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Review

The role of metabolic disorders in the development of atherosclerosis

Alexander V. Blagov[1*], Alexey V. Churov[1,3], Alexander L. Golovyuk[4], Arthur A. Lee[1], Vasily V. Kashtalap[5], Vasily N. Sukhorukov[1,2] Alexander N. Orekhov[1,2]

[1] Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, Moscow 125315, Russia
[2] Petrovsky National Research Centre of Surgery, 2, Abrikosovsky Lane, Moscow 119991, Russia
[3] Pirogov Russian National Research Medical University, Russian Gerontology Clinical Research Centre, Moscow, Institute on Aging Research, Russian Federation, 16 1st Leonova Street, 129226 Moscow, Russia
[4] Vascular Surgery Department, A. V. Vishnevsky National Medical Research Center of Surgery, 27 Bolshaya Serpukhovskaya Street, 117997Moscow, Russia
[5] Research Institute for Complex Issues of Cardiovascular Diseases, 6 Barbarash Boulevard, 650002 Kemerovo, Russia

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Abstract

Atherosclerosis is a major risk factor for cardiovascular disease (CVD), which is the leading cause of death worldwide. Atherosclerosis is initiated by endothelial activation, followed by a cascade of events (accumulation of lipids, fibrous elements, and calcification) triggering vasoconstriction and activation of inflammatory pathways. This review focuses on the various stages in the development of atherosclerosis, ranging from endothelial dysfunction to plaque rupture. In addition, disorders of lipid, glucose and amino acid metabolism in atherosclerosis are considered here. The key pathological stages of metabolism disruption and their role in atherosclerosis are considered in detail which may be helpful for the more better understanding of atherosclerosis pathogenesis. Finally, some therapeutic approaches aimed at modulating lipid metabolism will also be presented which show the therapeutic targets (enzymes and transport proteins) which modulation can prevent further deterioration of patients symptoms.

Keywords: Atherosclerosis, Inflammation, Lipoproteins, Metabolism

1. Introduction

Atherosclerosis is a chronic inflammatory disease of the arteries and is the main cause of about 50% of all deaths in society. It is mainly a lipid-dependent process initiated by the accumulation of low-density lipoprotein and residual lipoprotein particles, as well as an active inflammatory process in the focal areas of the arteries, especially in areas with impaired non-laminar flow at the bifurcation points of the arteries, and is considered the main cause of atherosclerotic cardiovascular disease leading to heart attacks, stroke, and peripheral arterial disease [1]. Atherosclerosis can manifest as coronary heart disease (CHD), cerebrovascular disease (CVD), transient ischemic attack (TIA), peripheral arterial disease (PAD), abdominal aneurysms, and renal artery stenosis in men [2].

The pathogenesis of atherosclerosis is multifaceted. The most prevalent risk factors include age (males over 45 and women over 55), gender, hypercholesterolemia (LDL cholesterol), diabetes mellitus, hypertension, cigarette smoking, and strong family history (male relative under 55, female relative under 65). The risk is further increased by obesity, a sedentary lifestyle, diets high in trans and saturated fatty acids, and certain genetic abnormalities [3]. Although low levels of high-density lipoprotein (HDL) cholesterol are thought to be a risk factor, the adverse effects of pharmacological therapy aimed at raising HDL levels have led to questions about the potential role of HDL in the onset of the disease [4].

Since atherosclerosis is predominantly an asymptomatic disease, it is difficult to accurately determine the incidence. Atherosclerosis is considered the main cause of cardiovascular disease. Atherosclerotic cardiovascular diseases mainly affect the heart and brain: coronary heart disease and ischemic stroke. Coronary artery disease and stroke are respectively the first and fifth causes of death in the world. According to reports, 75% of acute myocardial infarctions are caused by plaque rupture, with men over 45 having the highest incidence of the condition while women have a rise in frequency beyond the age of 50. The protective effect of female sex hormones accounts for

* Corresponding author.
E-mail address: al.blagov2014@gmail.com (A. V. Blagov).
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men's higher prevalence of atherosclerosis than women's, although this effect vanishes after menopause. Several risk factors have been found in numerous epidemiological studies to contribute to the onset and progression of atherosclerosis. Their impact on inflammation and low-density lipoprotein (LDL) particles may exacerbate atherosclerosis [5].

There are several different anti-atherosclerotic medications on the market, but none of them is completely effective. The primary goals of current atherosclerosis therapy strategies are to reduce the disease's symptoms and stop its side effects, which include thromboembolism, stroke, and heart attacks [6]. Thus, the study of the pathogenesis of this disease and the search for new therapeutic targets is extremely relevant today.

2. General pathogenesis of atherosclerosis

2.1. Lesion initiation

The endothelium, with its complexes of intercellular tight junctions, functions as a selectively permeable barrier between blood and tissues. The primary initiating event of atherosclerosis is the accumulation of low-density lipoprotein (LDL) in the subendothelial matrix. LDL diffuses passively through endothelial cell (EC) junctions and their retention in the vessel wall is associated with the interaction between LDL constituent apolipoprotein B (apoB) and matrix proteoglycans. In addition to LDL, other apoB-containing lipoproteins, namely lipoprotein (a) and its residues, can accumulate in the intima, contributing to the development of atherosclerosis [7].

It has been proposed that native LDL is "modified" in the arterial wall since macrophages cannot absorb it quickly enough to produce foam cells. Subsequent research has demonstrated that trapped LDL does, in fact, experience alterations such as oxidative stress, lipolysis, proteolysis, and accumulation, and that these modifications both encourage the production of foam cells and inflammation. Lipid oxidation brought on by exposure to oxidative waste products from vascular cells is one of the most important changes for the development of early lesions [7].

2.2. Inflammation

Atherosclerosis is characterized by the recruitment of monocytes and lymphocytes into the arterial wall. The trigger event for this process is the accumulation of minimally oxidized LDL, which stimulates upstream ECs to produce a range of proinflammatory molecules, including adhesion molecules and growth factors such as macrophage colony-stimulating factor (M-CSF). Additionally, nitric oxide (NO), a chemical mediator with several anti-atherogenic qualities, including vasodilating actions, can be inhibited by oxidized low-density lipoproteins [8]. Apart from oxidized low-density lipoprotein (LDL), various other factors can also influence inflammation, such as homocysteine levels, sex hormones, hemodynamic pressures, and infection. Among the endothelial cell adhesion molecules that are likely to be important for leukocyte recruitment are ICAM-1, P-selectin, E-selectin, PCAM-1 and VCAM-1. Important adhesion molecules on monocytes include integrin β2, VLA-4, and PCAM-1 [9].

2.3. Foam cell formation

LDL needs to undergo significant modification in order for macrophages to absorb it fast enough to produce foam cells. A number of enzymes, such as myeloperoxidase, sphingomyelinase, and secretory phospholipase, which are all seen in human atherosclerotic lesions, are also believed to be involved in this modification. Reactive oxygen species produced by ECs and macrophages appear to be implicated in this modification. A class of receptors, including SR-A, CD36, and CD68, mediates the fast uptake of highly oxidized LDL particles by macrophages, resulting in the development of foam cells. Cytokines including interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) stimulate the expression of scavenger receptors [10].

Apolipoprotein E (apoE), which is actively synthesized by macrophages, has the ability to facilitate the outflow of cholesterol into HDL and prevent macrophages from developing into foam cells. Studies on bone marrow transplantation provide evidence for the function of apoE, as they reveal that mice getting bone marrow from mice deficient in apoE experience significantly more damage than mice obtaining bone marrow from control group [11].

2.4. Fibrous plaques

The mass of extracellular lipids, primarily cholesterol and its esters, as well as the buildup of extracellular matrix and MMC, are the characteristics of fibrous plaques. The synthesis of extracellular matrix and the migration and proliferation of stem cells are dependent on the cytokines and growth factors released by T cells and macrophages. Research has indicated that T cells and macrophages are stimulated to express cytokines like IFN-γ when CD40 and CD40 ligand (CD40L) interact. These cytokines can impact inflammation, MMC development, and matrix accumulation. The extracellular matrix is secreted by MMC intima, which also forms a fibrous capsule. Fibrotic lesions can also arise as a result of other variables, such as hormones, hypertension, and high homocysteine levels. For example, the hormone estrogen has multiple anti-atherogenic properties, including effects on plasma lipoprotein levels and stimulation of prostacyclin and NO production [12].

2.5. Expanded lesions and thrombosis

Studies indicate that significant role in the development susceptibility and composition of plaque have a of thrombus-mediated acute coronary events. Thin fibrous caps covering vulnerable plaques are caused by suppression of matrix secretion and matrix disintegration by a variety of proteinases, including collagenases, gelatinases, stromolysins, and cathepsins. Infection is one of the variables that can cause thrombosis and destabilize plaques. It can also have local effects, such as declining plasminogen activator (PA) expression and increased tissue factor expression, as well as systemic consequences, such as the stimulation of acute phase proteins [7]. Neovascularization and calcification, which are typical characteristics of progressing lesions, might also have an impact on the stability of atherosclerotic lesions. The process of calcification is controlled and involves the secretion of a scaffold for the deposition of calcium phosphate by intima cells that resemble pericytes. Plaque rupture frequently results in thrombus development, which is made up of adhering platelets and fibrin cross-links [8].

3. Impaired lipid metabolism in atherosclerosis

Disorders in lipid metabolism are one of the key factors

in the development of atherosclerosis. Lipids are found in the plasma as lipoproteins, which are capable of undergoing a variety of changes, including demethylation and oxidation. These lipoproteins can also pierce the artery wall, which can result in the development of lipoidosis, the first phase of atherosclerosis [13]. Hyperlipidemia and hyperlipoproteinemia are manifestations of diseases related to lipid metabolism in atherosclerosis. At the same time, in the plasma of patients with atherosclerosis, not only an increase in the level of cholesterol and triglycerides but also phospholipids and their main fractions was noted [13]. Human plasma lipids are represented by cholesterol, triglycerides, phospholipids and fatty acids. Of great importance for maintaining normal lipid metabolism is the work of the so-called scavenger receptors, whose role is directly related to the formation of foam cells in atherosclerosis. One of the most well-known scavenger receptors is CD36, whose ligands are molecules of fatty acids, high-density lipoproteins (HDL), modified low-density lipoproteins (mLDL), as well as triacylglycerin-saturated lipoprotein molecules, such as Very-low-density lipoprotein (VLDL) [14]. Patients with reduced expression of CD36 have hyperlipidemia, expressed in high concentrations of apoB48, triglycerides, fatty acids and chylomicrons in plasma [15]. In skeletal muscle and the heart, CD36 plays a direct role in supplying cells with an energy substrate, fatty acids. In adipocytes, CD36 is responsible for lipid accumulation and lipolysis [15]. It has also been shown that mutations in the CD36 gene lead to increased hydrolysis of triglycerides and accumulation of free fatty acids in plasma. However, overexpression of CD36 also contributes to the development of atherosclerosis, leading to the formation of foam cells and enhancing the inflammatory response [15]. In atherosclerosis, there is a change in the expression of a number of enzymes involved in lipid metabolism. Thus, it has been shown that the LIPA gene encoding lysosomal acid lipase, which transforms molecules of cholesterol esters and triglycerides from LDL particles into free cholesterol and fatty acids, has an increased expression in foamy macrophages [14]. This can be explained by the mechanism of regulation in response to an increased intake of lipids into the cell. However, this strategy is not effective enough due to lysosomal stress, which reduces the activity of lysosomal acid lipase. The accumulation of lipids and, in particular, the formation of mLDL contributes to the inhibition of the oxidation of fatty acids in atherosclerosis. In a study [16], it was shown that the use of a model with non-functional mutant forms of the CPT1 and CP 2 enzymes involved in the transfer of fatty acids into mitochondria led to the formation of foam cells in macrophage culture. At the same time, enhanced lipid biosynthesis, including the synthesis of fatty acids and cholesterol, is one of the factors contributing to atherogenesis. Macrophages with increased lipid biosynthesis are characterized by the development of an inflammatory M1 profile and an increased likelihood of transformation into foam cells.

4. Impaired glucose metabolism in atherosclerosis

Throughout adulthood, ECs are primarily inactive; nevertheless, they can become active in response to a variety of physiological and pathological stimuli [17]. Atherosclerosis's precursor, disturbed blood flow dynamics, is a crucial starting point for EC activation [18]. The atheroprotective gene expression program in ECs is triggered by high unidirectional laminar shear stress (LSS), which also activates the transcription factor Krüppel-like factor 2 (KLF2). The vascular barrier's integrity and EC's latent state are both maintained by KLF2, which controls a network of genes that provide EC with its anti-inflammatory and antithrombotic characteristics [18]. It's interesting to note that through a KLF2-dependent mechanism, a high level of LSS reduces mitochondrial respiration, glycolysis, and EC glucose absorption [19].

On the other hand, ECs in the vasculature's atherosclerotic areas are more vulnerable to low LSS disruption, activate pro-inflammatory pathways, and express more glycolytic enzymes [20]. Even in environments with high oxygen content, low LSS increases EC glycolysis via nuclear factor κB (NF-κB) triggered by factor 1α-(HIF1α) [20].

Pro-inflammatory cytokines also promote uptake of glucose and glycolysis in ECs, which amplifies the activation of NF-κB triggered by cytokines, most likely via lactate, but further research is needed on this [21]. Yes-associated protein (YAP) and a transcription coactivator with a PDZ-binding motif (TAZ) are also activated by disrupted LSS and pro-inflammatory cytokines, which add to the pro-inflammatory phenotype of EC and the progression of atherosclerosis [22]. Similar to NF-κB, EC glycolysis is promoted by YAP/TAZ signaling and vice versa [23]. Pro-inflammatory signaling and glycolysis work together to promote glycolysis, which in turn can stimulate pro-inflammatory programs. This creates a vicious cycle that ultimately results in persistent pro-inflammatory signaling in ECs [17].

It has been demonstrated that risk factors including diabetes hasten the onset of atherosclerosis. and are distinguished by disruption of EC metabolism and endothelial dysfunction [24]. Diabetes is characterized by elevated blood glucose levels, which raise the formation of ROS by endothelial cells via glucose autoxidation, NADPH oxidase, uncoupling of endothelial nitric oxide synthase (eNOS), and malfunction of mitochondria. This causes DNA damage and subsequently activates poly(ADP-ribose)polymerase 1 (PARP1) [25]. The glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is inhibited by ADP-ribosylation by PARP1, which causes glycolytic intermediates to accumulate upstream of GAPDH and redistribute to the side branches of the glycolytic pathway. This, in turn, causes uncontrolled protein glycation via the hexosamine biosynthetic route (HBP), the generation of enhanced glycation end products (AGEs) via the polyol and methylglyoxal pathways, and increased activation of protein kinase C (PKC) by the de novo production of diacylglycerol from glyceraldehyde 3-phosphate (G3P) [26]. The activation of eNOS is inhibited by glycation, whereas PKC enhances the production of vasoconstrictor endothelin-1 and inhibits eNOS activation mediated by insulin [27].

Furthermore, AGEs cause extracellular matrix dysfunction by altering their proteins and constituents and activating AGE receptors, which increases pro-inflammatory NF-κB signaling, vascular leakage, and reactive oxygen species (ROS) generation. Interestingly, conversion of the glucose intermediates fructose 6-phosphate (F6P) and G3P towards the pentose phosphate pathway (PPP) via transketolase activation using a thiamine derivative reduces all

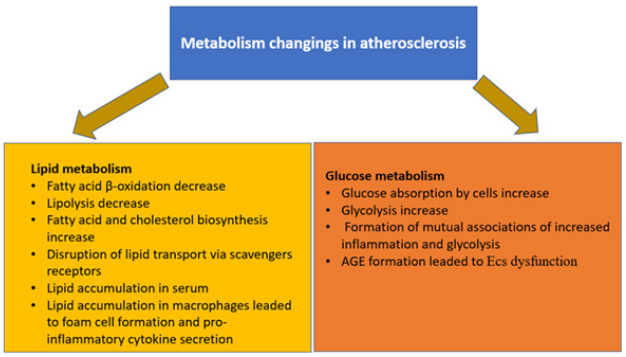

Fig. 1. Glucose and lipid metabolism disruptions in atherosclerosis which lead to increasing of pathological conditions in atherosclerosis.

three pathways induced by hyperglycemia, as well as NF-κB activity [17]. Changes in lipid and glucose metabolism in atherosclerosis are shown in Figure 1.

5. Impaired amino acid metabolism in atherosclerosis

While the significance of glutamine in EC migration is still up for debate, EC proliferation is impaired by glutamine withdrawal, pharmacological inhibition, or knockdown of glutaminase 1 (GLS1), the rate-limiting enzyme of glutaminolysis [28], [29]. It's interesting to note that asparagine replenishment during glutamine deficiency promotes protein synthesis and EC function [30]. Furthermore, the proliferation of ECs is restricted by the inhibition of asparagine synthase, which reduces glutamate-dependent asparagine production [29]. Glutamine plays a proatherogenic effect in EC, as evidenced by the proinflammatory YAP/TAZ pathway, which also increases EC glutaminolysis [31].

Remarkably, leukocyte adherence to ECs and pro-inflammatory gene expression are unaffected by pharmacological suppression of GLS1. On the other hand, glutamine deficiency decreases protein synthesis, which results in ER stress and apoptosis and pro-inflammatory signaling [30]. Furthermore, a glutamine shortage lowers nucleotide synthesis and raises ROS generation, which, in turn, causes death and a decrease in proliferation, respectively. Furthermore, it's been demonstrated that ECs can produce the anti-inflammatory neurotransmitter γ-aminobutyric acid from glutamate [32]. Thus, the precise role that EC glutaminolysis plays in the progression of atherosclerosis is yet unknown.

Mechanically, the interaction between lipids and the immune system during the progression of atherosclerotic plaques contributes to the chronic inflammation seen in the arterial wall in atherosclerosis. Localized inflammation and increased intercellular communication can influence the polarization and proliferation of immune cells through changes in amino acid metabolism. In particular, the amino acids L-arginine, L-homoarginine, and L-tryptophan have been extensively studied in the context of cardiovascular disease, and their actions have been established as key regulators of vascular homeostasis similar to those of immune cells. Cyclic effects between endothelial cells, and innate and adaptive immune cells occur with changes in the metabolism of arginine, homoarginine and tryptophan, which have a significant impact on the development of atherosclerosis [33]. Arginine, a semi-essential amino acid, serves as a precursor of nitric oxide, which affects the aggregation and adhesion ability of platelets, reducing the ability to form clots and reducing the vascular reactivity of atherosclerotic arteries, promotes the formation of collagen in the walls of blood vessels. Arginine can be converted via eNOS to citrulline and nitric oxide (NO), an endogenous gaseous signaling molecule that has a wide range of biological properties.

Several risk factors for atherosclerosis, such as low shear stress, oxidative stress or LDL and modified LDL cholesterol, contribute to EC dysfunction. In particular, the limited bioavailability and activity of antithrombotic and antihypertensive molecules such as arginine, eNOS, and NO may lead to eNOS uncoupling, a pathophysiological condition in which eNOS produces superoxide instead of NO [34]. In addition, in vitro and in vivo restriction of sulfur-containing amino acids, methionine and cysteine, triggers an angiogenic response by stimulating the production of vascular endothelial growth factor (VEGF) and hydrogen sulfide, thereby switching EC metabolism from oxidative metabolism to glycolysis [35].

6. The influence of metabolic disorders on the progression of atherosclerosis

An excessive level of free cholesterol in the ER leads to defective esterification by acyl-coenzyme A acyltransferase 1 (ACAT-1), and in the plasma membrane leads to an inflammatory response through the activation of NF-κB [36]. This dysfunctional lipid metabolism triggers an extensive protein response in the ER and, together with other damage, initiates apoptotic pathways. In the early stages of the disease, the effective absorption of apoptotic cells by neighboring phagocytes (efferocytosis) contributes to the elimination of pro-inflammatory processes and the maintenance of stability within the plaque [37]. However, dysfunctional efferocytosis is a key feature of progressive lesions, and as the disease progresses, the rate of apoptosis in the necrotic nucleus likely outstrips the phagocytic capacity of the phagocytes within it. Efficient clearance of apoptotic cells by surrounding macrophages requires intact lipid metabolism to deal with ingested lipids, and hence defective lipid homeostasis likely contributes to dysfunctional efferocytosis [37]. In addition, in vitro experiments have shown that modified LDL serves as a substrate for phagocytes and, therefore, can competitively prevent the efferocytosis of dying cells [38]. Ineffective efferocytosis also stimulates secondary necrosis of resident lesion cells and, in the case of macrophages, leads to the release of oxidized lipids and inflammatory propagators. As the disease progresses, the plaque becomes increasingly unstable and vulnerable as a result of reduced efferocytosis, chronic inflammation, and inefficient immune cell output [38]. Once inside the plaque, macrophage migration is restricted and therefore compromises the potential resolution of inflammation, thereby favoring pathogenic processes. Resident macrophages contribute to the inflammatory state through the secretion of protease enzymes and pro-inflammatory cytokines [39].

In the later stages of the disease, an atherosclerotic lesion is characterized by an abundance of disorganized cells, lipids, matrix components, and minerals. Clinical symptoms may occur during this phase of the disease, as the intima thickens and the lumen of the artery may decrease in size. Dying foam cells release their cytoplasmic contents, causing an accumulation of extracellular lipids,

which exacerbate inflammation and trigger secondary necrosis. Excessive cholesterol levels also contribute to the formation of hard crystals that are toxic to cells and initiate a pro-inflammatory response [40].

Locally produced cytokines, such as IFN-γ secreted by T cells, reduce the proliferation of SMCs and also inhibit the synthesis of ECM integral components such as type I and III collagen. Before rupture, the fibrous sheath becomes thinner, which reduces the stability of the structure. At this stage of the disease, the plaque contains depleted levels of fibrous material and may show signs of calcification, ulceration, and small vessel hemorrhage [41].

A number of factors may contribute to progression, including the presence of inflammatory cells, structural toxicity, activity of proteolytic enzymes released by macrophages, coronary spasms, physical vulnerability, and stress resulting from the altered composition of the lesion. Exposure to tissue factor from the plaque promotes coagulation and thrombus formation. A thrombus may instantly occlude a lumen or may break off as an embolus and block blood flow downstream. A common cause of myocardial infarction is rupture of a widespread atherosclerotic lesion, in which collagen and tissue factor are exposed, leading to platelet aggregation and coagulation [42].

7. Therapeutic metabolic targets in atherosclerosis

7.1. Cholesterol-O-acyltransferase inhibitors

An essential enzyme called cholesterol-O-acyltransferase (ACAT) helps enterocytes identify ingested cholesterol [43]. It is believed to play a role in the advancement of atherosclerotic lesions and the release of VLDL from the liver, as well as in the metabolism of cholesterol in macrophages, the liver, the intestines, and the adrenal cortex. ACAT1 and ACAT2, two ACAT enzymes, have been identified. ACAT2 is located in the ER of the liver and intestinal tissues and is in charge of forming cholesterol esters, whereas ACAT1 is present in the ER. In theory, inhibition of ACAT1 could prevent the transformation of macrophages into foam cells and thereby slow the progression of atherosclerosis and prevent the development of vulnerable plaque and inhibition of ACAT-2 could reduce serum lipid levels by reducing lipoprotein synthesis. Preclinically, HL-004 was found to be an effective inhibitor of ACAT [44].

7.2. Microsomal triglyceride transporter protein inhibitors

The lipid transport protein known as microsomal TG transport protein (MTTP) is a heterodimer that facilitates the transfer of TG, cholesteryl ester, and phosphatidylcholine across membranes. In chylomicrons (in enterocytes) and VLDL (in hepatocytes), MTTP is a protein that is found in the intestinal and hepatic tissues and is involved in the lipid assembly, transport, and release of lipoproteins high in triglycerides [45]. According to in vitro research, MTTP is involved in the creation of developing lipoprotein molecules in the lumen and extracellular space (ER) as well as the transport of chemicals between phospholipid membranes. Lower plasma TG and cholesterol levels should result from small compounds' inhibition of MTTP. Several clinical candidates, such as CP-346086 and BMS 201038, have been shown to inhibit MTTP in both enterocytes and the liver [46].

7.3. AMP-activated protein kinase activators

AMP-activated protein kinase (AMPK), is a heterotrimetric energy-sensitive protein that restores cellular energy balance by stimulating ATP generation pathways (for example, FA oxidation) and inhibiting ATP utilization pathways (for example, FA synthesis) [43]. CYP27A1 converts cholesterol to 27-hydroxycholesterol via an oxygenation reaction, and this is thought to be an important reaction for the elimination of cholesterol from human lung macrophages and arterial endothelial cells. The AMPK system plays an important role in the regulation of glucose and lipid metabolism through its influence on energy metabolism and long-term effects on liver gene expression. In the liver, AMPK activation leads to a decrease in the production of TG and cholesterol in plasma and an increase in FA oxidation [47]. WS070117 is a synthetic lipid-lowering agent preclinically approved as an effective AMPK activator with the potential to inhibit de novo hepatic lipogenesis [46], [48].

7.4. Lanosterol synthase inhibitors

Lanosterol synthase (LSS) is an enzyme that has been identified as a target for new anti-cholesterol drugs that could complement statins. LSS is found in the ER and converts 2,3-oxidosqualene to lanosterol, the initial four-ring sterol intermediate in the cholesterol synthesis pathway. 24(S),25-epoxycholesterol is a liver X receptor ligand [49]. It also sets the template for the development of inhibitors with improved pharmacological properties for lowering cholesterol levels and treating atherosclerosis. Due to the dual mechanism of action of LSS (formation of lanosterol; formation of ligands for the liver X receptor), LSS inhibitors have the potential to lower plasma LDL levels and prevent cholesterol deposition in macrophages [46]. The therapeutic strategies described above are summarized in Table 1.

Table 1. Therapeutic strategies targeting metabolic targets in atherosclerosis, which include modulation of key metabolic protein functions.

Group of therapeutic agents	Role of target in atherosclerosis	Therapeutic effect
ACAT inhibitors	Secretion of VLDL and the development of atherosclerotic lesions	Inhibition of the formation of foam cells and increase the serum lipid levels
MTTP inhibitors	Lipid transport between membranes and synthesis of lipoprotein particles	Decrease in plasma TG and cholesterol levels
AMPK activators	FA oxidation stimulating and FA synthesis inhibiting	Inhibition of lipogenesis and lipoprotein accumulation
LSS inhibitors	Cholesterol synthesis	Decline of plasma LDL levels and prevention of cholesterol deposition in macrophages

8. Discussion

Drug therapy-based therapeutic approaches are typically employed for atherosclerosis. Typically prescribe a range of medications intended to lower blood cholesterol and restore normal blood pressure. Statins, which work to control cholesterol levels, are the most often used medications for the treatment of atherosclerosis. The important enzyme HMG-CoA reductase, which is involved in the manufacture of cholesterol, is inhibited by statins. The liver cell increases the quantity of LDL membrane receptors on its surface in response to a decrease in intracellular cholesterol content. These receptors bind and eliminate LDL from the bloodstream, lowering the blood's cholesterol concentration.

Nicotinic acid is another medication used to treat atherosclerosis; it has demonstrated a number of beneficial benefits on lipid metabolism, however, the precise mechanism underlying these effects is still unknown [51]. Nicotinic acid causes a deficit in plasma by lowering the liver's production of VLDL and partially preventing the secretion of fatty acids from adipose tissue. As previously stated, the exact mode of action of niacin is yet unknown; nevertheless, a number of possible pathways may combine to produce the observed lipid-modifying activity [52].

All currently available medications do not treat atherosclerosis or induce remission; rather, they merely assist in managing the condition of blood arteries. This illustrates the necessity of creating combination medications because the target disease has a complicated etiology. Furthermore, a deeper comprehension of the metabolic processes involved in atherogenesis is required. This could aid in identifying novel treatment targets.

9. Conclusion

Over the past few years, we have seen an increase in the burden of atherosclerotic diseases, which contributes to the risk of cardiovascular disease, which is becoming a global epidemic. The study of the cellular and molecular biological mechanisms of atherosclerosis has made it possible to better understand the processes leading to the progression of the disease and its clinical manifestations. Knowledge and ongoing research on the pathogenesis of atherosclerosis and changes in metabolic pathways will allow the development of effective drugs for the treatment of this disease. Several therapeutic strategies, namely ACAT inhibitors, MTTP inhibitors, AMPK activators and lanosterol synthase inhibitors have already shown their effectiveness in clinical trials.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed Consent

The authors declare that no patients were used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors had equal roles in study design, work, statistical analysis and manuscript writing.

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