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Reivew Article

A brief overview of currently used atherosclerosis treatment approaches targeting lipid metabolism alterations

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Abstract: Non-contagious diseases such as atherosclerosis, diabetes, cardiovascular disease, cancer, chronic respiratory diseases, and mental disorders hold responsibility for major health losses worldwide. Atherosclerosis was found to be the leading cause of deaths due to the major consequences, such as cardiovascular disease, stroke, ischemic heart disease, myocardial infarction, and others. The number of patients with atherosclerosis increases with every passing year. If treatment is not started on time, every second patient dies within 10 years. Moreover, the disease leads to persistent disability of patients, most of whom are of active working age. Atherosclerosis is a metabolic disorder characterized by hyperlipidemia and chronic inflammation. Although this disease annually kills a huge number of people, patients are now offered various therapeutic techniques, however, with different efficiencies. The scientific community is working to develop more effective means for treatment and precaution of the disease, regardless of the difficulties in understanding the causes of the health problem and the characteristics of its course. There are numerous strategies in the treatment and prevention of atherosclerosis, focusing on different aspects of the disease, such as inflammation, lipid metabolism alterations, or others, but none of them, unfortunately, is absolutely effective. In this review, we focused on the treatment approaches aimed at remedy the disruptions of lipid metabolism that are currently used in clinical practice.

Keywords: Atherosclerosis, cardiovascular disease, statins, ischemic heart disease

Atherosclerosis and lipids

Atherosclerosis is the most common chronic disease of large arteries, with the formation of single and multiple foci of lipid, mainly cholesterol deposits - atheromatous plaques - in the inner lining of the arteries [1, 2]. Subsequent growths of connective tissue in it (sclerosis) and vessel wall calcification lead to a slowly progressive deformation and narrowing of its lumen (obliteration) of the artery and thereby cause chronic, slowly decreasing blood supply to the organ fed through the affected artery [3, 4]. Also, acute blockage (occlusion) of the artery lumen is possible, either by a blood clot or (much less often) by the contents of a disintegrated atheromatous plaque, or both at the same time, which leads to the formation of foci of necrosis (heart attack) or gangrene in the body parts fed by the artery.

The leading role in the development of atherosclerosis belongs to lipid metabolism alterations [5, 6]. In blood plasma, lipids circulate in the form of lipoproteins that can undergo numerous modifications, such as desialylation, oxidation, etc. and penetrate the arterial wall leading to the development of lipoidosis, the initial stage of atherosclerosis [7, 8].

Disorders of lipid metabolism in atherosclerosis are expressed in hyperlipidemia and hyperlipo-

proteinemia. At the same time, the plasma of patients increases not only cholesterol and triglyceride levels but also phospholipids and their main fractions. Lipids are transported by blood in the form of complexes with proteins - lipoproteins, among which there are several fractions: very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL).

Human blood plasma lipids are presented with cholesterol (CH), triglycerides (TG), phospholipids (PL), and fatty acids (FA) [9].

Concerning atherosclerosis, the most important among all lipid types is the cholesterol that normally performs important biochemical functions in the human body. Free cholesterol is necessary for the synthesis of steroid hormones, and the formation of bile acids, it is part of the nervous tissue and all cell membranes. Esterified cholesterol predominates in the cells of the adrenal cortex, in plasma, and atherosclerotic plaques [10].

Triglycerides are the esters of fatty acids and glycerol alcohol, which are part of various drugs, but predominate in chylomicrons and VLDL [11, 12].

Fatty acids are synthesized from the decomposition products of carbohydrates and come from food. FAs play an important role in lipid metabolism, esterifying cholesterol, and glycerin. The degree of saturation depends on the number of double bonds in the composition of the FA. In blood plasma, FAs in the esterified state are presented in TG, cholesterol, and PL esters and are transported by lipoprotein; In non-esterified form, FAs are transferred in combination with albumin.

Lipoprotein is a specific lipid-protein formation consisting of apoproteins, cholesterol, TG, and PL and is intended for the transport of lipids in the bloodstream. In clinical practice, LDL and HDL are considered to play a significant role in the development of vascular pathology: LDL is considered to be proatherogenic and HDL - to be antiatherogenic [12, 13].

In patients with coronary artery disease or atherosclerosis, the following peculiarities of lipid spectrum disturbances most often occur: total cholesterol is moderately elevated, LDL (low-density lipoprotein) cholesterol is elevated significantly [14]. These particles easily penetrate the subendothelial space, are actively captured by macrophages, pericytes-like cells, and other sedentary cells and thus initiate an atherosclerotic process through the foam cell formation [15].

In patients with metabolic syndrome, type 2 diabetes, lipid metabolism disorders are more common, characterized by increased levels of TG and lower concentrations of HDL cholesterol. However, there are often cases of increased concentrations of LDL cholesterol [16, 17].

One of the dominating factors increasing modifiable trigger for atherosclerosis is the lipid storage alterations. The development of atherosclerotic plaques is partially attributed to genetic predisposition and environmental factors. Further still, immune and inflammatory mediators have a complex role in the emergence of atherosclerosis and its pathogenic pathway [18]. Fundamental understanding of all these processes will help to come up with an invention of the newest cutting-edge biomarkers as well as a therapeutic intervention in order to prevent atherosclerosis by destroying cellular events in acute and chronic inflammation.

One of the most prime triggers for the initiation and progression of atherosclerosis is continual aggrandizement in circulating low-density lipoprotein (LDL) levels in the body.

General treatment approaches for atherosclerosis

In the initial stages, it is enough to cure the reason for the sickness and take preventive measures for the reduction in the rate of disease development. Among such measures are the weight-lose, following sugar and pressure, giving up bad habits, keeping diet [5, 19].

The unique distinction of vascular atherosclerosis is that even with proper treatment, vascular blockage does not go away. Drug administration and other control measures significantly slow down the growth of atherosclerotic plaques, and with the intensive treatment, they are also reduced in size.

The most recent, increasingly purposive approach is being used that is aimed at preventing

the elaborateness and advancement of atherosclerosis [20, 21].

In the treatment of atherosclerosis, strategies based on drug therapy are usually used. Various drugs designed to reduce the amount of cholesterol in the blood and normalize blood pressure are usually prescribed. The most commonly used compounds for atherosclerosis treatment are statins aiming to regulate cholesterol levels. However, these drugs only help to control the state of the vessels but do not cause remission and do not cure atherosclerosis. The most widespread compounds with the antiatherosclerotic potential are summarized in **Table 1**.

Drug therapy for lipid metabolism disruptions

Since the lipid metabolism alterations are the cornerstone of the atherogenesis, it seemed to be obvious to target various elements of lipid-related pathways that are known to be involved in atherosclerosis development. However, these mechanisms are not fully understood to date.

The four most promising strategies considering the lipid metabolism modifications was aimed at removing modified LDL from the circulation; suppressing the rate of atherogenic LDL modifications; decreasing the uptake of modified LDL by vulnerable cells; removing modified atherogenic LDL from the cells [33].

Unfortunately, the totally effective drug is still not identified. Therefore, the first step towards the creation of the drug with direct action is to test the drugs that already exist and have a potential to affect the atherogenesis in some way. These drugs usually have the ability to lower the inflammation or to reduce atherogenic potential of atherosclerosis patients serum.

More detailed information about the most promising drug is provided below.

Drug therapy should be initiated in individuals with a high and very high risk of developing fatal complications simultaneously with non-drug prevention measures. In patients with a low risk (<5%) of fatal complications, an algorithm for correcting lipid metabolism disorders should be used [34].

Groups of compounds normalizing lipid metabolism include: (1) inhibitors of the enzyme MMC-CoA reductase (statins); (2) bile acid sequestrants (resins); (3) derivatives of fibric acid (fibrates); (4) nicotinic acid (niacin, enduracin); (5) cholesterol absorption inhibitor in the intestine (ezetimibe); (6) PNZhS - ω-3 PUFA.

Statins

In randomized clinical studies, their high efficacy in reducing cholesterol and LDL-C has been demonstrated [35]. In the same studies, a decrease in the frequency of recurrent complications of ischemic heart disease - myocardial infarction, unstable angina, atrial fibrillation was observed by more than 25-40% [36]. Mortality was reduced from all other causes.

Currently, the following statins are considered to be the most effective: Zokor®, atorvastatin (Liprimar®), pravastatin (Lipostat®), fluvastatin (Lescol®), rosuvastatin (Crestor®), lovastatin (Mevacor®) [37].

The first statins (simvastatin, pravastatin, and lovastatin) were isolated from the culture of penicillin fungi [38] and *Aspergillus terrens*; fluvastatin and atorvastatin are synthetic drugs [39].

Statins differ in their physicochemical and pharmacological properties: simvastatin and lovastatin are more lipophilic; atorvastatin, rosuvastatin, and pravastatin are more hydrophilic; fluvastatin is relatively hydrophilic. These properties provide different permeability of drugs through the cell membrane, in particular of the liver cells. The half-life of statins does not exceed 2 hours, except atorvastatin, and rosuvastatin, the half-life of which exceeds 14 hours, which probably explains their higher efficacy in reducing LDL [40].

Mechanism of action: Statins work as inhibitors of the enzyme called HMG-CoA reductase, the key enzyme for the synthesis of cholesterol. As a result of a decrease in the intracellular content of cholesterol, the liver cell increases the number of membrane receptors to LDL on its surface, which binds and removes LDL from the bloodstream, thus reducing the concentration of cholesterol in the blood. Along with the lipid-lowering action, statins have pleiotropic effects: they improve endothelial function, reduce the

Table 1. The most widespread and promising compounds used for modulation of lipid metabolism and mechanisms of their action

Name	Action	Reference
Omega-3 FAs	Inhibit expression of SREBP-1 and thus reduce TG level and atherogenic lipoproteins level	[22]
PPARγ	selective modulator which lowers insulin resistance and causes anti-inflammatory effects in macrophage-derived foam cells	[23]
Lanosterol synthase inhibitor	restrains four-ringed sterol intermediates formation and prevents the deposition of cholesterol within macrophages	[23]
Endoglin receptor modulator	reduces expression of inflammatory cell adhesion molecules, increases vascular smooth muscle cell and stabilize prothrombogenic state	[24]
CETP inhibitor	increases HDL cholesterol levels and reverses the cholesterol transport system	[25]
ACAT enzyme inhibitor	prevents the transformation of macrophages into foam cells and lower synthesis of lipoproteins	[23]
DGAT enzyme inhibitor	obstructs the transfer of the acyl group from acyl-coenzyme-A to the C-3 position of 1,2-diacylglycerol and reduces triacylglycerol formation	[23, 26]
MTTP protein inhibitor	prevents lipid assembly, transport, secretion of lipoproteins, triglyceride-rich chylomicrons (in enterocytes) and VLDL while modulating transportation of TG, cholesteryl ester, and phosphatidylcholine	[23]
Squalene synthase inhibitor	prevents the biosynthesis of the sterol nucleus of cholesterol	[23]
PPARα agonist	decreases TG-rich lipoproteins, increases HDL and has an anti-inflammatory effect in the vessel wall	[23]
Thyroid hormone analogs	increase the activity of lipoprotein lipase and accelerate LDL-C clearance	[27]
Cytochrome P450 modulator	regulates the conversion of cholesterol to 7α-hydroxycholesterol	[28]
AMPK activator	regulates glucose metabolism, decreases hepatic lipogenesis, synthesis of new FA and cholesterol, increases FA oxidation	[29]
Heat shock protein-65 and CETP vaccine	reduce immune tolerance against self-antigens and prevent the transfer of cholesteryl ester into triglyceride-rich lipoproteins or LDL	[30]
sPLA2 inhibitor	prevents inflammatory, autoimmune and allergic reactions	[31]
Lp-PLA2 inhibitor	restrains the formation of LysoPC and oxNEFA, and reduces proinflammatory and cytotoxic products	[32]

content of C-reactive protein, inhibit platelet aggregation, and proliferative activity of smooth muscle cells [41].

Side effects: Statins are being well-tolerated, but their reception may be accompanied by abdominal pain, flatulence, and constipation. An increase in the level of liver enzymes ALT, AST is observed in 1-5% of patients when taking statins. If the level of at least one of the listed enzymes in two consecutive measurements exceeds 3 times the upper limits of normal values, the use of a statin should be stopped. In cases of a more moderate increase in the content of enzymes, it suffices to limit the decrease in the dose of the drug. Usually, enzyme levels return to normal in a short time, and treatment can be resumed with either the same drug at a lower dose or another statin. Rarely (0.1-0.5%), when taking statins, myopathy and myalgia are observed, which manifest as pain and weakness in muscles, are accompanied by an increase in creatine phosphokinase levels by more than 5 times and require discontinuation of the drug. The most dangerous complication of statin therapy is rhabdomyolysis or muscle breakdown with possible damage to the renal tubules. The complication is accompanied by an increase in the level of CPK more than 10 times and a darkening of the color of urine due to myoglobinuria. In the case of rhabdomyolysis (renal failure), statins should be stopped immediately. In severe cases of rhabdomyolysis, extracorporeal blood purification methods are used to treat it: plasmapheresis and hemodialysis. Rhabdomyolysis is more often observed with the simultaneous administration of statins with fibrates, cytotoxic drugs, macrolide antibiotics. In these cases, patients should be under the careful, intensive supervision of a physician with the control of all the enzymes listed at least once a month. In the usual practice of using each of the statins in monotherapy, the first control of enzyme activity is prescribed after 3 months from the start of treatment, and then every 6 months [41].

Bile acid sequestrants

Bile acid sequestrants (ion exchange resins) have been used as lipid-lowering agents for more than 30 years [42]. Clinical studies have proven their effectiveness in reducing coronary complications and deaths from myocardial infarction. Today these drugs are not implemented in practice but are still an object of investigations concerning the treatment of atherosclerosis.

Mechanism of action: Ion-exchange resins bind bile acids that are metabolic products of cholesterol in the lumen of the small intestine and increase their excretion with fecals. Representative resins are cholestyramine and colestipol [43].

Side effects: Ion exchange resins often cause constipation, flatulence, and dyspepsia; Many patients refuse to take them because of unpleasant taste sensations. If patients are treated with digoxin, warfarin, thiazide diuretics, and β-adrenergic blockers, ion exchange resins are prescribed 1-2 hours before or 4 hours after ingestion of the listed remedies to avoid a decrease in their absorption [44].

Fibric acid derivatives (fibrates)

The currently used fibrates include clofibrate, gemfibrozil, bezafibrate, ciprofibrate (Lipanor®), and fenofibrate (Lipantil® 200 M) [45]. In randomized clinical studies, fibrates reduced mortality from CVD, but the data are not as extensive as for statins [46].

Mechanism of action: Fibrates are agonists of a subclass of nuclear receptors activated by peroxisome proliferator (PPARs), intracellular components containing a set of enzymes, the activation of which enhances the processes in the cell nucleus, in particular, regulating the metabolism of lipoproteins, the synthesis of apoproteins, the oxidation of fatty acids. The implementation of these mechanisms leads to the activation of plasma lipoprotein lipases, enzymes that regulate the hydrolysis of VLDL, and thus reduces their plasma levels [47].

Therapy with fibrates is accompanied by a distinct increase in the concentration of cholesterol due to increased synthesis of apo A-I and A-II.

Side effects: Fibrates are well-tolerated, but in 5-10% of patients, side effects are possible in the form of abdominal pain, constipation, diarrhea, flatulence, as well as rashes, itching, headaches, insomnia. These phenomena are not severe and do not require interruption of

therapy. Long-term fibrates can increase the mitogenicity of bile, so they are not recommended for patients with gallstone disease. An increase in liver enzymes is possible, but AST and ALT alkaline phosphatase is often reduced. The combination of fibrates with statins increases the risk of elevated liver enzymes and the development of myalgia, myopathy. In this case, it is necessary to monitor indicators of liver enzymes and CK at least once a month [46].

Nicotinic acid

A nicotinic acid showed multiple beneficial effects on lipid metabolism, but there are still no exact data about the mechanism through which these effects are realized [48]. In the long-term study of the Coronary Drug Project (CDP), it was shown that only in the group of patients who took niacin in the long-term period all-cause mortality was 11% lower compared with the placebo group [49, 50].

Mechanism of action: Nicotinic acid reduces the synthesis of VLDL in the liver and partially blocks the release of FA from adipose tissue, creating a deficit in plasma. As was mentioned above, the mechanism of the niacin action is still unclear, but several potential mechanisms may act synergistically and thus form the observed lipid-modifying effect [48].

Side effects: Acceptance of nicotinic acid is often accompanied by side effects in the form of a sharp reddening of the face and upper torso with a feeling of heat and hot flushes. The reaction is due to the active release of prostaglandins under the influence of nicotinic acid. Side effects can be significantly reduced by prescribing 0.5 g of aspirin half an hour before taking nicotinic acid and gradually titrating its dose. When prescribing enduracin, side reactions occur less frequently. Of the other side effects, abdominal pain is possible, up to 5% of patients complain and which may be associated with exacerbation of gastritis. However, the most formidable, but at the same time, a rare complication, is the development of liver failure. Hepatic insufficiency is manifested by a sudden drop in cholesterol concentration, a pronounced increase in liver enzyme levels, and a hepatic coma clinic. Care should be taken when combining nicotinic acid with statins or fibrates. In 5-10% of patients with gout, an exacerbation of the underlying disease is possible; they should avoid prescribing any form of nicotinic acid [51].

Ezetimibe

Ezetimibe (Ezetrol) belongs to a fundamentally new class of hypolipidemic agents that selectively block the process of cholesterol absorption in the epithelium of the small intestine.

Currently, the drug has been registered in many countries as a means of complementary therapy to statins to reduce free serum cholesterol and LDL cholesterol [52]. When used alone, ezetimibe showed the same protective effect against a moderate atherosclerotic lesion as atorvastatin [53].

Mechanism of action: Ezetimibe selectively inhibits the absorption of bile cholesterol and cholesterol in the brush border of the villi of the small intestine, which leads to a decrease in cholesterol from the intestine to the liver, cholesterol content in liver cells and an increase in cholesterol clearance from blood plasma [52, 54].

Side effects: Ezetimibe is well tolerated. The drug may be accompanied with the increase in serum transaminases, especially when combined with statins. Ezetimibe is not recommended to be used and combined with statins in patients with the content of liver enzymes 3 times the upper limit of normal, and in the acute period of liver disease. Simultaneous administration of cyclosporine can significantly increase the plasma concentration of Ezetimibe. Therefore it is better not to use this combination [55].

Polyunsaturated ω-3 FA (Omacor®)

Omega - 3 PUFA in large doses is used to treat hypertriglyceridemia. Currently, the drug Omacor consists of highly purified and highly concentrated ω-3 PUFAs (about 90%) according to indications: secondary prevention of myocardial infarction and hypertriglyceridemia. In 1997, the results of a study were published, showing that Omacor at a dose of 2-4 g/day reduces the level of TG in the blood by 45% ($P<0.0001$) [56].

Mechanism of action

Polyunsaturated omega-3 fatty acids are able to reduce triglyceride synthesis in the liver. Al-

so, serum levels of pro-inflammatory markers, such as ICAM-1, VCAM-1, IL-6, and C-reactive protein, were showed to be decreased in response to Omega - 3 PUFA [57].

Side effects

Omacor is generally well-tolerated and doesn't exhibit any adverse interactions with other drugs. The most widespread side effects concern gastrointestinal. This includes diarrhea, nausea, abdominal pain, and others [58].

Perspectives

After all, it seems clear that all tested drugs are not sufficiently effective against atherosclerosis. This reflects the need for the development of drugs with combined action due to the complex origin of the target disease. For example, statins exhibit anti-inflammatory properties as well as an ability to reduce cellular cholesterol and LDL-C. However, statins turned out not to be effective enough. Thus, this group of therapeutic compounds can be used as the basis for future development.

Also, a more detailed understanding of lipid-related pathways in atherogenesis is necessary. This can help to establish a more promising target than currently used.

Conclusions

Despite the wide range of existing antiatherosclerotic drugs, none of them can be considered as absolutely effective. Modern treatment approaches for atherosclerosis are mainly aimed at stopping the symptoms of the disease and preventing its complications like heart attack, stroke, and thromboembolism.

Drug therapy may include drugs from various pharmacological groups that are aimed at reducing the level of lipids and cholesterol in the blood.

Exclusion of provoking factors also plays an important role in delaying disease progression [59, 60].

Lipid metabolism disorders are an important factor in the development and progression of CVD. Timely and correct diagnosis, assessment of concomitant factors of CVD development are necessary conditions for the organization of their rational prevention and therapy [60-63].

An important aspect of the prevention of CVD and atherosclerosis is the identification of individuals with impaired lipid metabolism without clinical manifestations of coronary heart disease.

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