression [8]. Moreover, they also promote the expression of SR-BI/CLA-I, which is the HDL receptor [9]. Thus, by increasing the expression of ABC-A1 and SR-BI/CLA-I, PPARs  $\alpha$  agonists accelerate cholesterol efflux from peripheral cells and its uptake by the liver.

These actions of PPARs  $\alpha$  agonists (fibrates) on several genes controlling lipid metabolism explain their significant effect on plasma lipids. Indeed, substantial quantitative modifications of plasma lipids are observed, with fibrates, such as reduction in free fatty acids, triglycerides ( $-30\%$  to  $-50\%$ ) and LDL-cholesterol ( $-10\%$  to  $-25\%$ ) levels and an increase in HDL-cholesterol level ( $+10\%$  to  $+22\%$ ). For instance, in the Helsinki Heart study, treatment with gemfibrozil induced a 35% reduction in triglycerides, an 11% decrease in LDL-cholesterol and an 11% increase in HDL-cholesterol [10]. Furthermore, qualitative modifications of plasma lipoproteins are also observed with fibrates such as reduction of triglyceride-content of VLDL and decrease of small dense (triglyceride-rich) LDL particles, which are known to be atherogenic [11].

### Vascular and anti-inflammatory effects

PPARs  $\alpha$  agonists have a direct effect on the endothelium by inhibiting the production of the vasoconstrictor factor, endothelin -1 [12]. Furthermore, some anti-inflammatory effects of PPARs  $\alpha$  agonists have been shown. Hyperlipidemic patients, treated with fibrates, display reduction of some inflammatory proteins such as C-Reactive Protein (CRP), TNF  $\alpha$  and interferon  $\gamma$  [13]. It has been shown that fibrates inhibit cyclooxygenase-2 and IL-6 induced IL-1 secretion in the smooth-muscle cell [14]. In monocytes, fibrates reduce the expression of IL-2 and TNF  $\alpha$  [15]. Recent studies indicate that PPARs  $\alpha$  agonists reduce inflammation *via* negative control of NF $\kappa$ B (Nuclear Factor  $\kappa$ B) and AP-1 (Activator Protein 1) [14, 16].

### Effects on thrombosis and fibrinolysis

Fibrates reduce thrombosis. They reduce platelet hyperaggregability and inhibit the expression of platelet-activating factor receptor and Tissue Factor in human monocytes and macrophages [17]. Bezafibrate, ciprofibrate and fenofibrate decrease fibrinogen plasma level [18, 19]. It has been shown that this effect is due to repression of the fibrinogen gene by PPARs  $\alpha$  agonists [20].

Moreover, PPARs  $\alpha$  agonists reduce PAI-1 (Platelet Activator Inhibitor-1) plasma level, which will promote fibrinolysis [19].

### PPARs $\alpha$ agonists and reduction of cardiovascular disease

Although less clinical intervention studies have been performed with fibrates than with statins, we now have pieces of evidence indicating that fibrates may significantly reduce

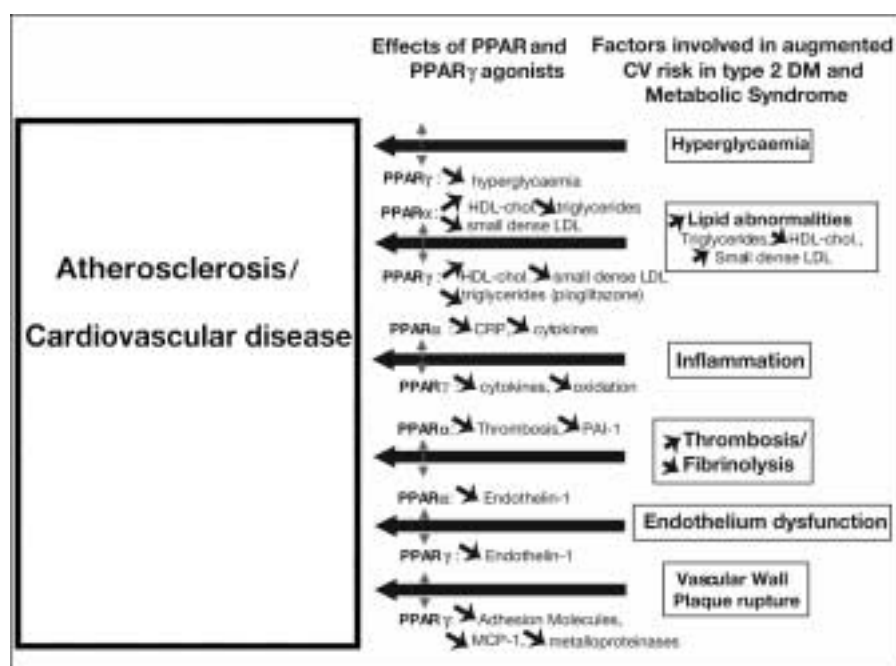


Figure 1

Main effects of PPAR $\alpha$  agonists (fibrates) and PPAR $\gamma$  agonists (glitazones) on the different factors involved in the promotion of atherosclerosis and cardiovascular disease in type 2 diabetes and metabolic syndrome. CV: cardiovascular; DM: Diabetes Mellitus; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; CRP: C-Reactive Protein; PAI-1: Platelet Activator Inhibitor-1; MCP-1: Monocyte Chemoattractant Protein-1.

cardiovascular disease. The primary-prevention trial Helsinki Heart Study, performed in 4081 middle-aged men with dyslipidemia, showed that treatment with gemfibrozil led to a significant 34% reduction in major cardiovascular events ( $p < 0.02$ ) [21]. Interestingly, in the Helsinki Heart Study, reduction of cardiovascular disease with gemfibrozil was more pronounced ( $-71\%$ ,  $p < 0.001$ ) in patients displaying baseline triglyceride values above 2 g/l and a LDL/HDL ratio above 5, which is very similar to the lipid profile usually observed in patients with metabolic syndrome or type 2 diabetes [22]. In secondary prevention, the VAHIT study (Veterans Affairs High-density lipoprotein cholesterol Intervention Trial), performed in coronary men with low HDL-cholesterol levels ( $\leq 0.40$  g/l) and near-normal LDL-cholesterol levels ( $\leq 1.40$  g/l), demonstrated that treatment with gemfibrozil reduced significantly the occurrence of major cardiovascular events ( $-22\%$ ,  $p = 0.006$ ) [23].

Thus, PPARs  $\alpha$  agonists (fibrates) significantly improve the lipid profile, have a favorable action on the endothelium, reduce vascular inflammation and thrombosis and promote fibrinolysis (Fig 1). These positive effects explain their beneficial action in reducing cardiovascular disease and more particularly in patients displaying lipid abnormalities typical of metabolic syndrome and type 2 diabetes (high triglycerides, low HDL-cholesterol).

### Clinical interest of PPARs $\gamma$ agonists (glitazones)

Two PPARs  $\gamma$  agonists (glitazones), pioglitazone and rosiglitazone are now available for clinical use. Glitazones have not only significant hypoglycemic effects but also po-

tential positive effects on lipid metabolism, endothelium, oxidative stress and vascular inflammation. These additive actions of glitazones may reduce the development of atherosclerosis.

### Effects on glucose metabolism

Both rosiglitazone and pioglitazone significantly improve insulin sensitivity, in type 2 diabetic subjects [24, 25]. In monotherapy, rosiglitazone and pioglitazone induce a significant decrease of fasting blood glucose and HbA<sub>1c</sub> ( $-1.2\%$  to  $-1.5\%$ ) [26, 27]. A similar drop in HbA<sub>1c</sub> is observed when glitazones are used in combination therapy with sulfonylureas [28, 29] or with metformin [30, 31]. Interestingly, recent reports indicate that decrease of HbA<sub>1c</sub> with glitazones is maintained over time.

### Effects on lipid metabolism

Lipid metabolism is significantly modified by both rosiglitazone and pioglitazone. Both drugs induce quantitative modification of lipids [26-32]:

- *Free fatty acids*: a significant decrease of plasma levels of free fatty acids is observed with pioglitazone ( $-9\%$  to  $-38\%$ ) and rosiglitazone ( $-17\%$  to  $-24\%$ ), in monotherapy as in combination therapy.
- *Triglycerides*: rosiglitazone does not modify plasma triglyceride level while pioglitazone significantly decreases plasma triglycerides ( $-10\%$  to  $-36\%$ ).
- *HDL-cholesterol*: a significant increase of plasma HDL-cholesterol is noted with both pioglitazone ( $+8\%$  to  $+18\%$ ) and rosiglitazone ( $+10\%$  to  $+14\%$ ).

– *LDL-cholesterol*: plasma LDL-cholesterol level is usually not significantly modified by pioglitazone, when it is increased by rosiglitazone (+9% to +18%).

Total cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratios are decreased by pioglitazone and usually not modified by rosiglitazone.

Furthermore, qualitative modifications of lipoproteins are observed with glitazones. Indeed, the use of rosiglitazone or pioglitazone induces an increase of the size of LDLs with a reduction of small dense LDL particles, which are known to be atherogenic [33-35].

### Vascular effects of PPARs $\gamma$ agonists

PPARs  $\gamma$  agonists show positive vascular effects susceptible to reduce the development of atherosclerosis. They decrease cytokine-induced expression of adhesion molecules such as E-selectin [36] and VCAM-1 (Vascular Cell Adhesion Molecule 1) [37]. It has been shown that glitazones inhibit monocyte chemotaxis by reducing the expression of monocyte chemoattractant protein (MCP)-1 [38]. An inhibition of proliferation and migration of smooth muscle cells in the vascular wall has been observed with glitazones [39, 40]. Metalloproteinase MMP-9, which is an enzyme involved in atherosclerotic plaque rupture, is decreased by glitazones *in vitro* [41] and *in vivo* [42]. Furthermore, glitazones inhibit the production by the endothelium of the vasoconstrictor factor, endothelin -1 *in vitro* and *in vivo* [43, 44].

### Anti-inflammatory effects of PPARs $\gamma$ agonists

Several anti-inflammatory effects of PPARs  $\gamma$  agonists (glitazones) have been described. They inhibit the production of a number of cytokines such as TNF $\alpha$ , IL-6 and IL-1 $\beta$  [45, 46]. It has been shown that PPARs  $\gamma$  agonists inhibit oxidized LDL-induced TNF $\alpha$  production [47].

### PPARs $\gamma$ agonists and reduction of atherosclerosis

Studies performed in animal models have shown a significant reduction of atherosclerosis in mice treated with PPARs  $\gamma$  agonists. Indeed, an inhibition of formation of atherosclerotic lesions by troglitazone and rosiglitazone has been demonstrated in diabetic and non-diabetic low density lipoprotein receptor-deficient mice [48, 49]. Furthermore, it has been shown that rosiglitazone and pioglitazone reduce the size of myocardial infarction in rat [50].

In humans, it has been demonstrated that treatment with pioglitazone reduces the carotid arterial wall thickness in type 2 diabetes [51]. Two large prospective long term outcome trials are currently underway, one with pioglitazone (PROactive study) the other with rosiglitazone (RECORD study) to determine whether the use of these PPARs  $\gamma$  agonists may reduce cardiovascular complications in type 2 diabetes.

Thus, PPARs  $\gamma$  agonists (glitazones) have beneficial effects not only on glucose homeostasis but also on lipid metabolism. Furthermore, they reduce vascular inflammation and show positive effects susceptible to reduce the development of atherosclerosis (Fig 1). The potential clinical benefit of PPARs  $\gamma$  agonists on the reduction of cardiovascular disease, in type 2 diabetes, will be specified by the ongoing intervention studies.

### Association of PPAR $\alpha$ and PPARs $\gamma$ agonists

Because of the clinical interest of both PPAR $\alpha$  (fibrates) and PPAR $\gamma$  (glitazones) in patients with metabolic syndrome and type 2 diabetes, we may expect that using both drugs may be very efficient in reducing cardiovascular risk. So far, the evaluation of the effect of a combined therapy on the reduction of cardiovascular morbidity and mortality (in comparison with each drug alone) has not yet been performed.

Moreover, several drug companies are now developing new agents, which are PPAR $\alpha$ - $\gamma$  agonists. These new agents may be potentially interesting in reducing cardiovascular risk in patients with metabolic syndrome and type 2 diabetes. However, the absence of important side effects of these new compounds has still to be demonstrated.

In conclusion, cardiovascular disease is significantly increased in patients with metabolic syndrome and type 2 diabetes. Several factors such as chronic hyperglycemia, lipid abnormalities, inflammation, oxidative stress, endothelium dysfunction, increased thrombosis and decreased fibrinolysis are likely to promote cardiovascular events in patients with metabolic syndrome or type 2 diabetes. PPARs agonists (fibrates, glitazones) display beneficial effects not only on glucose homeostasis and lipid metabolism but also on endothelium function, inflammation, thrombosis and fibrinolysis. Because of these multiple effects, PPARs  $\alpha$  and  $\gamma$  agonists are good candidates to reduce cardiovascular disease, more precisely in subjects with metabolic syndrome or type 2 diabetes. Running trials such as the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD), PROactive (with pioglitazone) and RECORD (with rosiglitazone) will provide additional evidence for possible clinical cardiovascular benefits of PPARs agonists, in type 2 diabetic patients.

### References

1. Desvergne B, Wahli W. Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr Rev*, 1999, 20, 649-88.
2. Schoonjans K, Staels B, Auwerx J. Role of the peroxisome proliferator-activated receptor (PPAR) in mediating the effects of fibrates and fatty acids on gene expression. *J Lipid Res*, 1996, 37, 907-25.
3. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation*, 1998, 98, 2088-93.

4. Fruchart JC. Peroxisome proliferator-activated receptor- $\alpha$  activation and high-density lipoprotein metabolism. *Am J Cardiol*, 2001, 88, 24N-29N.
5. Schoonjans K, Watanabe M, Suzuki H, *et al*. Induction of the acyl-coenzyme A synthetase gene by fibrates and fatty acids is mediated by a peroxisome proliferator response element in the C promoter. *J Biol Chem*, 1995, 270, 19269-76.
6. Brooks-Wilson A, Marcil M, Clee SM, *et al*. Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency. *Nat Genet*, 1999, 22, 336-45.
7. Bodzioch M, Orso E, Klucken J, *et al*. The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease. *Nat Genet*, 1999, 22, 347-51.
8. Chinetti G, Lestavel S, Bocher V, AT, *et al*. PPAR- $\alpha$  and PPAR- $\gamma$  activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABC-I pathway. *Nat Med*, 2001, 7, 53-8.
9. Chinetti G, Gbaguidi FG, Griglio S, *et al*. CLA-1/SR-BI is expressed in atherosclerotic lesion macrophages and regulated by activators of peroxisome proliferator-activated receptors. *Circulation*, 2000, 23, 101, 2411-7.
10. Manninen V, Elo MO, Frick MH, *et al*. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA*, 1988, 260, 641-51.
11. Bruckert E, Dejager S, Chapman MJ. Ciprofibrate therapy normalises the atherogenic low-density lipoprotein subspecies profile in combined hyperlipidemia. *Atherosclerosis*, 1993, 100, 91-102.
12. Delerive P, Martin-Nizard F, Chinetti G, *et al*. Peroxisome proliferator-activated receptor activators inhibit thrombin-induced endothelin-1 production in human vascular endothelial cells by inhibiting the activator protein-1 signaling pathway. *Circ Res*, 1999, 85, 394-402.
13. Madej A, Okopien B, Kowalski J, *et al*. Effects of fenofibrate on plasma cytokine concentrations in patients with atherosclerosis and hyperlipoproteinemia IIb. *Int J Clin Pharmacol Ther*, 1998, 36, 345-9.
14. Staels B, Koenig W, Habib A, *et al*. Activation of human aortic smooth-muscle cells is inhibited by PPAR $\alpha$  but not by PPAR $\gamma$  activators. *Nature*, 1998, 393, 790-3.
15. Jiang C, Ting AT, Seed B. PPAR- $\gamma$  agonists inhibit production of monocyte inflammatory cytokines. *Nature*, 1998, 391, 82-6.
16. Fruchart JC, Duriez P, Staels B. Peroxisome proliferator-activated receptor- $\alpha$  activators regulate genes governing lipoprotein metabolism, vascular inflammation and atherosclerosis. *Curr Opin Lipidol*, 1999, 10, 245-57.
17. Marx N, Mackman N, Schonbeck U, *et al*. PPAR $\alpha$  Activators Inhibit Tissue Factor Expression and Activity in Human Monocytes. *Circulation*, 2001, 103, 213-9.
18. Durrington PN, Mackness MI, Bhatnagar D, *et al*. Effects of two different fibric acid derivatives on lipoproteins, cholesteryl ester transfer, fibrinogen, plasminogen activator inhibitor and paraoxonase activity in type 2b hyperlipoproteinaemia. *Atherosclerosis*, 1998, 138, 217-25.
19. Okopien B, Cwalina L, Lebek M, *et al*. Effects of fibrates on plasma prothrombotic activity in patients with type 2b dyslipidemia. *Int J Clin Pharmacol Ther*, 2001, 39, 551-7.
20. Kockx M, Gervois PP, Poulain P, *et al*. Fibrates suppress fibrinogen gene expression in rodents via activation of the peroxisome proliferator-activated receptor- $\alpha$ . *Blood*, 1999, 93, 2991-8.
21. Frick MH, Elo O, Haapa K, *et al*. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*, 1987, 317, 1237-45.
22. Manninen V, Tenkanen L, Koskinen P, *et al*. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation*, 1992, 85, 37-45.
23. Rubins HB, Robins SJ, Collins D, *et al*. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*, 1999, 341, 410-8.
24. Miyazaki Y, Mahankali A, Matsuda M, *et al*. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab*, 2002, 87, 2784-91.
25. Iozzo P, Hallsten K, Oikonen V, *et al*. Effects of Metformin and Rosiglitazone Monotherapy on Insulin-Mediated Hepatic Glucose Uptake and Their Relation to Visceral Fat in Type 2 Diabetes. *Diabetes Care*, 2003, 26, 2069-74.
26. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. *Diabetes Care*, 2000, 23, 1605-11.
27. Lebovitz HE, Dole JF, Patwardhan R, Rappaport EB, Freed MI. Rosiglitazone Clinical Trials Study Group. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab*, 2001, 86, 280-8.
28. Wolffenbuttel BH, Gomis R, Squatrito S, Jones NP, Patwardhan RN. Addition of low-dose rosiglitazone to sulphonylurea therapy improves glycaemic control in Type 2 diabetic patients. *Diabet Med*, 2000, 17, 40-7.
29. Kipnes MS, Krosnick A, Rendell MS, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with sulphonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med*, 2001, 111, 10-7.
30. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA*, 2000, 283, 1695-702.
31. Einhorn D, Rendell MS, Rosenzweig J, *et al*. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. *Clin Ther*, 2000, 22, 1395-1409.
32. Vergès B. Oral antidiabetics and lipids. *Ann Endocrinol*, 2002, 63, 1S45-1S50.
33. Brunzell J, Cohen BR, Kreider M, *et al*. Rosiglitazone favorably affects LDL-C and HDL-C heterogeneity in type 2 diabetes. *Diabetes*, 2001, 50, A141.
34. Ovalle B, Bell DSH. Differing effects of thiazolidinediones in LDL subfractions. *Diabetes*, 2001, 51, A457.
35. Winkler K, Friedrich I, Baumstark MW, Wieland H, März W. Pioglitazone reduces atherogenic dense low density lipoprotein (LDL) particles in patients with type 2 diabetes mellitus. *B J Diabetes Vasc Dis*, 2002, 2, 143-8.
36. Nawa T, Nawa MT, Cai Y, *et al*. Repression of TNF- $\alpha$ -induced E-selectin expression by PPAR activators: involvement of transcriptional repressor LRF-1/ATF3. *Biochem Biophys Res Commun*, 2000, 275, 406-11.
37. Marx N, Sukhova GK, Collins T, Libby P, Plutzky J. PPAR $\alpha$  activators inhibit cytokine-induced vascular cell adhesion molecule-1 expression in human endothelial cells. *Circulation*, 1999, 99, 3125-31.

38. Murao K, Imachi H, Momoi A, *et al.* Thiazolidinedione inhibits the production of monocyte chemoattractant protein-1 in cytokine-treated human vascular endothelial cells. *FEBS Lett*, 1999, 454, 27-30.
39. Marx N, Schonbeck U, Lazar MA, Libby P, Plutzky J. Peroxisome proliferator-activated receptor gamma activators inhibit gene expression and migration in human vascular smooth muscle cells. *Circ Res*, 1998, 83, 1097-103.
40. Law RE, Goetze S, Xi XP, *et al.* Expression and function of PPAR-gamma in rat and human vascular smooth muscle cells. *Circulation*, 2000, 101, 1311-8.
41. Marx N, Sukhova G, Murphy C, Libby P, Plutzky J. Macrophages in human atheroma contain PPARgamma: differentiation-dependent peroxisomal proliferator-activated receptor gamma(PPARgamma) expression and reduction of MMP-9 activity through PPARgamma activation in mononuclear phagocytes in vitro. *Am J Pathol*, 1998, 153, 17-23.
42. Marx N, Froehlich J, Siam L, *et al.* Antidiabetic PPAR gamma-activator rosiglitazone reduces MMP-9 serum levels in type 2 diabetic patients with coronary artery disease. *Arterioscler Thromb Vasc Biol*, 2003, 23, 283-8.
43. Satoh H, Tsukamoto K, Hashimoto Y, *et al.* Thiazolidinediones suppress endothelin-1 secretion from bovine vascular endothelial cells: a new possible role of PPARgamma on vascular endothelial function. *Biochem Biophys Res Commun*, 1999, 254, 757-63.
44. Nakamura T, Ushiyama C, Shimada N, Hayashi K, Ebihara I, Koide H. Comparative effects of pioglitazone, glibenclamide, and voglibose on urinary endothelin-1 and albumin excretion in diabetes patients. *J Diabetes Complications*, 2000, 14, 250-4.
45. Jiang C, Ting AT, Seed B. PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. *Nature*, 1998, 391, 82-6.
46. Ricote M, Huang JT, Welch JS, Glass CK. The peroxisome proliferator-activated receptor (PPARgamma) as a regulator of monocyte/macrophage function. *J Leukoc Biol*, 1999, 66, 733-9.
47. Chiba Y, Ogita T, Ando K, Fujita T. PPARgamma ligands inhibit TNF-alpha-induced LOX-1 expression in cultured endothelial cells. *Biochem Biophys Res Commun*, 2001, 286, 541-6.
48. Collins AR, Meehan WP, Kintscher U, *et al.* Troglitazone inhibits formation of early atherosclerotic lesions in diabetic and nondiabetic low density lipoprotein receptor-deficient mice. *Arterioscler Thromb Vasc Biol*, 2001, 21, 365-71.
49. Rosen ED, Spiegelman BM. Peroxisome proliferator-activated receptor gamma ligands and atherosclerosis: ending the heartache. *J Clin Invest*, 2000, 106, 629-31.
50. Wayman NS, Hattori Y, McDonald MC, *et al.* Ligands of the peroxisome proliferator-activated receptors (PPAR-gamma and PPAR-alpha) reduce myocardial infarct size. *FASEB J*, 2002, 16, 1027-40.
51. Koshiyama H, Shimono D, Kuwamura N, Minamikawa J, Nakamura Y. Rapid communication: inhibitory effect of pioglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab*, 2001, 86, 3452-6.