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Biochemistry and Molecular Biology of Mechanisms of Action of Fibrates – An Overview

A.S.V. Prasad[1*]

[1]G.I.T.A.M Dental Collage, Rishikonda, Visakhapatnam, Andhra Pradesh, India.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Opinion Article

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ABSTRACT

Fibrates are a class of medication that mainly lowers the blood triglyceride levels. They reduce the LDL and increase the levels of HDL C, in the blood. Clofibrate, the first member to be discovered in 1962 , and introduced in USA in 1967, is withdrawn in 2002, due to unexplained hepatomegaly, hepato-toxicity and possible risk of hepatic cancer. Other fibrates are introduced in the late 1970s and early 1980s, such as gemfibrozil in the United States and bezafibrate and ciprofibrate in Europe. Their lipid lowering effects are found to decrease CVS risk , progression of atherosclerosis and metabolic syndrome, macrovascular and microvascular diabetic complications like stroke, myocardial infarction, peripheral vascular disease and diabetic retinopathy .Various clinical trials like VA-HIT trial (Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial) , FIELD trail. (the Fenofibrate Intervention and Event Lowering in Diabetes) Helsinki Heart Study, ACCORD -Lipid trial (The lipid component of the Action to Control Cardiovascular Risk in Diabetes trial) and BIP (Bezafibrate Infarction Prevention Study) trial and angiography trials, like LOCAT (Lopid Coronary Angiography Trial) and BECLAIT (Bezafibrate Coronary Atherosclerosis Intervention Trial) demonstrated the beneficial effects of gemfibrozil and fenofibrate. Their mechanism of action remained obscure for three decades, ie till 1990s, when their mode of action was found. The Mechanism of action of fibrates include limitation of substrate availability for triglyceride synthesis in the liver, promotion of the action of lipoprotein lipase, (LPL) modulation of low density lipoprotein receptor/ligand interaction and stimulation of reverse cholesterol transport The biochemical and molecular mechanisms involving the various enzymes

**Corresponding author: E-mail: drasv@ymail.com;*

like LCAT (Lecithin-cholesterol acyl transferase) and CYP7A1 etc. (cholesterol 7-alpha-monooxygenase or cytochrome P450 7A1 (CYP7A1)) , transporters like ABC , CETP (ATP-binding cassette transporter, Cholesterol ester binding protein) and NTCP, OATP (Na^+-dependent taurocholate transporter / organic anion transporters) . These are the.) and nuclear factors like LXR, PPAR alfa etc. (liver orphan receptor α , and peroxisome proliferative nuclear factor) , in relation to the mechanisms of action of fibrates are discussed . Areas of current interests in literature are briefed.

Keywords: Fenofibrate; gemfibrozil; reverse cholesterol transport; CETP; PPARs; CYP7A 1; LCAT; NTCP; OATP.

1. INTRODUCTION

Fibric acid derivatives (fibrates) are a class of medication that lowers blood triglyceride levels. The triglycerides are made up of a molecule of glycerol inked to three molecules of fatty acids by an ester bondage [1].

To understand the biochemical basis of mechanism of action of the fibrates, a sound understanding of the triglyceride metabolism is necessary. The fatty acid is either saturated or unsaturated. Hydrolysis of the triglycerides molecule (TG) releases the two components, the glycerol and the FA (fatty acid) moieties. This process is called the lipolysis. The FFA (free fatty acid) liberated is used for beta oxidation to generate ATP. They are also esterified in the liver and incorporated into VLD L (very low density lipoproteins) or used for synthesis of other lipids like phospho- lipids. High levels of FFA are linked to IR(insulin resistance states. Since TAG (trial glycerol) can not pass through cell membrane, be it an enterocyte or adipocyte, break down to its continents by lipolysis is necessary. Pancreatic lipase does this in the intestinal lumen and HSL (harmone sensitive lipase) is responsible for lypolysis occurring in adipocyte. The lipoprotein lipase does this to enable the TAG of VLDL and Chylomicrons to enter into adipocyte. Like wise lipogenesis occurs in the enterocyte before they are packed into Chylomicrons along with cholesterol and proteins. The TAG synthesis occurs mainly in adipocyte. The enzymes involved in TAG synthesis at both these sites are the same- mono, di and tri acyal glycerol transferase. The first enzyme links one glycerol to one FA moiety to form mono glycerol (which is capable of crossing the cell membranes of enterocyte and adipocyte) The second and third enzymes respectively produce, DAG (diacyl glycerol) and TAG respectively. Thus, the synthesised glycerol is stored as fat in adipocyte, to be used as reserve energy source, as and when required TAG is also temporarily stored in liver, skeletal muscle, heart and testis etc. to be used for local energy requirements, but the quantity is commensurate with the organ's capacity to catabolise . Any excess fat that is stored in these organs beyond a certain limit (5% in liver) is called 'ectopic fat' which is harmful and is connected to peripheral insulin resistance with its organ specific effects, Met S, (metabolic syndrome) Cardiovascular disease and Beta cell dysfunction of pancreas. In liver it causes NAFLD (non-alcoholic fatty liver) which may progress to steatohepatitis, cirrhosis of liver and even to liver cancer. Increase In TAG in blood is called hypertriglyceridemia The normal level is 150 mg/dl. The risk proportionately increases when it crosses 200 and 500 mg/dl [2]. The AHA (American Heart Association) sets a goal of below 100 mg / dl of TAG as a desirable limit. Hypertriglyceridemia is linked to Heart disease, Stroke and atherosclerosis at high level. Above 500mg/ dl it causes pancreatitis.

2. BRIEF REVIEW OF THE HISTORY OF FIBRATES

The quest for synthesis of lipid lowering agents, the fibrates, started in mid 1950. The earlier compounds were discarded as they were too toxic for human use. The first fibrate to be approved clinically was clofibrate. It was discovered by Thorp and Waring in 1962, approved in US in1967 but was withdrawn in 2002 because of unexplained hepatomegaly, risk of malignancy and toxicity caused by it. Other fibrates were introduced in the late 1970s and early 1980s, such as gemfibrozil in the United States and bezafibrate and ciprofibrate in Europe. further epidemiological studies in humans confirmed the absence of increased risk of cancer in patients treated with fibrates, allowing these drugs to be safely used in the clinic. Consequently, a renewed interest in fibrates appeared in the 1990s when the mode of action of fibrates became understood. gemfibrozil and fenofibrate are primarily used in the United

States and bezafibrate and ciprofibrate are available in Europe. Pemafibrate, is the latest fibrate to be introduced in 2017. It is a selective peroxisome proliferator-activated receptor alpha modulator (SPPARM) It decreases total cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B, while it increases high-density lipoprotein and apolipoprotein AI. It has better safety profile than fenofibrate as regards to renal and hepatic complications. It is currently being evaluated in the PROMINENT clinical trial.

2.1 Some Important Trials on Fibrates

There are a number of clinical and angiographic trials on fibrates.

Clinical trials:

The Prominent Clinical Trial: (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides IN patiENts With diabeTes). It is a multicentric, randomised, clinical trial conducted simultaneously in 24 countries including India .The study population has 10000 volunteers, of which one third, meant for primary prevention and two thirds for secondary prevention (established cardio-vascular disease) .The period of study is between March 2017 and may 2020. The study has, clearly defined primary, secondary and tertiary end points as well as inclusion and exclusion criteria.

The VA-HIT (Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial): The VA-HIT trial studied patients with coronary artery disease, who had low HDL-C (≤40 mg/dl), and LDL-C (≤140 mg/dl).The trial documented a 22% reduction in death or MI with the use of gemfibrozil [3].

The FIELD trial (The Fenofibrate Intervention and Event Lowering in Diabetes): The study demonstrated the beneficial effects on microvascular complications of DM 2 with fenofibrate. FIELD study revealed 14% risk reduction in low HDL subgroup, 23% significant risk reduction in high triglycerides subgroup and 27% significant risk reduction in patients with atherogenic dyslipidaemia [4].

The Helsinki Heart Study: Helsinki Heart Study is a randomized, double-blind five-year trial on dyslipidaemia patients treated with gemfibrozil. A 34% reduction in the incidence of coronary heart disease (CHD) was observed .The decline in incidence in the gemfibrozil group became evident in the second year and continued throughout the study. The drug produced, a mean decreases of 10% in serum total cholesterol level, 14% in non-high-density lipoprotein (HDL) cholesterol level, 11% in low-density lipoprotein (LDL) cholesterol level, 35% in triglyceride level, and a mean increase of 11% in HDL cholesterol level from baseline levels with gemfibrozil, nearly all benefits were derived from the patients with atherogenic dyslipidaemia without any impressive effects in other subgroups [5].

The BIP trial: (Bezafibrate Infarction Prevention Study) The goal of the trial was to evaluate treatment with the fibric acid deravative, bezafibrate compared with placebo in patients with coronary artery disease .There was 11% reduction in mortality with the use of bezafibrate. This benefit was most pronounced among those with greater than 8mg/do increase in the HDL-C (hazard (HR0.78, p = 0.008) verses those with less than 8 mg / dl increase (HR 0.95, p = 0 .43) [6].

The ACCORD-Lipid trial: (The lipid component of the Action to Control Cardiovascular Risk in Diabetes) was a landmark, publicly funded study demonstrating that fenofibrate, when added to statin therapy, was not associated with improved cardiovascular outcomes among patients with diabetes mellitus. 2 5 years follow-up of ACCORD study provides additional support about the benefit of fenofibrate in patients with type 2 diabetes in whom triglycerides remain elevated and HDL-C levels remain low despite statin therapy (Marshall B. Elam, Henry N. Ginsberg, Laura C. Lovato et al 2017).

Angiographic trials:

LOCAT Trial: (Lopid Coronary Angiography Trial): Gemfibrozil therapy retarded the progression of coronary atherosclerosis and the formation of bypass-graft lesions after coronary bypass surgery in men with low HDL cholesterol as their main lipid abnormality Gemfibrozil therapy retarded the progression of coronary atherosclerosis and the formation of bypass-graft lesions after coronary bypass surgery in men with low HDL cholesterol as their main lipid abnormality [7].

The BECAIT Trial: (Bezafibrate Coronary Atherosclerosis Intervention Trial) was a double-blind, placebo-controlled trial over 5 years

to assess the angiographic benefits of bezafibrate retard post-myocardial infarction patients. The trial demonstrated that without lowering serum low density lipoprotein cholesterol, progression of coronary atherosclerosis was prevented and the coronary event rate reduced. In subgroup analyse, bezafibrate decreased the rate of progression of coronary atherosclerosis and coronary event rate in young post-MI patients, primarily by slowing the progression of mild-to-moderate lesions [8].

Recent studies on fibrates:

The review of literature showed that the studies are mainly about, reduction of cardiovascular risk with fibrates ,the effect of fibrates when used alone and in combination with statins , their role in metabolic syndrome, diabetic dyslipidaemias, atherogenic dyslipidaemias, diabetic retinopathy, and about the risk of getting cancer. Interesting data is published on fibres vs rhabdomyolysis. A brief survey of these studies is given below.

Risk reduction in CVD: The Coronary Drug Project, conducted between 1966 and 1975,was the first large randomized, double-blind clinical trial to show that lowering lipids reduced cardiovascular disease

Helsinki Heart Study: Already considered above.

Fibrates used alone as monotherapy: Roussel R, Chaignot C, et al. (2015) in a French countywide cohort study concluded that Fibrates mono therapy: Poor outcome with fibrates monotherapy compared to statins as regards to CVS risk in diabetics [9].

Combined statins and fibrates vs fibates alone: Statins are most effective in LDL-C reduction and have beneficial effect in CVD risk reduction. However, for residual CVD risk, there is need for additional measures. Fibrates with their effects on triglycerides, high-density lipoprotein cholesterol HDL-C) and LDL-C subspecies modulation, offer a good choice Fenofibrate is the most commonly used fibric acid derivative [10].

5 years follow-up of the ACCORD study provides additional support about the benefit of fenofibrate therapy in patients with type 2 diabetes in whom triglycerides remain elevated and HDL-C levels remain low despite statin therapy [11].

Atherogenic dyslipidaemias: Fibrates as monotherapy or in combination with statins currently constitute an indispensable part of the modern anti-dyslipidaemia arsenal for patients with DM2 [12]. The FIELD study, as already seen above, revealed. 27% significant risk reduction in patients with atherogenic dyslipidaemia.

Fibrates in diabetic retinopathy: The treatment with fibrates in people with type 2 diabetes was independently associated with reduced progression to a first diagnosis of DR [13].

Fibrates in metabolic syndrome: Beneficial effect of fibrates in metabolic syndrome is reported among patients with augmented features of Met S (4–5 risk factors for Met S) a marked 56% reduction in cardiac mortality on bezafibrate was observed [14].

Cancer risk with fibrates: Some studies identified fenofibrate as a liver tumor promoter in rodents. However, whether fenofibrate increases the risk of liver cancer in humans remained controversial. Bonovas S, Nikolopoulos GK et al (2012) reported that no appreciable risk is seen with use of fibrates [15] Xin Lian , Gang Wang, Honglan Zhou et (2018) et al. suggested the anticancer activities of fenofibrate and the related pathways involved in apoptosis, cell-cycle arrest, invasion, and migration. [16] They confirmed that fenofibrate exert positive effects against various tumor types, although only its application in high doses (200 mg/kg or 0.3%) inhibited the tumor growth. Therefore, fenofibrate might be regarded as an adjuvant drug in cancer treatment, which can be used in combination with chemotherapy or targeted molecular drugs in future research.

Fibrates and rhabdomyolysis: Destruction of skeletal muscle, causing acute rhabdomyolysis was a disturbing side effect of both fibrates and stains, more so when both are used together. Fenofibrate causing rhabdomyolysis is considered rare but it is reported by some to cause the same when used with statins. Others consider that the combination is safer than when gemfibrozil is used along with statins, a combination which is advised not to be used. Wu J, et al. 2009) reviewed 76 cases of fibrate associated rhabdomyolysis and concluded that chronic renal failure associated with rhabdomyolysis occurred on fibrate therapy. The reported conclusions are- The onset time of the reaction varied between 36 h and 6 months. Gemfibrozil was the most frequent agent

associated with rhabdomyolysis, followed by bezafibrate, fenofibrate, ciprofibrate, and clofibrate. Twenty-three cases were associated with fibrate monotherapy and with fibrate therapy combined with statins or other drugs potentially interacting with fibrates. Sixteen cases had chronic renal failure before fibrate therapy, and 6 had hypothyroidism. Fifty-four complicated acute renal failure. After discontinuation of the fibrates and hydration, most patients recovered Kazuya Kato,(2011) reported a case of fibrate induced rhabdomyolysis in a chronic myeloid leukaemia. [17] Wang, and Yaquis Wang, (2018) reported a case of fibre induced rhabdomyolysis with a brief review of the literature [18].

Mechanisms of action of the Fibrates:

Table 1. Summary of the mechanisms of action of the fibrates

1) Limitation of substrate availability for triglyceride synthesis in the liver
2) Promotion of the action of lipoprotein lipase;
3) Modulation of low density lipoprotein (LDL) receptor/ligand interaction
4) And stimulation of reverse cholesterol transport.
5) The role of PPARs

Substrate limitation as a means of fibrates action in hypertriglyceridemia.

Role of FFA as substrate: As seen above the FA (fatty acid) and glycerol are both substrates for TAGl synthesis. It is the FA Substrate which is considered to be limited in supply to liver (Table 1). The FFA comes from lypolysis of adipocyte TAG and also from endogenous or denovo synthesis of FA in the liver. The FFA is seen already to be taken up for Beta Oxidation by the tissues of the body including liver. In liver the FFA is esterified and is packed into VLDL(very low density lipoproteins).

Suppressed lipolysis in adipocyte adversely effects the hepatic VLDL synthesis: If the lypolysis is Suppressed, the FFA in blood is reduced and the liver contribution to VLDL is reduced and hence the VLDL levels in the blood are reduced. Fenofibrate is shown to inhibit the release of FFA from adipose tissue in rats , dogs, and man [19]. It has a similar action in norepinephrine (NE)-stimulated fat cells isolated from rat epididymal adipose tissue . Because the antilipolytic effect occurred in the presence of glucose and without altering cellular ATP levels, the reduction in intracellular cyclic AMP(adenosine mono phosphate) levels could not be attributed to uncoupling of oxidative metabolism or to secondary effects of free fatty acid accumulation. In the presence of procaine-HCl, which blocks hormone-stimulated lipolysis without inhibiting cyclic AMP accumulation, addition of calibrate prevented the hormone stimulated rise in cyclic AMP. If this8 lipolytic effect of fibrates administration is seen to be associated with both FFA of blood and VLDL levels, which supports this concept. How the lipolysis in the adipocyte is inhibited is explained by inhibition of glucagon-adenylyl cyclase- C amp- PKA pathway. lipolytic hormones not only can activate PKA, but also the mitogen activated protein kinase pathway and extracellular signal-regulated kinase (ERK). Activation of the ERK pathway appears to be able to regulate adipocyte lipolysis by phosphorylating HSL on S600 and increasing the activity of HSL [20] HSL has broad substrate specificity; in addition to triacylglycerol, HSL can also catalyze the hydrolysis of diacylglycerol, 1(3) monoacylglycerol, cholesteryl esters, lipoidal esters of steroid hormones, and retinyl esters in adipose tissue, as well as water-soluble butyrate substrates. [21,22,23,24,] Both the harmonies glucagon and epinephrine are ligands to the different membrane protein receptors capable of inhibiting the above pathway, the glucagon through the action of G- coupled receptors and the epinephrine through, beta adrenoreceptors The natriuretic peptides (atrial, B-type, and C-type natriuretic peptides) were recently identified to be involved in fat-cell metabolism. The natriuretic peptides control lipid mobilization and lipid oxidation by increasing intracellular cGMP and lipolysis. [25] They also reduce leptin production, increase circulating free fatty acids, and increase insulin resistance. Much knowledge us gainedsince inception of this concept till date. The TAG is stored in the adipocyte as lipid droplets (LD). They are considered as specialised organelles inthe adipocyte. They are active sites of neutral lipid metabolism, and comprise neutral lipid or cholesterol cores surrounded by phospholipid monolayers containing specialized proteins. The HSL and the perilipins are phosphorylated normally by the PKA. The hyper phosphorylated perilipins increase by 50 folds the activity of phosphorylated HSL. They help on the synthesis of TAG from phosphatidic acid by dephosphorylating. The family of perilipins has six members (1-6) and perilipins 1 is highly expressed in adipocyte. Translocation of

phosphorylated HSL to the lipid droplet(LD) is considered to be the crucial step in the operation of this pathway. The HSL is tethered to 'lipotransin' and the lipid droplets are surrounded by 'perilipins'precluding the contact between the both . Lipotransin is homologous to p60 katanin and is a member of the AAA protein superfamily, possessing ATPase and microtubule severing activities [26]. The perilipins' precluding are lipid droplet associated proteins. But when the pathway is normally stimulated by the harmony ligands mentioned above, translocation of the phosphorylated HSL by ALBP (adipocyte lipid droplet binding protein) to the lipid droplet occurs and the lipolysis process starts. ALBP is a lipid transporter which binds to HSL, preventing fatty acid inhibition of the enzyme's hydrolytic activity, and sequesters and transports the released fatty acids. Conversely inhibition of this signalling pathway inhibits lypolysis which limits FFA, the substrate for VLDL synthesis by the liver.

Endogenous or de novo FA synthesis (DNL): This is another source of triglyceride synthesis. This occurs when excess of glucose is available to liver. The substrate is acetyl Coa. Normally, the enzyme citrate lyase produces this from citrate in the citric acid cycle. The enzyme ACC (acetyl coenzyme A) is stimulated when acetyl Coa is converted to melanin- Co A. Increased melanin Coa inhibits CPT 1 inhibiting the B oxidation of fats and opens the lipogenic pathway PPAR γ, stimulates lipogenesis. The relevance to hyper triglyceredemia is that DNL(denovo lipogenesis) also contributes TAG to VLDL formation, but the contribution under normal condition is limited to about 5% only. This contribution may substantially increase in conditions of IR like DM2 and obesity, in which conditions it assumes importance in causing hyper triglyceremia. The fibrates may act by lowering the over all VLDL level but have no action on the subtracted of DNL. In DM2, the acetate is believed to be the major substrate for the DNL.

Role of Glycerol as a substrate: The glycerol liberated during lypolysis is not implicated in substrate limitation theory of fibrates action. However, it is transported to the liver and converted to DPHA and then to G3P. The later enters the glycolysis pathway or gluconeogenesis pathway or through Kennedy pathway or MG pathway for TAG synthesis in tissues including the adipocyte. The G3P formed in the glycolysis pathway is the source for the TAG synthesis, in the adipocyte. In DM2 since glycolysis pathway is blocked at the FBP level, this author suggested (ref) opening of HMP shunt, the end product to of which is G3P which I will be the source for TAG synthesis in adipocyte. The ketone formed in DPHA for utilising as energy source by the brain. However fibrates by their action in reducing the bile and it's saturation may through entero-hepatic cycle limit the absorption of the TAG of dietary origin by failure to emulsify the fats in duodenum as:

It is prerequisite for enteric absorption of the dietary fats. The matter is considered in detail video infra, under reverse cholesterol transport.

Reverse cholesterol transport: The liver supplies the cholesterol to the nonhepatic peripheral tissues through LDL and the unmet abolished excess cholesterol from these tissues is transported by HDL, to the liver to be metabolised and excreted in bile. The later process is named as the reverse cholesterol transport. Certain transporter proteins), transcription factors (like LXR, PPAR alfa etc.) and enzymes (CEPT ,CYP7A1 etc.) that play an important role in the reverse cholesterol transport are believed to be involved in the mechanism of action of the fibrates. The evidence for the involvement of reverse cholesterol transport comes from the evidence that the moderate fall in total plasma cholesterol is not explained by a reduction of whole-body cholesterol synthesis, and the increase in LXR- and ABCAI mRNA levels suggests that fenofibrate stimulated reverse cholesterol transport.

Decrease in plasma LDL-C and increase in plasma HDL-C by fibrate treatments, biliary cholesterol secretion was found to be increased in both normal and hyperlipidemic individuals after fibrate treatments. Biliary bile acid secretion was also reported to be decreased by fibrates. [27,28] This suggests that fibres stimulate reverse cholesterol transport.

ABC A1: The ATP-binding cassette transporter A1 (ABCA1) is expressed in liver, intestine, and macrophages. ABCA1 plays a central role in HDL formation by transporting intracellular cholesterol to pre- HDL particles. (nascent HDL). The Apo A of HDL acts as the cholesterol acceptor and the phospho- lipid fraction acts as a sink. Both human patients with non-functional ABCA1 due to autosomal recessive disorder like Tangier disease, and ABCA1 knockout mice showed extremely low plasma HDL levels, of ABCA1 in

HDL metabolism [29,30]. ABCA1 is a direct target of the oxysterol receptor, liver orphan receptor α (LXRα), which induces ABCA1 in response to high cellular cholesterol activation. The pre HDL or also called nascent HDL, contains mainly cholesterol and is discoid in shape. As cholesterol is esterified enroute to liver, by the LCET enzyme and more of the ester accumulates, the HDL assumes a spherical shape and becomes more dense .it is known as HDL 2, the form in which HDL is transported to and metabolised in the liver.

The other ABC transporters:

ABC 4: This helps the phospholipid part of the HDL to be excreted into the bile. Since fihrate treatment does not effect the phospholipid concentration in bile, the ABC 4 is not a target of the fibrate action.

ABC 5/8: Biliary free cholesterol secretion mediated by ABC G5/G8 transporters is an important route for hepatic cholesterol elimination. Mice lacking ABC G5 and ABC G8 showed decreased biliary cholesterol concentration, while transgenic expression of ABCG5 and ABCG8 in mice resulted in increased biliary cholesterol secretion. Bile acids, phospholipids, and cholesterol are three major organic solutes of the bile and once secreted, they form mixed micelles to increase cholesterol solubility and reduce their toxicity to the bile duct. Normal bile formation depends largely on balanced secretion of these constituents. Impaired secretions will disrupt the bile flow and result in cholestasis or cholesterol gallstone disease. Since cholesterol saturation in bile is increased by fibrates action and since fibrates favour gall bladder stones, there is reason to believe that fibrates affect teise transporters also.

CETP (Cholesterol ester transporter protein)**:** This transporter, exchanges cholesterol esters in the HDL 2 with triglycerides in the LDL and VLDL normally. Fibrates inhibit CET, which results in less triglyceride enrichment of HDL particles and less opportunity for hepatic lipase remodelling of them to a smaller size. Human CETP transgenic mouse model showed that fenofibrate significantly reduced plasma CETP activity, which was correlated with elevated plasma HDL-C levels [31] (88) This study suggests that PPAR activation may inhibit plasma CETP activity in humans and may contribute to elevated HDL-C by fibrate treatment.

NTCP and **OATPs (** Na^+-dependent taurocholate transporter/ organic anion transporters). These are the hepatic bile acid transporters.

Trough the basolateral membrane, which is in direct contact with the portal blood plasma, the HDL2 is transported into the hepatocyte, which synthesise the primary bile acids and excrete them at the canalicular membrane into the bile. [32] Two transporters are involved in the hepatic bile acid transport, the Na^+-dependent taurocholate transporter protein (NTCP) and organic anion transporters (OATPs).

The BSEP (ABC B11): The concentration of bile is about 100 to 1000 times more concentrated than the canaliculi, they are transported across the canaliculi membrane against a concentration gradient . The bile salt export pump salt export pump (BSEP, ABC B11), originally identified as the sister of P-glycoprotein (SPGP), is mainly responsible for bile acid transport at the canalicular membrane [25]. This is a rate limiting step. Pumping of bile salts stimulate secretion of phospholipids (by ABC) followed by passive transfer of water into the bile and free cholesterol is secreted (by ABC). Since the bile is more saturated and contain more cholesterol but same concentration of phospholipids after the fibre treatment of the hyperlipidemics, the BSEP may be stimulated by the fibres.

The Enzyme targets of fibrate's action:

LCAT (Lecithin-cholesterol acyl transferase): This is the enzyme responsible for esterification of the cholesterol in the nascent HDL and transforming it into the HDL2, in which form the HDL is transported to and metabolised by the liver. Fibrates are not shown to have any effect on this enzyme.

CYP7A1 catalyses the first the rate-limiting step in the classic pathway to convert cholesterol into 7-hydroxycholesterol. Fibrates inhibit this enzyme as evidenced by decrease bile quantity. The bile that enters the entero- hepatic circulation is reduced and hence the emulsifying function of bile of the intestinal fats is reduced, perhaps explaining the decreased ATGA (anti-thyroglobulin antibody) and its reduced blood levels seen under fibrate's treatment.

CYP8B1 regulates the cholic acid synthesis(C A) in the classic pathway. CYP8B1 regulates CA formation in the classic bile acid synthesis pathway and plays an important role in controlling

the CA: CDCA ratio. Clofibrate treatment has been shown to increase CYP8B1 activity and mRNA level in rat liver microsomes [CYP27A1 initiates the alternative pathway by converting cholesterol into 27-hydroxycholesterol, which is then 7-hydroxylated by oyster 7-hydroxylase (CYP7B1).

There is evidence that fibrates act on CYP27A1 inhibiting it as well as CYP8B1.

Nuclear factors:

LXR α & PPARs (liver orphan receptor α, and peroxisome proliferative nuclear factor) LXR α induces ABCA1 in response to high cellular cholesterol activation. [33] LXR α expression is induced by both PPAR and PPAR agonists in human and murine macrophages. In PPAR knockout mice, both ABCA1 expression and cholesterol efflux were reduced in macrophages. PPRE has been identified in both human and mouse LXR α promoter [34,35].

Fibrates acting through modulation of LDL receptor- mediated clearance: LDL(low density lipoproteins) has two separate catabolic pathways one involving involving the LDL receptor and the other, the scavenger mechanism(s). The former route is anti-atherogenic; the latter, pro-atherogenic. When triglyceride levels are low, the fractional clearance of LDL by the receptor is high. Fibrate treatment results in the formation of LDL with a higher affinity for the LDL receptor, which are thus catabolized more rapidly. Catabolism of this fraction increases from 40% of the plasma pool per day in untreated to 60% per day in treated subjects. By activating lipoprotein lipase, fibrates also reduce the amount of small dense LDL, the fraction which is most likely to generate peroxidation products. Hence, fibrates stimulate LDL receptor-dependent clearance mechanisms and reduce the amount of LDL available for oxidation.

Fibrates act by promoting the action of lipoprotein lipase (LPL): Lipoprotein lipase catalyses the partial hydrolysis of the core triglycerides of chylomicrons and VLDL to monoglycerides and fatty acids. The fatty acids are taken up by the tissue and either re-esterified and stored (in adipose tissue), utilized as an energy source (in muscle) or secreted (in lactating breast tissue). The monoglycerides are further hydrolysed to glycerol and fatty acids. Fibres lower the triglyceride levels by stimulating the action of LPL. The role of PPARs in the induction of LPL is considered below.

Role of PPARS: PPARs inhibit overall hepatic bile acid synthesis and stimulate reverse cholesterol transport. Fibrates act as ligands for PPAR alfa in achieving this by inhibiting the two enzymes that control the main and alternate pathway of bile acid synthesis ie CYP A7 and CYP 27 A1 respectively.

PPARα inhibited Cyp7a1 by decreasing the cellular levels of HNF4. Consistent with these in vitro studies, ciprofibrate treatment was shown to inhibit CYP7A1 mRNA expression and enzyme activity in both rat and mouse livers in vivo. The repressive effect of ciprofibrate on CYP7A1 mRNA expression and enzyme activity was completely abolished in mice lacking PPAR , providing an in vivo evidence that fibrates inhibition of Cyp7a1 was PPAR-dependent. [36] CYP27A1 is the rate-limiting enzyme in the alternative bile acid synthetic pathway, and is also responsible for the side chain oxidation in the classic bile acid synthetic pathway The Cyp27a1 transcription was also repressed by fibrate treatment in mice, despite a much weaker reduction in the mRNA level and enzyme activity when compared to those of CYP7A1. [37] The fibrate inhibition of CYP27A1 was also likely to be PPAR-dependent, but the molecular mechanism of this regulation is still not clear. Simultaneous inhibition of both bile acid synthetic pathways may result in decreased hepatic cholesterol catabolism and overall bile acid production in the liver. CYP27A1 is also expressed in peripheral tissues such as macrophages and intestines and is thought to play a role in cellular cholesterol efflux by converting cholesterol into oxysterols [38,39] It was found that CYP27A1 was upregulated by PPAR activation in human macrophages. [40,41] Treatment of a PPAR agonist caused an increased cholesterol efflux from human macrophages . Although how activation of PPAR isoforms led to tissue specific regulation of CYP27A1 in the liver and macrophages is not clear.

Treating mice a PPAR agonist, Wy14643 resulted in an up regulation of CYP8B1 mRNA levels and increased CA to CDCA/-muricholic acid ratio, and knockout of PPAR reversed that [42] A functional PPRE was identified in both mouse and rat CYP8B1 promoter, suggesting a direct transcriptional activation of CYP8B1 by PPAR.

Bezafibrate treatment has been shown to increase the CA to CDCA ratio in human patients, which further suggests that PPAR regulation of CYP8B1 may likely be conserved in humans.

PPARs may play a role in regulation of bile acid conjugation and transport in the liver and intestine. An early study showed that ciprofibrate feeding for two weeks resulted in a significant decrease of hepatic NTCP, OATP1 and BSEP in mice, and these effects were largely abolished in PPAR a null mice. [43] binding protein (I-BABP) was also found to be induced upon PPAR activation in Caco2 cells [44]. Up regulation of ASBT and I-BABP presumably increases intestinal bile acid uptake and intracellular transport.

PPAR regulate HDL metabolism by promoting reverse cholesterol transport. It is supported by the clinical studies showing that fibrate treatments reduced plasma triglycerides but also caused 5–15% increase in plasma HDL-C levels, with a modest reduction in LDL-C. [45] fibrate effects on plasma HDL-C level are thought to be mediated by PPAR induction of the Apolipoprotein AI (Apo A-I). PPAR activation by fibrates induced Apo A-I mRNA expression in human hepatocytes . A PPRE has been identified in the human Apo A-I promoter [46].

Action of PPAR on lipoprotein metabolism: PPARs are nuclear transcription factors. Four isoforms of PPAR family are identified (α, δ, γ).

PPAR α: (Hypolipidemic effects of fibrates are mainly a result of activation of the nuclear receptor peroxisome proliferator-activated receptor α(PPAR α). PPAR forms a heterodimer with nuclear receptor RXR and recognizes a consensus PPAR responsive element (PPRE) on its target gene promoters. PPAR α regulates a network of genes that promote lipolysis and fatty acid -oxidation, the FoxO1 deregulation is implicated in the pathogenesis of hypertriglyceridemia in high-fructose-fed hamsters. Counter regulation of hepatic FoxO1 activity by PPARα constitutes an important mechanism by which fibrates act to curb Apo C-III overproduction and ameliorate hypertriglyceridemia mechanisms mediating the lipid lowering effects of fibrates [47,48].

PPAR γ: plays critical roles in adipocyte differentiation, lipid storage, inflammation, and energy metabolism. Fibrates by stimulating this, increases lipogenesis and lowers the circulating TAG.

PPARδ: plays a role in fatty acid and energy metabolism in the muscle.

PPAR alfa cause induction of LPL at transcription level and inhibits the apo C111 gene there by decreasing it's synthesis. The combined effect is increased catabolism of VLDL. Also PPAR decreases the synthesis of Apo B there by decreasing the VLDL secretion. reduced secretion of VLDL particles, together with the enhanced catabolism of triglyceride-rich particles, most likely accounts for the hypolipidemic effect of fibrates also increase the hepatic uptake of free FAs (FFAs) by specific FATPs19 and generation of acyl-CoA esters by ACS.20 Owing to an increased b-oxidation activity and a reduction in acetyl-CoA carboxylase and FA synthase activities, FFA metabolism is shifted from triglyceride synthesis to catabolism.

Action of Fibrate on LPL: Increased activity of lipoprotein lipase (LPL) may explain the hypotriglyceridemic effects of fibrates, which are known activators (and/or ligands) of the peroxisomeproliferator-activated receptor alfa (PPAR α) Fenofibrate, induced LPL expression exclusivelyin rat liver. Transcriptional activation of the LPL gene by fibrates is mediated by PPAR-RXR heterodimers and contributes significantly to their hypotriglyceridemic effects in vivo. The action of LPL is crucial both in energy metabolism (supply of free fatty acids) and in lipoprotein metabolism (conversion of triglyceride-rich lipoproteins).

3. CONCLUSION

The indications for fibrates alone and Combination with a statin are clear. Among the fibrate group, efficacy -wise, perhaps there is little to chose among the group. But when used as combination therapy statin with gemfibrozil is to be avoided as the risk for rhabdomyolyses is greater, compared to that with fenofibrate. Pemafibrate is considered safer and superior to fenofibrate as regarding residual cardiovas cular risk. The last word will be said when PROMINENT trial results become available.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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