

Fenofibrate: Metabolic and Pleiotropic Effects

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Abstract: Disturbances of lipoprotein metabolism represent one of the most important risk factors for vascular events. However, dyslipidaemic patients often have a number of additional abnormalities (such as endothelial dysfunction, hypertension, low-grade inflammation, haemostatic abnormalities and hyperuricaemia) that may accelerate the atherosclerotic process. Thus, the ideal lipid-modifying drug, along with exerting beneficial effects on lipoprotein metabolism, should also improve these coexisting disturbances.

Fibric acid derivatives (fibrates) are a class of lipid-modifying drugs mainly used in patients with elevated triglyceride levels. These drugs mainly exert their actions via the activation of specific nuclear receptors called peroxisome proliferator-activated receptors (PPAR).

In this review, we summarize the current evidence suggesting that fenofibrate, one of the most widely used fibric acid derivatives, along with its well established actions on lipids also exerts several other antiatherogenic actions. Based on recently published studies, fenofibrate is a useful option for patients with primary combined dyslipidaemias or secondary dyslipidaemias, such as those associated with diabetes mellitus, metabolic syndrome or HIV infection. Additionally, in cases of refractory dyslipidaemia, the combination of fenofibrate with statins is a therapeutic option.

Keywords: Fenofibrate, metabolic effects, pleiotropic effects, inflammation, endothelial dysfunction, dyslipidaemia, uric acid, homocysteine.

INTRODUCTION

Fenofibrate, a third generation fibric acid derivative, is a prodrug, which is hydrolysed by tissue and plasma esterases to the active metabolite fenofibric acid [1-7]. Fenofibrate is >90% plasma bound and has an elimination half-life of approximately 20 h allowing once-daily administration. The bioavailability of the micronised form is around 30% greater than that of the unmodified drug [1-3]. More recently, the dissolution of micronised fenofibrate was further enhanced by the development of a modified release tablet formulation (bioavailability was increased by a further 25%). This new tablet formulation will replace the micronised fenofibrate capsules (the fenofibrate 160 mg modified release tablet is equivalent to the micronised fenofibrate 200 mg capsule) [4-6].

Fenofibrate is primarily excreted in the urine (60%), but faecal excretion also occurs to a variable extent depending on the rate of absorption. The clearance of fenofibrate is substantially reduced in patients with renal failure. Thus, the dose should be modified in these patients [7]. Fenofibrate has a low potential for drug-interactions, since *in vivo* data suggest that both fenofibrate and fenofibric acid do not undergo significant oxidative metabolism by cytochrome P450 and do not inhibit most CYP450 isoforms. There is,

however, a moderate inhibition of CYP2C9 at therapeutic doses [1]. Accordingly, clinical and experimental data have shown that the drug can be used in combination with other lipid modifying agents (especially statins) for the treatment of patients with refractory dyslipidaemia [8-13]. However, fenofibrate can potentiate the effect of coumarin-like anticoagulants with a prolongation of the prothrombin time [14, 15]. Furthermore, fenofibrate should be taken at least 1 h before or 4-6 h after cholestyramine [5]. There is an interaction between fenofibrate and ciclosporin [16]. Thus, caution is needed when fenofibrate is combined with ciclosporin [16]. Finally, the drug can interfere with the high performance liquid chromatography (HPLC) assay of urinary free cortisol thus leading to the false-positive diagnosis of Cushing syndrome in apparently healthy individuals [17].

Micronised fenofibrate is generally well tolerated. The most common adverse events observed after drug administration affected the gastrointestinal system, the skin and appendages. Abnormal liver function tests and increased creatine kinase activity are infrequently reported [1, 2, 18-20].

Fenofibrate is a useful drug for the treatment of atherogenic dyslipidaemias producing a substantial decrease in the levels of triglyceride-rich lipoproteins and an increase in high density lipoprotein cholesterol (HDL-C) levels. These changes are of greater magnitude than those reported for older fibric acid derivatives (e.g. gemfibrozil) [21]. The rise in HDL-C is more pronounced than that achieved after

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statin administration [22] and is related to the baseline HDL-C levels [23-28]. Hence, the largest proportional increase in HDL-C is seen in patients with the lowest baseline levels [29]. Fenofibrate specifically increases the dense HDL subfractions, which are more potent in reverse cholesterol transport from peripheral tissues [30].

A significant decrease in postprandial lipaemia is also observed after drug administration [31-33].

Significant decreases in total cholesterol and low density lipoprotein cholesterol (LDL-C) levels in hypercholesterolaemic patients were reported. These changes are similar to those found after cholestyramine or low/mid-dose statin (e.g. atorvastatin 10 mg, pravastatin 20 mg or simvastatin 20 mg) administration in patients with primary type IIa and IIb hyperlipidaemia [23-25, 34]. Furthermore, fenofibrate can correct abnormalities in the LDL subfraction profile with a shift away from atherogenic small dense LDL. This shift in LDL particle distribution towards larger, more buoyant, LDL particles probably accounts for the increased LDL catabolism noted with fenofibrate [35-40]. Several studies showed that the impact of fenofibrate on lipoprotein kinetics in patients with combined dyslipidaemia is different from that of statins [41-43], thus raising important questions concerning the need of combination therapy in this patient group. The combination of fenofibrate with statins appears to be safe and well tolerated and can induce considerable improvements in both lipid and non-lipid components of the atherosclerotic process when compared with monotherapy [44-49].

The effect of fenofibrate on serum lipoprotein (a) [Lp(a)] is small and inconsistent. However, a significant decrease in Lp(a) levels in patients with high pre-treatment values was also reported (Table 1) [25, 50, 51]. The influence of fenofibrate on serum lipid parameters is significantly affected by mutations in genes involved in the metabolism of triglyceride-rich lipoproteins [52].

Table 1. Effects of Fenofibrate on Lipids

↓↓	TG
↑	HDL-C
↓	Small dense LDL
↓	LDL-C (in hypercholesterolaemic patients)
↓	Postprandial lipaemia
↓	Lp(a)*

*In a few studies

TG: triglycerides, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, Lp(a): lipoprotein (a).

In addition to its beneficial effects on lipoprotein metabolism in patients with primary forms of dyslipidaemia, several studies indicate that fenofibrate may represent a therapeutic option in special patient populations. A number of studies reported that micronised fenofibrate in patients with type 2 diabetes mellitus (DM) significantly improved their atherogenic lipoprotein profile [53-55]. This is followed by a considerable retardation of the atherosclerotic process,

as was seen in the Diabetes Atherosclerosis Intervention Study (DAIS) [56]. DAIS is a double blind, randomised, placebo controlled trial comparing micronised fenofibrate (200 mg/day) to placebo in 418 patients with type 2 DM (305 men, 113 women). Lipid entry criteria were that the total cholesterol/HDL-C ratio should be 4 or higher plus either LDL-C should be 3.5-4.5 mmol/l (135-173 mg/dl) and triglycerides 5.2 mmol/l (460 mg/dl) or lower or triglycerides 1.7-5.2 mmol/l (150-460 mg/dl) and LDL-C should be 4.5 mmol/l (173 mg/dl) or less. Diabetic control was described as adequate. Of 731 patients screened 418 were included; 207 were randomised to fenofibrate and 211 to placebo. The two groups were well matched at baseline for demographic and clinical features. Fenofibrate treatment was associated with significant lipid and lipoprotein changes compared with placebo. There were significant reductions (40%) in progression in minimum lumen diameter ($p = 0.029$) and progression in percentage diameter stenosis (42% less; $p = 0.02$). Associations were observed between means in treatment concentrations of total cholesterol, LDL-C, HDL-C and triglycerides and angiographic changes but the correlation coefficients were small. There were 38 subjects with events in the fenofibrate group compared with 50 in the placebo group. This represents a 23% risk reduction, which, however, was not statistically significant given the small number of patients studied [56].

The term "metabolic syndrome" (MetS) is used to describe a cluster of risk factors that has become a health problem of epidemic proportions [57, 58]. Individuals with the MetS are at an increased risk for vascular events [59, 60]. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines underlie the importance of targeting therapeutic strategies in this patient population [61]. The International and United Kingdom HDL-C guidelines also support this statement [62, 63]. A recently published study showed that fenofibrate beneficially affects the lipid profile of patients with MetS by decreasing the concentration of triglyceride-rich lipoproteins and increasing the values of HDL-C [64]. Insulin resistance, one of the most important metabolic abnormalities in patients with the MetS, was decreased significantly after 3 months of fenofibrate therapy [64]. Experimental studies have shown that in contrast to peroxisome proliferator-activated receptors (PPAR) agonists, which directly increase hepatic insulin sensitivity, fenofibrate increases glucose tolerance by improving hepatic glycogen metabolism in GK rats [65]. In addition, fenofibrate prevented diet-induced obesity (another important component of the MetS) in LDL receptor-null mice [66].

The increasing incidence of HIV infection and the widespread use of antiretroviral therapy led to the recognition of a new entity called HIV-associated lipodystrophy. Although this disorder is mainly attributed to the use of protease inhibitors [67], several studies indicate that disturbances in lipoprotein metabolism in HIV-infected patients are present before the initiation of antiretroviral therapy [68]. This dyslipidaemia is characterized by elevated plasma concentrations of triglycerides, apolipoprotein (Apo) E and Apo C III and decreased levels of HDL-C [68, 69]. An altered distribution of LDL subfraction towards smaller particles has also been observed [70]. Fenofibrate represents

a safe and effective therapeutic option in patients with HIV-associated dyslipidaemia, since it decreases the concentration of triglyceride-rich lipoproteins, increases the levels of HDL-C and normalizes the distribution of LDL subfractions [71-73]. In addition, the drug may act synergistically with antiretroviral therapy, since the activation of PPAR receptors may result in inhibition of HIV replication [74].

MECHANISMS OF ACTION OF FENOFIBRATE

The mechanism of the action of fenofibrate on lipoprotein metabolism appears to involve the activation of transcription factors, known as PPAR, principally PPAR α , which are expressed in the liver. PPAR modulate the expression of genes involved in lipid metabolism through PPAR response elements [75-77]. Specifically, PPAR α activators stimulate the β -oxidation of fatty acids in the liver resulting in a reduced availability of fatty acids for triglyceride synthesis [78, 79]. Furthermore, the activation of PPAR α by fenofibrate induces lipoprotein lipase in the liver, which plays a key role in triglyceride-rich lipoprotein catabolism. It also affects the binding and clearance in the liver of remnant lipoprotein particles by LDL-related receptors [80, 81]. The fenofibrate-induced increased lipoprotein catabolism may also be related to a PPAR-mediated lower hepatic Apo CIII synthesis [82]. It is well known that Apo CIII delays the catabolism of triglyceride-rich lipoproteins, since it inhibits their binding to the endothelial surface and lipolysis by lipoprotein lipase and interferes with Apo E-mediated receptor clearance of remnant particles from plasma [77]. Finally, a new additional mechanism contributing to the fenofibrate-induced reduction in triglyceride rich-lipoproteins was also proposed. Apo AV is a recently discovered lipoprotein that influences plasma triglyceride levels [83]. Specifically, the overexpression of Apo AV results in a significant reduction in serum triglycerides [83]. Human hepatocytes treated with fenofibrate display a significant induction of this lipoprotein; this effect is mediated by PPAR α activation [84].

The improvement of serum lipolytic activity may account for the improvement in postprandial dyslipidaemia noted with fenofibrate [31, 32]. The decrease in plasma concentrations of triglyceride-rich lipoproteins could be responsible for the decreased cholesteryl ester transfer protein (CETP) activity observed after fenofibrate administration, leading to increased HDL-C levels and to reduced concentrations of small dense LDL particles [38, 85, 86].

Fibrates also induce the expression of the human Apo AI and Apo AII genes leading to elevated HDL levels [87]. However, fibrates also affect HDL metabolism by other ways. In fact, the increase in HDL-C may be related to accelerated triglyceride-rich lipoprotein catabolism leading to an increase in pre-HDL, which is the key acceptor of cholesterol for peripheral cells during reverse cholesterol transport [88]. It was also demonstrated that PPAR activation by fenofibrate: a) induces ABC-1 gene expression in human monocytes leading to enhanced transport of unesterified cholesterol and phospholipids from cells [89, 90], and, b) induces CLA-1/SR-B1 expression which are cellular receptors that bind with HDL with high affinity and mediate the selective uptake of cholesterol from HDL in liver and steroidogenic tissues [91].

PLEIOTROPIC EFFECTS OF FENOFIBRATE (TABLE 2)

I) Endothelial Function

Some studies showed that fenofibrate can improve endothelial function. Liang *et al.* showed that fenofibrate attenuated the oxidized LDL-induced impairment of endothelial-dependent relaxation [92]. Other studies demonstrated that fenofibrate can significantly improve endothelial function in patients with hypertriglyceridaemia, during fasting and postprandially [93-96]. Fenofibrate also significantly inhibited migration of human endothelial cells in a concentration-dependent manner. Thus, fenofibrate and other PPAR α activators by inhibiting endothelial cell migration may protect the vasculature from pathological alterations associated with metabolic disorders [97, 98].

Table 2. Pleiotropic Effects of Fenofibrate

1)	Beneficial effect on endothelial function
2)	Antioxidant effects
3)	Anti-inflammatory effects
4)	Antithrombotic effects

Delerive *et al.* showed that PPAR α activators inhibit thrombin-induced endothelin-1 production in human endothelial cells. Endothelin-1 is a very potent vasoconstrictor peptide that induces smooth muscle cell proliferation and may play a role in the development of atherosclerosis [99].

The improvement in serum lipid profile, namely the decrease in triglycerides and small dense LDL particles and the increase in HDL-C, may partly explain the effect of fenofibrate on vascular reactivity [100]. Changes in LDL size and plasma lipid levels account for part of the antiatherogenic effect of fenofibrate in type 2 DM within the DAI study [101]. Moreover, the pleiotropic effects of fenofibrate (e.g. the decrease in insulin resistance and the inhibition of the inflammatory process) may also play a role in the improvement in endothelial function [100]. In this report [100] the effect on endothelial function was related to the changes in C-reactive protein (CRP) and insulinaemia. Both atorvastatin and micronised fenofibrate were associated with a significant increase in peak blood flow in patients with mixed dyslipidaemia [100]. These results were confirmed in another study [102] where the co-administration of fenofibrate and coenzyme Q₁₀ improved endothelial and non-endothelial forearm vasodilator function in patients with type 2 DM. The improvement in blood flow was independent of changes in plasma lipids but was significantly correlated with HbA_{1c} [102]. In addition to its beneficial effects on the arterial circulation, another study showed that fenofibrate can also improve capillary circulation in patients with hyperlipidaemia [103].

Blann *et al.* [104] showed that lipid-lowering therapy (fenofibrate and fluvastatin) was associated with a reduction in plasma vascular endothelial growth factor (VEGF) levels, which is considered a determinant of the rate and extent of

angiogenesis and may be important in cardiovascular pathophysiology [104].

II) Antioxidant Effects of Fenofibrate

Fenofibrate exhibits antioxidant actions partly due to its effects on lipoprotein metabolism. Fenofibrate can increase HDL levels that exhibit antioxidant and anti-inflammatory activities. Furthermore, fibrates can induce a reduction in the atherogenic small dense LDL particles and changes in the distribution of LDL towards larger, more buoyant, LDL particles [105]. Fenofibrate as an activator of PPAR increased Cu²⁺-Zn²⁺-superoxide dismutase and decreased p22 phox message expression in endothelial cells, suggesting that the drug may also exhibit antioxidant activity [106]. In addition, other studies demonstrated that fenofibrate may decrease the production of reactive oxygen species [107], whereas it reduces the concentration of lipid peroxidation products [108].

III) Anti-inflammatory Effects of Fenofibrate

Fenofibrate as well as ciprofibrate can decrease the circulating levels of CRP, a marker of the underlying subacute inflammatory process in the vascular wall [109-111]. In a comparative study, micronised fenofibrate was significantly more effective than atorvastatin in reducing CRP levels [100]. The anti-inflammatory properties of fenofibrate were also confirmed when it was shown that it inhibited reactive amyloidosis in mice by reducing the levels of serum amyloid A (SAA) [112].

Plasma platelet activating factor (PAF) acetylhydrolase (PAF-AH) is a Ca²⁺-independent phospholipase A2 that circulates in association with lipoprotein particles [113]. LDL-associated PAF-AH represents the majority of the enzymatic activity in human plasma (this is referred to as plasma PAF-AH), while a small proportion is associated with HDL [113]. An analysis of the WOSCOPS trial revealed that plasma PAF-AH activity is an independent risk factor for the development of cardiovascular disease [114]. On the other hand, HDL-associated PAF-AH activity exerts anti-inflammatory properties, since it protects LDL from oxidation, and abolishes the actions of oxidized LDL [115]. We evaluated the effect of micronised fenofibrate on PAF-AH activity in patients with primary dyslipidaemia [116]. The administration of micronised fenofibrate resulted in a significant decrease in plasma PAF-AH activity by 20%. This decrease was higher than that observed in Apo B concentration (12%). Since the Apo content of LDL particles is constant (one Apo B molecule per LDL particle) these results indicate a drug-induced reduction in PAF-AH activity per LDL particle. Fenofibrate also induced a significant increase in HDL-associated PAF-AH activity in these patients [116].

Paraoxonase-1 (PON-1) is a HDL-associated esterase produced by the liver [117]. This enzyme can hydrolyse organophosphate compounds, as well as endogenously produced oxidized phospholipids. Thus, from a pathophysiological viewpoint PON-1 is considered to play a protective role against cardiovascular disease [117]. However, the results from studies that evaluated the effect of fibrates on PON-1 activity were inconclusive. Thus, some

studies showed a significant increase in PON-1 gene expression via a non-PPAR-mediated pathway [118, 119], whereas other studies showed no effect or even a decrease in PON-1 activity after fenofibrate administration [108, 115].

Inflammation is considered to play a role in atherogenesis. PPAR agonists, such as fenofibric acids, inhibit the expression of inducible factors implicated in endothelial, macrophage and smooth muscle cell function, as well as in the promotion of a local inflammatory response within the atherosclerotic plaque [120]. Thus, Staels *et al.* showed that fenofibric acids prevented the interleukin-1-induced secretion of interleukin-6 in a dose-dependent manner [82]. Furthermore, fenofibric acids prevented the formation of 6-keto-prostaglandin F₁ (6-keto-PGF₁) by inhibiting cyclooxygenase-2 (COX-2) induction by interleukin [109]. Fenofibrate also reduced plasma cytokine concentration [interferon- (INF-) or tumour necrosis factor- (TNF-)] in patients with dyslipidaemia and atherosclerosis [121]. Marx *et al.* demonstrated that fenofibrate inhibits the TNF-mediated induction of vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells *in vitro* [122]. This adhesion molecule plays a role in the recruitment of leukocytes and monocytes to atherosclerotic lesions. Furthermore, PPAR activators repress thrombin-induced expression of endothelin-1, which induces smooth muscle cells proliferation [99]. Pasceri *et al.* showed that fenofibrate (100 µg/l) almost abolished the CRP-mediated induction of monocyte chemoattractant protein 1 (MCP-1) in human endothelial cells [123]. These results strengthen the role of CRP in the pathogenesis of vascular inflammation and atherosclerosis and provide further evidence of the antiatherogenic effect of fibric acid derivatives [123]. The decrease in CRP was related to the changes of vascular reactivity observed. Therefore, the anti-inflammatory effects of fenofibrate may partly explain the beneficial effects on endothelial function [100].

Experimental data suggested that fenofibrate-induced activation of PPAR in human CD4-positive T cells limits the expression of proinflammatory cytokines, such as INF- [124]. Moreover, fenofibrate downregulates endotoxin-induced secretion of matrix metalloproteinase 9 (MMP-9) in human monocytic THP-1 cells [125], a finding, which further confirms the anti-inflammatory and plaque stabilizing effect of fibrates [125].

VI) Effect of Fenofibrate on Serum Thrombotic Parameters

Several studies showed that fenofibrate can significantly decrease plasma fibrinogen levels [25, 100, 126-138]. Kockx *et al.* showed that in mice fibric acid derivatives suppress fibrinogen gene expression via activation of the PPAR [139]. The fall in fibrinogen levels was associated with a decrease in plasma viscosity and red cell aggregation [130]. These effects may account for the improvement in the microcirculation in patients with hyperlipidaemia [103].

Neve *et al.* as well as Marx *et al.* demonstrated that PPAR activators inhibit tissue factor expression and activity in human monocytes and macrophages [140, 141]. These data point to a novel role for these drugs in the control of atherosclerotic plaque thrombogenicity through their

effects on tissue factor expression in monocytes or macrophages.

There are insufficient data on the effects of fibrates on plasminogen activator inhibitor-1 (PAI-1) production or PAI-1 activity in humans [131, 142]. However, studies of the effects of fibrates on PAI-1 synthesis in liver cells in culture were more conclusive [142]. Even though individual fibrates have diverse effects on PAI-1 expression in endothelial cells, fenofibrate and gemfibrozil markedly decreased PAI-1 transcription and secretion from endothelial cells [143]. Furthermore, Kaneko *et al.* showed that fenofibric acid inhibited basic fibroblast growth factor-stimulated PAI-1 expression [144].

Fibrates also inhibit platelet activation [145, 146], another potentially beneficial antithrombotic action.

EFFECTS OF FIBRATES ON SERUM METABOLIC PARAMETERS (TABLE 3)

A) Effects of Fibrates on Carbohydrate Metabolism

In some, but not all studies, fenofibrate improved carbohydrate metabolism in both rodent models of insulin resistance and in patients with dyslipidaemia, including diabetic patients [100, 147-149]. The discrepancies between the studies may reflect differences in glycaemic control and the extent to which triglyceride-rich lipoproteins were reduced by treatment [150]. The importance of the hypotriglyceridaemic effect of these drugs is further strengthened by the results of some studies, which showed that fibrates improve glucose metabolism in hypertriglyceridaemic patients reaching normalisation of serum triglycerides or when the triglycerides were reduced [151, 152]. Consequently, an inverse correlation between triglyceride levels and glucose metabolism may exist [151, 152]. Furthermore, in another study the improvement of carbohydrate metabolism was noted in patients with impaired glucose tolerance [153]. It is possible that hypertriglyceridaemia contributes to the induction of glucose intolerance and fibrates are effective in lowering triglycerides and enhancing insulin action [154]. Another possible explanation for the fenofibrate-induced improvement in insulin sensitivity could be the induction of fatty acid-binding protein as well as the stimulation of -oxidation in skeletal muscles [155].

Table 3. Metabolic and Haemostatic Effects of Fenofibrate

Effects on:	
1.	Carbohydrate metabolism
2.	Blood pressure
3.	Uric acid
4.	Renal function
5.	Homocysteine levels
6.	Liver function enzymes
7.	Thrombotic parameters (fibrinogen/PAI-1/Tissue factor)

B) Effects of Fibrates on Blood Pressure (BP)

Some, but not all, studies suggest that the fibrate-induced improvement in serum lipids is associated with a decrease in BP values [153, 156, 157]. This decrease in BP may be related to the improvement in insulin resistance and the subsequent decrease in insulin levels. Moreover, fibrates were reported to improve endothelial function [see section (I), above] resulting in a decrease in peripheral vascular resistance and BP. Furthermore, the fibrate-induced increase in HDL-C may improve abnormal arterial contractility [153]. Experimental data in genetic models of hypertension showed that fenofibrate not only lowers BP but also reduces proteinuria in Dahl salt sensitive rats on a high protein diet and in stroke prone spontaneously hypertensive rats [156]. Fenofibrate could also increase urine output and plasma renin activity, a finding consistent with a natriuretic effect of fenofibrate [156].

C) Effect of Fibrates on Uric Acid Metabolism

Among fibrates only fenofibrate significantly lowers serum uric acid levels. Several studies confirmed that fenofibrate significantly enhanced renal urate excretion [158-162]. Micronised fenofibrate (200 mg once daily) administered to dyslipidaemic patients significantly reduced serum uric acid levels by 27.9% [from $405 \pm 71 \mu\text{mol/l}$ ($6.8 \pm 1.19 \text{ mg/dl}$) to $292 \pm 83 \mu\text{mol/l}$ ($4.90 \pm 1.39 \text{ mg/dl}$), $p < 0.001$] by increasing uric acid excretion, as evidenced by a significant increase in the fractional excretion of uric acid (from $8 \pm 3\%$ to $13 \pm 4\%$, $p < 0.01$). The fenofibrate-induced decrease in serum uric acid levels was independent of any change in serum triglycerides or other lipid parameters, confirming the hypouricaemic and uricosuric action of the drug [160]. Thus, fenofibrate could be a useful drug or even the drug of choice for the treatment of dyslipidaemia associated with hyperuricaemia [163]. The uricosuric effect of fenofibrate could also "reverse" the hyperuricaemic effect of thiazides or indapamide [158]. The combination of micronised fenofibrate and losartan (another uricosuric drug) is followed by an additional decrease in serum uric acid levels [159, 162, 163]. Thus, this combination is useful for the management of patients with multiple metabolic abnormalities, including hyperuricaemia [159, 162, 164]. The hypouricaemic effect of fenofibrate could be a reliable marker of compliance to drug therapy [161].

Yamamoto *et al.* suggested that fenofibrate derivatives increase the fractional excretion of xanthine, uric acid and allopurinol by acting on their common renal pathways [165]. However, it is suggested that the hypouricaemic effect of combination using allopurinol and fenofibrate may be less than additive [166].

The uric acid lowering effect of losartan is thought to have contributed 29% of the reduction in vascular events when atenolol and losartan were compared in the LIFE trial [167]. Therefore, any fall in serum urate levels may not only help lower the risk of gout but may also contribute to a reduction in the risk of vascular events [167, 168].

There is evidence that long-term fenofibrate treatment is associated with a sustained reduction in serum urate levels together with remission from recurrent attacks of gout [169].

Fenofibrate may be a potential treatment for hyperuricaemia and the prevention of gout, particularly in patients with hyperlipidaemia or those resistant to conventional therapy for hyperuricaemia [170].

D) Effects of Fibrates on Renal Function

There is convincing evidence that fibrates, with the possible exception of gemfibrozil, significantly increase serum urea and creatinine levels [171-175]. A significant increase in serum creatinine levels occurred after fenofibrate (by 12%; $p < 0.0001$) and ciprofibrate (by 17%; $p < 0.0001$) administration [175]. However, there was a non-significant increase (by 6%) in serum creatinine after taking gemfibrozil [175]. The increase in serum urea and creatinine levels were evident at the patients' first follow-up (mean: 6 weeks of therapy) and remained unchanged or slightly elevated during a follow-up period of 8 months (3-18 months) [175]. One possible explanation for these diverse effects could be that fibrates, such as fenofibrate, ciprofibrate and bezafibrate, impair the generation of vasodilatory prostaglandins, probably via the activation of PPARs, which can downregulate the expression of the inducible COX-2 enzyme [176, 177]. In contrast, gemfibrozil fails to bind and activate PPARs, which may account for the observed absence of an increase in serum creatinine [178]. Even though renal function returned to baseline after fibrate discontinuation in most patients, permanent increases in serum creatinine levels were also reported. Thus, fibrates should be used with caution in patients with renal dysfunction and especially in renal transplant recipients [179]. However, in some studies this increase in serum creatinine levels was not followed by a reciprocal decrease in glomerular fibrate rate [173, 180, 181] or any alteration in renal haemodynamics [180, 181]. Thus, it was suggested that the fenofibrate-induced increase in serum creatinine levels may represent an increase in the metabolic production of creatinine rather than a deterioration in renal function [180]. This interpretation is also supported by evidence showing that folic acid supplementation can inhibit the fenofibrate-induced increase in serum creatinine [181]. The precise effect of fenofibrate on renal function is not clear and will require further investigation. In this setting it is important to note that most fibric acid derivatives are protein bound and may accumulate in patients with impaired renal function.

E) Effect of Fibrates on Plasma Homocysteine Levels

Several studies showed that fibrates can significantly increase plasma homocysteine levels in both the fasting and fed state [182-191]. The addition of vitamin supplementation (folic acid and vitamins B6 and B12) can markedly reduce the homocysteine elevation induced by fenofibrate [182, 185-188, 190]. The underlying mechanisms by which fibrates increase total homocysteine levels are unknown. However, in contrast to fenofibrate and bezafibrate, gemfibrozil does not raise plasma homocysteine levels [184-187]. It was speculated that fibrates exhibit different interactions with PPAR. Unlike other fibrates, gemfibrozil does not bind and activate the PPAR, which downregulates the renal COX-2 enzyme system. This downregulation may impair the synthesis of vasodilating prostaglandins and influence the glomerular filtration rate. Yoshinari *et al.*

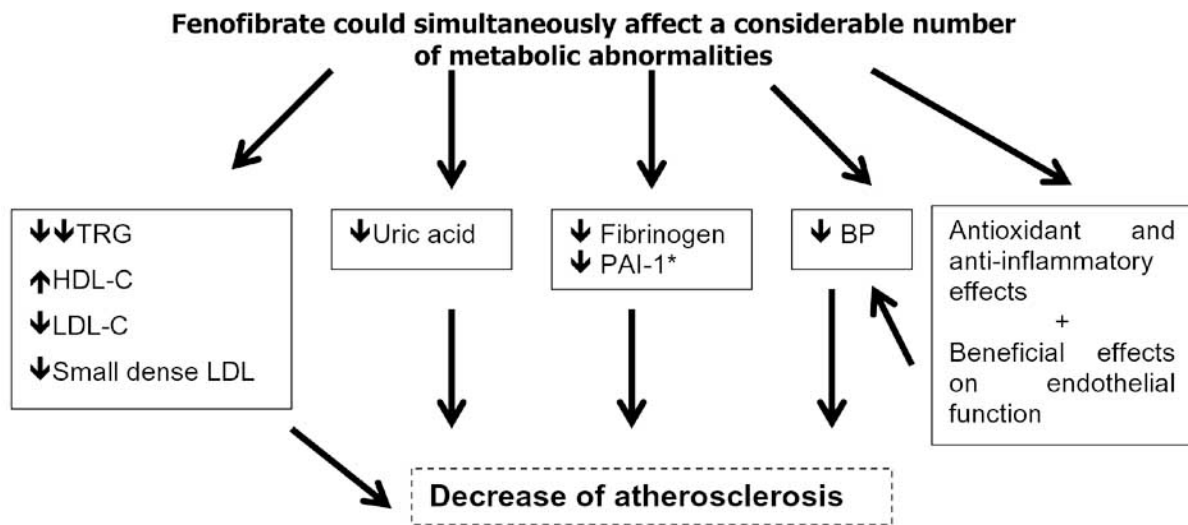
showed that unlike ciprofibrate and clofibrate, gemfibrozil does not inhibit prostaglandin synthesis in patients with type 2 DM [178]. In other words, the increase of plasma homocysteine levels may correlate with the fibrate-induced impairment of renal function, while gemfibrozil does not affect renal function or homocysteine levels. This increase in homocysteine is only evident in wild type mice but not in PPAR deficient mice, suggesting that the fibrate-induced change in homocysteine levels is mediated by the PPAR [191].

The relevance of the influence of fibrates on homocysteine levels is not known. However, since homocysteine is considered to be an emerging vascular risk factor, the ability of these drugs to increase total homocysteine levels could potentially limit their effectiveness in the prevention of vascular disease. Legendre *et al.* showed that fenofibrate induced a selective increase of protein bound homocysteine in rodents, whereas the atherogenic reduced fraction of homocysteine remained unchanged [191]. Thus, in spite of an increase in homocysteine, fenofibrate reduced the *ex vivo* peroxidation of very low density lipoproteins (VLDL) + LDL along with a simultaneous prolongation of the lag time of lipoprotein oxidation [191]. In addition, an analysis of DAIS revealed that the fenofibrate-induced increase in homocysteine levels does not attenuate the beneficial effects of the drug on coronary artery disease progression or clinical events [192].

The differences in homocysteine and creatinine effects between gemfibrozil and other fibrates may give the impression that the gemfibrozil is a superior fibrate. However, this conclusion is inappropriate since there are other differences between these fibrates. For example, the fibrinogen lowering effect favours the other fibrates over gemfibrozil [127, 145, 146]. Furthermore, the effect of statins on plasma fibrinogen levels remains controversial [146, 193-195]. It is also relevant to consider that the LDL lowering potency of fenofibrate is significantly ($p < 0.001$) greater than that of gemfibrozil [21, 128, 150]. Fenofibrate remains the only fibrate to consistently lower serum urate levels [see section (C), above].

F) Effects of Fibrates on Liver Enzymes

A reduction in serum alkaline phosphatase (ALP) and -glutamyltranspeptidase (-GT) activity is a well-documented effect of fibric acid derivatives [51, 196-198]. The effect of bezafibrate on serum ALP is confined to the liver and biliary isoenzymes [198]. In one study, all fibrates significantly reduced serum ALP activity with bezafibrate inducing the greatest changes [199]. Fenofibrate reduced serum ALP activity by 14% from a mean value of 168 iu/l to a mean value of 144 iu/l ($p < 0.0001$) [199]. The changes induced by ciprofibrate, bezafibrate and fenofibrate were significantly greater than those seen after gemfibrozil ($p < 0.0001$, for all comparisons). This study [199] showed that the effect of gemfibrozil on ALP activity is considerably weaker compared to the other fibric acid derivatives tested [199]. The mechanisms accounting for these results remain undefined. However, it was speculated that changes in hepatic fat deposition may be involved in the decrease in serum cholestatic enzymes [51]. It is well established that the



*In some studies

TG: triglycerides, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, Lp(a): lipoprotein (a), PAI-1: plasminogen activator inhibitor-1, BP: blood pressure.

Fig. (1). Mechanisms by which fenofibrate may decrease atherosclerosis.

fenofibrate-induced PPAR activation can stimulate the oxidative metabolism of free fatty acids in the liver thus reducing the quantity of fatty acids available for VLDL synthesis and secretion but also the potential for lipid deposition in the liver [51]. This mechanism could also account for the slight decrease in serum ALP after gemfibrozil administration. Gemfibrozil, in contrast to the other fibrates, fails to bind and activate PPAR [200]. Accordingly, gemfibrozil appears to be devoid of the fibrate-induced increase in serum creatinine levels as discussed in section (IV), above. Alternatively, the decreased liver ALP release results from a reduction in the rate of hepatic bile acid secretion [198]. Fibrates suppress bile acid biosynthesis in rodents via a PPAR-mediated downregulation of cholesterol 7 α -hydroxylase and sterol 27-hydroxylase expression [200]. Among the fibrates tested, gemfibrozil appeared to be less active in the suppression of mRNA levels of both enzymes [200, 201].

The decrease in serum ALP activity has been used to monitor compliance to fibrate treatment [51, 150, 198].

The administration of bezafibrate in patients with refractory primary biliary cirrhosis results in a significant decrease in serum γ -GT, alanine aminotransferase and ALP activity [202-204]. If these results are confirmed histologically and in a randomised trial, a combination therapy of bezafibrate and ursodeoxycholic acid may become the treatment of choice for primary biliary cirrhosis.

Non-alcoholic liver disease (NAFLD) includes a broad spectrum of changes from simple steatosis to non-alcoholic steatohepatitis (NASH) which may advance to cirrhosis and end-stage liver disease [58, 205-212]. It is estimated that NAFLD and NASH are the commonest liver diseases in the USA. NAFLD is associated with insulin resistance, diabetes and obesity (i.e. MetS) [58, 205-212]. In patients with NAFLD fat deposition occurs in the liver [58, 205-212]. It

follows that fibrates may exert a beneficial effect in this common disorder [58, 205-212].

CONCLUSIONS

In conclusion, along with its well established lipid modifying effects, fenofibrate also exhibits several metabolic and pleiotropic properties [213] (Fig. 1). As a consequence, fenofibrate monotherapy may represent the treatment of choice in patients with primary combined dyslipidaemia as well as in patients with specific forms of secondary dyslipidaemias such as diabetic dyslipidaemia and dyslipidaemias associated with the MetS and HIV infection. In addition, fenofibrate may diminish the hyperuricaemia of concurrently used medications (e.g. diuretics). The combination of fenofibrate with statins is a treatment option in cases with refractory dyslipidaemia [44].

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