Among many compounds that affect change in concentration of TG (triglycerides) in plasma are selected clofibric acid derivatives. These compounds modify concentration of structural and enzymatic proteins both in plasma, cytoplasm, and other organelles, such as mitochondria or peroxisomes. Elevated concentrations of TG in plasma entail serious health consequences as a development of atherosclerosis, and therefore coronary heart disease. In contrast, clofibric acid derivatives are among very few therapeutic agents lowering TG levels by affecting structural and regulatory proteins of lipoprotein fraction as well as enzymatic and receptor proteins.

TG are esters of glycerol and higher fatty acids. In the body, TG are formed in liver, intestine and in adipose tissue. Then, triglycerides are bound in lipoprotein fractions, which move to plasma. In the body, as a TG are transported most of the long chain fatty acids taken with food. TG constitute lipid material in white adipose tissue (90% of lipid content) as well as reserve and energy materials.

In humans, there are lipoprotein fractions such as chylomicrons, very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high-density lipoprotein (HDL). TG-rich are VLDL and chylomicrons. TG hydrolisis occurs with simultaneous degradation of these fractions and is prerequisite for proper lipid metabolism because it provides fatty acids to all tissues and organs. This process depends on activities of many proteins including apolipoproteins (apo). In conditions when amount of TG fractions in plasma is increased, are used lipid-lowering drugs.

Fibrates as clofibric acid derivatives
Clofibric acid derivatives called fibrates, are quite commonly used lipid-lowering drugs, so it is necessary to know beneficial and adverse effects of these compounds on the body. The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has concluded that benefits of four fibrates such as: bezafibrate, ciprofibrate, fenofibrate and gemfibrozil continue outweigh their risk in treatment of people with blood lipid disorders. According to recommendations of the CHMP fibrates should not be used as first-line drugs, except in patients with severe hypertriglyceridemia and patients who cannot use statins. In this paper, we focused on effect of clofibric acid derivatives on lipid metabolism, in particular on apo proteins and regulatory enzymes.


**Keywords:** clofibric acid derivatives, apo proteins, regulatory enzymes, lipid metabolism

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Clofibrac acid derivatives impact on hepatocytes in different organelles, especially in nucleus, mitochondrions and peroxisomes (Fig. 1). Most studies relating to the effect of clofibrac acid derivatives were performed in order to determine their impact on the activity of peroxisomal enzymes (1-3). For example, in studies conducted on rats it was

Figure 1. Half structural formulas of clofibrac acid, clofibrate, and fenofibrate, bezafibrate, ciprofibrate, simfibrate and gemfibrozil (according to the IUPAC systematic name).
Coronary effect of fibrates on proteins and enzymes which hydrolyze triacylglycerols demonstrated that clofibrate acid derivatives cause significant hypertrophy of peroxisome in liver tissue (4, 5). In turn, in humans, it is assumed that peroxisome hypertrophy under the influence of clofibrate occurs only to a limited extent (6). Clofibrate in patients increases amount of liver mitochondrions (7). In consequence, it leads to increase of acetyl-CoA which is involved in Krebs cycle.

**Structure and mechanism of effects of clofibrin acid derivatives**

Clofibrate (KF) was the first one to be used in the early sixties (1967, in the U.S.) but then, due to numerous side effects, it was withdrawn from use (8). Successively, fenofibrate (FF), bezafibrate (BF), ciprofibrate (CF) and gemfibrozil (GF) were put on the market in the seventies. Fibrates are halogen derivatives and contain chlorine atom (excluding gemfibrozil). Their chemical structure refers to short chain fatty acids. In molecules of KF, FF and BF one of substituents is chlorine connected by covalent bond to aromatic ring. It affects biological function of clofibrin acid derivatives. Replacement of chlorine atom in the molecule of clofibrin acid with extensive substituent such as 4-chlorobenzoyl in case of FF, or 2-(4-chlorobenzamide)-ethyl in case of BF increased lipophilicity of these compounds (9, 10).

Drugs with pharmacological properties similar to FF and BF are: CF - (2-[4-(2,2-dichlorocyclopropyl)-phenoxy]-2-methylpropanoic acid) and simfibrate - (2-(4-chlorophenoxy)-2-methylpropanoic acid 1,3-propanediy1 ester). Gemfibrozil - 5-(2,5-dimethylphenoxy)-2,2-dimethyl-pentanoic acid) is another drug belonging to clofibrin acid derivatives. This compound is ω-hydroxyvaleric acid derivative connected by ester bond with dimethylphenyl group (Fig. 1).

Micronized FF and CF, currently used in clinical practice, cause less severe side effects. Micronization - size of particle less than 50 μm, results in improved absorption compared to a standard substance. It increases about 30% bioavailability of drug. Fibrates are very well absorbed into blood from gastrointestinal tract. In blood, about 95% of fibrates are bound to plasma albumin. BF, CF and GF reach maximum concentration after 2 h while FF after 4-6 h. The metabolism of these compounds takes place in the liver whereas they are excreted in 60-90% by kidney. Biological half-life of FF is equal to 22 h; BF - 2 h; CF - 18 h and GF - 1.1 h (Table 1).

Fenofibrate is well absorbed after oral administration, with peak plasma levels attained in 6 to 8 hours. It is insoluble in aqueous media suitable for injection. It creates a metabolite - fenofibric acid, which has a half life of about 20 hours (11). Bezafibrate in serum half life of a single 20 mg/kg oral dose in monkeys was 2-3 hours. This is comparable to t1/2 in man. Tissue distribution studies in animals found the highest bezafibrate concentration in the liver and intestine 8 hours after oral dosing. Serum protein binding ranges from 88.4 to 93.5% after 0.5 to 8 hours, respectively. Male and female beagle dogs receiving oral bezafibrate at 30 mg/kg had t1/2 = 3 and 2.7 hours. Bezafibrate half-life in normal volunteers averages 18 to 22 hours (range 14 to 35 hours) but can vary by up to 7 hours in the same subject at different times (13).

Half-life CF in normal volunteers averages 18 to 22 hours (range 14 to 35 hours) but can vary by up to 7 hours in the same subject at different times (13).

Fibrates have been used in treatment of endogenous hypertriglyceridemia, mixed hyperlipidemia, chylomicronemia syndrome, hypercholesterolemia or polymetabolic syndrome which includes hyperinsulinemia, diabetes type II, hypertension and obesity. These disorders occur with coronary heart disease, ischemic heart disease, or diabetes type II (11, 12). Clofibrin acid derivatives are well tolerated drugs be the system and side effects occur in approx. 10% of patients. Usually they are associated with gastro-intestinal disorders (46%), although they may also include other symptoms (e.g., muscle pain - 9%) (11, 13).

<table>
<thead>
<tr>
<th>Fibrates</th>
<th>Degree of protein binding [%]</th>
<th>Half-life [h]</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenofibrate</td>
<td>&gt; 99</td>
<td>19-27*</td>
<td>100% renal as glucuronides form</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>96</td>
<td>18-22**</td>
<td>100% renal as metabolized form</td>
</tr>
<tr>
<td>Bezafibrate</td>
<td>95</td>
<td>1.5-3.0***</td>
<td>100% renal as unchanged form</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>98</td>
<td>1.1-3.7*****</td>
<td>100% renal as metabolized and glucuronides form</td>
</tr>
<tr>
<td>Ciprofibrate</td>
<td>99</td>
<td>70-81******</td>
<td>100% renal as glucuronides form</td>
</tr>
</tbody>
</table>

* The values are based on the publications: *(11, 13), **(12, 13), ***(13), ****(13, 58, 59), *****.(60).
Knowledge of mechanisms of action of fibrates has been extended and thus clearly explained at the time when, in 1990, was discovered nuclear receptor activated by peroxisome proliferator, so-called, PPAR (peroxysome proliferator activated receptor) (13). It includes three types of PPAR: α, δ (also called β, NUC-1 or FAAR) and γ, each of which are encoded by separate genes (16). These receptors are present in various tissues, and are transcription factors that allow signal transmitted from fat-soluble substances (natural fatty acids, hormones such as glucocorticoids, vitamins, some lipid-lowering drugs) to target sites, which are genes responsible for synthesis of proteins involved in lipid metabolism (15, 17).

Fibrates, after entering to cytoplasm, connect to specific transporter proteins, and then are passed to nucleus where bind to PPAR. Similarly to Wy 14.643 (4-chloro-6-[(2,3-dimethylphenyl)amino]-2-pyrimidinyl]thio]-acetic acid (pirinix acid), unsaturated fatty acids and their fibrate derivatives are ligands of PPARα receptor. After activation, PPAR-α forms a heterodimer with a nuclear receptor for 9-cis retinoic acid : RXR. Then, thus formed transcription factor PPAR/RXR combines with a strictly defined sequence of DNA known as PPRE (PPAR response-element).

Effects of fibrates on apo proteins and transporting and regulators enzymes

These effects cause a change in regulation of gene expression for particular proteins involved in lipid metabolism such as LPL, HL (hepatic lipase), protein apoA-I, A-II, AV, apoB-100, apoC-III, and

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Function</th>
<th>Main place of synthesis of enzymes</th>
<th>Effect induced by fibrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-I</td>
<td>Structural protein of HDL activates LCAT, stimulates excretion of cholesterol from cytoplasmic membrane, binding fractions pre-β – HDL with SR-BI and ABCA1</td>
<td>Liver, intestine</td>
<td>Acceleration of synthesis of protein apoA-I in liver</td>
</tr>
<tr>
<td>ApoA-II</td>
<td>HDL protein, inhibitor for HL</td>
<td>Liver</td>
<td>Acceleration synthesis of protein apoA-II</td>
</tr>
<tr>
<td>ApoA-V</td>
<td>Activates LPL</td>
<td>Liver</td>
<td>Acceleration synthesis of protein apoA-V</td>
</tr>
<tr>
<td>ApoC-III</td>
<td>Inhibitor LPL, inhibitor for download by hepatocites TGRL</td>
<td>Liver</td>
<td>Limited synthesis of protein apoC-III</td>
</tr>
<tr>
<td>ApoB-100</td>
<td>Structural protein of LDL, IDL, LDL, involved in binding to receptor ‘B-100,E’</td>
<td>Liver</td>
<td>Acceleration synthesis of protein apoB-100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enzymes and transport proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPL</td>
</tr>
<tr>
<td>HL</td>
</tr>
<tr>
<td>SR-B1</td>
</tr>
<tr>
<td>PLTP</td>
</tr>
<tr>
<td>ABCA1 FC</td>
</tr>
</tbody>
</table>
Coronary effect of fibrates on proteins and enzymes which hydrolyze triacylglycerols

Table 3. Summary of apo proteins, their location, functions, concentration and half-life.

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>Fractions in which occur apo protein</th>
<th>Functions</th>
<th>Concentration in plasma (mg/dL)</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-I</td>
<td>HDL, chylomicrons</td>
<td>the main structural protein of HDL, activator of LCAT</td>
<td>100-150</td>
<td>about 4 days</td>
</tr>
<tr>
<td>ApoA-II</td>
<td>HDL, chylomicrons</td>
<td>structural protein of HDL, inhibitor of HL</td>
<td>30-40</td>
<td>about 4 days</td>
</tr>
<tr>
<td>ApoA-IV</td>
<td>chylomicrons, HDL</td>
<td>facilitates release of chylomicrons from intestine, activator of LCAT</td>
<td>15</td>
<td>about 1 day</td>
</tr>
<tr>
<td>ApoC-I</td>
<td>chylomicrons, VLDL, HDL, IDL</td>
<td>activator of LCAT, inhibits download residual fraction by hepatocytes</td>
<td>6</td>
<td>about 6 h</td>
</tr>
<tr>
<td>ApoC-II</td>
<td>chylomicrons, VLDL, HDL, IDL</td>
<td>activator of LPL</td>
<td>4</td>
<td>about 6 h</td>
</tr>
<tr>
<td>ApoC-III</td>
<td>chylomicrons, VLDL, HDL, IDL</td>
<td>inhibitor of LPL</td>
<td>12</td>
<td>about 6 h</td>
</tr>
<tr>
<td>ApoB-48</td>
<td>chylomicrons, residual chylomicrons</td>
<td>structural protein of chylomicrons</td>
<td>fasting</td>
<td>under 1 h</td>
</tr>
<tr>
<td>ApoB-100</td>
<td>VLDL, IDL, LDL</td>
<td>structural protein of VLDL, IDL, ligand of „B-100,E” receptor</td>
<td>80-100</td>
<td>about 3 days</td>
</tr>
<tr>
<td>ApoD</td>
<td>HDL</td>
<td>transports of free cholesterol</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>ApoE</td>
<td>chylomicrons, residual chylomicrons, VLDL, IDL, HDL</td>
<td>binding of residual fractions of LDLR and LRP</td>
<td>3-7 under</td>
<td>1 day</td>
</tr>
</tbody>
</table>

receptor proteins such as SR-B1 (scavenger receptor class B) (Tables 2 and 3) (11, 18-21).

Fibrates activate degradation of TG-rich fractions, such as VLDL and chylomicrons by increasing their lipolysis. In addition, this activates LPL or causes an increase in availability of these fractions to lipolysis catalyzed by this enzyme. Lowering concentration of apoC-III, which is an inhibitor of LPL, allows for efficient action of the enzyme (19). FF results in inhibition of transport of cholesterol esters HDL₃ to VLDL fraction, leading to an increase in HDL-C (22). FF causes a slight decrease in apoE mRNA expression, but this effect was not observed for KF or GF (23). It has been shown that fibrates increase concentration of apoB-100 which is structural protein of VLDL (24). Administration of KF as well as FF to animals caused an increase of expression of hepatic apoB mRNA (apoB-100), but there was no such influence on intestinal apoB mRNA (apoB-48) (24). Clofibric acid increases elimination of LDL particles, since it affects on forming complexes LDL with LDLR and LRP receptor (LDL receptor-related protein) (25, 26). Simultaneously, under influence of fibrates, takes place intensification of synthesis and activity of these receptors in the membranes of hepatocytes. In plasma, in fraction of HDL, it is a protein PLTP which is transporting phospholipids between fraction of VLDL and chylomicrons as well as subfraction of pre-β-HDL. Fibrates accelerate synthesis of protein mainly in liver (27).

In liver, clofibric acid derivatives increase rate of fatty acids uptake and their conversion into acyl-CoA because they activate fatty acids transporter protein (FATP) and acyl-CoA synthetase (28). It leads to formation of large amounts of TG. In such conditions may occur more of VLDL particles. Fibrates induce pyruvate dehydrogenase kinase (PDK) mRNA mainly in skeletal muscle and liver (29). This results in inactivation of PDH complex by
phosphorylating enzyme catalyzing irreversible decarboxylation of pyruvate. Limitation of activity of this complex results in inhibition of conversion reaction of pyruvate to acetyl-CoA (29, 30). Under these conditions, β-oxidation pathway is activated, which can be directly induced by fibrates, because they affect expression of enzymatic proteins such as acyl-CoA oxidase, enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase (19, 23, 25, 26). Fibrates, by increasing expression of proteins involved in β-oxidation, limit synthesis of fatty acids.

In the human liver, fibrates stimulate expression of genes encoding structural apolipoproteins of HDL: apoA-I and apoA-II. Thereby, they increase production of pre-β-HDL, resulting in efficient return transport of cholesterol from peripheral tissues. Opposite effects of fibrates on apoA-I and apoA-II were observed in mice and rats (31). In animals, there was a significant decrease in expression of hepatic apoA-I mRNA but not in intestinal tract. Decreased amount of structural protein causes lowering of HDL. In animals, probably reduced synthesis of apoA-I is due to lack of PPRE action (31-33). Similar observations were made by Duez et al. (34). They investigated effect of fibrates on size of atherosclerotic lesion and concentration of apolipoprotein apoA-I and lipid fractions in apoE knockout mice (control group) and in apoE knockout mice with transgenic human apoA-I (study group). It was found that in study group fibrates increase level of HDL in plasma, thus received amount of cholesterol from peripheral tissues in humans is higer, whereas in animals is lower. Also expression of apoA-I mRNA - main protein component of HDL in plasma, increased (33).

Morishima et al. (35) as Vu-Dac (31) and others (36, 37) found that transcriptional regulation of apoA-I by PPAR-α is species specific. Administration of fenofibrate in experimental animals resulted in a decrease in expression of hepatic apoA-I mRNA. In humans the effect was opposite. Fibrates, by activation of PPAR-α, increase expression of SR-B1 receptors mRNA causing intensification of their numbers. SR-B1-mediated in selective uptake CE by hepatocytes from HDL₂, and therefore have opposite effect on transport of cholesterol (37, 38). Results of Fu et al. (39) suggest that apoE knockout mice fibrates (CF 0.05% above-mentioned) caused a decrease in expression of hepatic SR-B1 protein, which contributed to overaccumulation of residual lipoprotein in plasma. Similar conclusions have provided Mardones et al. (38), wherein they found no effect of fibrates expression of SR-B1 mRNA in animals. Observations of ciprofibrate (0.2%) and other PPAR-α agonists effect on SR-B1 expression in humans have shown that these drugs, in opposite way than in animals, regulate expression of this protein (38).

Vu-Dac et al. (31) study demonstrated that fibrates effectively decrease level of TG contained in lipoprotein fractions both in humans and rodents. This study has also shown that use of FF for 7 days in transgenic mice with human apoA-I gene increased concentration in plasma of apoA-I to 750% and HDL to 200% (31). Similar results were obtained by Berthou et al. (40). In addition, it was noted importance of dose and duration of therapy. Maximum effects of FF were obtained at a dose of 0.5% applied for seven days (40). Steals et al. (25) and Elisaf (41) concluded that fibrates also decrease concentration of cholesterol and TG in plasma by accelerating catabolism of VLDL. In their studies were used transgenic mice with overexpression of human apoA-I gene, thereby showing changes in vivo.

Blanco et al. (42) also conducted research on apoA-I and apoA-II protein. By isolating genes of these proteins they identified their role in lipid metabolism and development of atherosclerosis. They found that apoA-II is a genetic determinant of HDL concentrations. Fibrates through complex PPAR/RXR may affect on expression of apoA-I and apoA-II genes. Peters et al. (19) explained mechanism of PPAR-α receptor activity. In their experiment were used two groups of mice: control and research with isolated PPAR-α gene. Group of mice with isolated PPAR-α receptor (PPARα -/-) showed increased levels of total cholesterol and HDL (approximately by 63%) compared to control (PPAR-α +/-). In turn, composition of HDL particles remained unchanged. Furthermore, in PPAR-α -/- group was observed a slight increase in amount of apoA-I, apoA-II in plasma and its mRNA and thus increased concentration of HDL. Thus, it confirms active role of PPAR-α in control of HDL metabolism. This experiment shown also that in mice PPAR-α +/- both Wy 14.643 and fibrates decrease level of hepatic apoC-III mRNA and TG. Activation of PPAR-α stimulates uptake of fatty acids in liver and conversion to acyl-CoA derivatives. Indeed there is induction of genes such as: fatty acid transport proteins and acyl-CoA synthetase - catalyzing conversion of fatty acids in acyl-CoA (19, 23, 25, 28).

Regulation by fibrates also relates apolipoprotein apoA-V gene, specified by Vu-Dac et al. (43) as a key determinant of level of TG. The experiment
performed on animals (transgenic mice with apoA-V) has demonstrated that fibrates significantly induce apoA-V mRNA. Researchers determined the effect of apoA-V on level of VLDL TG and chylomicrons. ApoA-V decreases secretion of VLDL and chylomicrons but this has not been confirmed by Merkel et al. (44). ApoA-V influences an increase of catabolism of these particles fractions and facilitates their binding to proteoglycan which is joining LPL to cell membrane. Thus, this protein is an activator of LPL. It was also observed that animals with overexpression of apoA-V showed a decreased level of apoC-III. A decrease in apolipoprotein apoC-III inhibiting LPL also reduced concentration of VLDL TG and chylomicrons. Similar conclusions are provided Oliva et al. (45).

Fu et al. (24) conducted an experiment on LDL receptor knockout mice checking effect of administration of PPAR-α agonist - CF on apoB mRNA expression and lipid parameters. Administration of CF to control group with current LDLR (low-density lipoprotein receptor – LDLR+) resulted in decreased levels of TG and a slightly decreased concentration of cholesterol (FC) compared to groups that were not receiving CF. In group with LDL receptor knockout (LDLR-) there were observed elevated levels of both TG and FC (free

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cholesterol) compared to control group (LDLR+). Administration of CF resulted in decreased level of TG in both groups. Increasing concentration of apoB-100 in LDLR knockout mice explained intensified release into plasma apolipoprotein and retarded clearance of IDL and LDL leading to increased its concentration in plasma. In turn, in LDLR+ group together with an increase in secretion of VLDL containing apoB-100, did not occur accumulation of IDL and LDL. On surface of liver cells were efficient uptake IDL and LDL by LDL receptors (24).

Observation of impact of HF and Wy 14.643 on secretion and circulation of apoB-100 and apoB-48 was also made by Linden et al. (46). They conducted experiment on human cell cultures and isolated rat hepatocytes. In control cells group, predominantly amount of apoB-100 occurred within VLDL and smaller amount in particles of more dense fraction (i.e., IDL, LDL). Administration of clofibrate or Wy 14.643 resulted both in increase in relative amount of apoB-100 in VLDL and proportion of apoB-100 within IDL and LDL fractions. In contrast, there was not such effect on apoB-48. They also found decreased biosynthesis of TG. These effects occurred after administration to cell both KF and Wy 14.643.

Opposite conclusions about effects of FF on level of apoB-100 delivered Winger et al. (47). They studied effect of FF on lipid parameters in obese rhesus monkeys (Macaca mulatta). The animals had increased level of TG and decreased level of HDL-cholesterol. After administration of this drug, it was observed a decrease levels of TG by 55%, LDL cholesterol by 27% while HDL-cholesterol increased by 35%. It was also pointed a trend of decreasing concentration of apoB-100 and apoC-III during FF therapy in these animals. The effect of decrease concentration of TG and increase concentration of HDL-cholesterol was explained by the fact that fibrates intensify lipoprotein lipolysis. Gemfibrozil does not affect as efficiently on lowering concentration of ApoC-III as FF and BF. However, GF does not decrease concentration of apoE (48, 49).

In studies of Coste and Rodriguez (50), it was found that both concentration in plasma and ratio of synthesis of apoC-III are positively correlated with level of TG in plasma in normo- as well as in hypertriglyceridemia. Deficiency of apoC-III is observed in humans with intensified catabolism of VLDL whereas an excess of this apolipoprotein occured with hypertriglyceridemia. It was confirmed that regulation of apoC-III gene expression through use of fibrates takes place in transcription (25, 37, 48, 49, 51).

Raspe et al. (32) demonstrated that fibrates induce expression of Rev-erb α receptor that specifically decreases activity of apoC-III promoter. In this experiment, were used mice both with lack and overexpression of Rev-erb α receptor (Rev-erb α-/-; Rev-erb α +/-). The presence of this receptor decreased activity of apoC-III promoter, while in Rev-erb α-/- group was shown an increase in hepatic apoC-III mRNA as well as in concentration of this apolipoprotein in plasma and elevated level of TG contained in VLDL fraction. The metabolism of some lipoprotein fractions in plasma with an indication of effect of fibrates are shown in Figure 2.

Degradation of TG with participation of these proteins is a several-step process, which involves a number of conditions to allow proper lipid metabolism in the system. TG contained in chylomicrons allow transport of fatty acids (including exogenous such as: linoleic, linolenic and arachidonic acid) from intestine to extrahepatic tissues. Fatty acids (including exogenous acids), vitamins A, D, E and K as well as choline and inositol (obtained from food) enter liver along with residual chylomicrons. Vitamins can be stored in hepatocytes. In addition, residual chylomicrons participate in direct and indirect transport of cholesterol to liver in postprandial period (53).

Production of VLDL allows to remove insoluble TG and CE (cholesterol esters) off liver. Between digestive periods, VLDL-TG are beside adipose tissue a source of fatty acids for extrahepatic tissues. In liver, part of cholesterol taken from particles of LDL and other residual fraction undergoes biotransformation to bile acids. This allows excretion of cholesterol with bile from the system. In addition, cholesterol that gets into hepatocytes modifies rate of VLDL formation. HDL as the richest in protein fraction, provides mainly apolipoproteins, which are necessary for degradation of chylomicrons and VLDL in plasma. Moreover, within HDL particles occurs esterification of free cholesterol, which is moved from other fractions of plasma lipoprotein or is taken from tissues with participation of ABCA1 protein (54, 55, 57).

HDL fraction, especially HDL2, and HDL3, are involved in direct transport of cholesterol and phospholipids from extrahepatic tissues to liver. Intensification of synthesis of all apoA proteins leads to easier formation of native HDL particles in liver, and consequently, to increase concentration of this fraction in plasma. The effect of fibrates and protein apoA-V is visible in the impact of increasing LPL activity and rate of chylomicrons and VLDL degradation. ApoC-V like fibrates decreases concentration of apoC-III in plasma (45).

Effect of fibrates on lipid profile in plasma reflects decreased levels of TG and LDL as well as...
increased concentration of HDL. Lowering concentration of TG is done by regulation of genes expression of proteins involved in its metabolism. To decrease of TG in plasma by fibrates also contributes stimulation of LPL gene expression (which catalyzes hydrolysis of TG) as well as lowering expression of apoC-III gene (19, 49).

In hepatocytes, fibrates intensify expression of enzymes β-oxidation process of fatty acids genes, which results in a decrease in concentration of fatty acids necessary for synthesis of VLDL-TG. Fibrates not only lower but also normalize content of VLDL-TG. Under these conditions, after degradation of VLDL, LDL particles are formed. These drugs have an impact on efficient removal of LDL from plasma, because they facilitate formation of complexes: LDL - LRP and LDL – LDLR (21).

Fibrates also regulate amount of HDL, because, these drugs intensify expression of apoA-I and apoA-II genes, which are structural proteins of this fraction. Consequently, there is an increase in concentrations of HDL in plasma and efficient receiving FC from extrahepatic tissues. Effect of these drugs was also noted in regulation of apoB-100 mRNA, because fibrates increased its amount (46).

Effect of fibrates includes not only enzymatic, regulatory and structural proteins but also receptor proteins. These compounds stimulate expression of SR-B1 and ABCA1 receptors genes. The first of them - (SR-B1) is involved in transport of cholesterol from extrahepatic tissues to hepatocytes, while ABCA1 protein mediated in displacement of cholesterol and phospholipids from cells of peripheral tissues and their incorporation into HDL particles (53, 55).

CONCLUSIONS AND PERSPECTIVE

In conclusion, fibrates have a beneficial effect on lipid profile in plasma because of observed decreased concentration of TG both in LDL and VLDL fractions as well as an increase in concentration of HDL. However, there is growing number of publications reporting on incidents of side effects of these drugs. Research groups are charged that studies are conducted too rarely and include only a small number of patients (also animals) which is disproportionate with percentage of patients with coronary-vascular disease. Thus, results may be inadequate in relation to the entire population.

Conflict of interests

All authors declare that they have no conflict of interests.

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