# Innovative Drug Targets and Treatments for Types of Hyperlipidemia- A Review

Pranali S. Band*[1], Apali A. Jain[2], Riya Warshe [3], Nikita N. Musale [4], Tejaswini S. Patle [5], Aditya Pise [6,] Sejal K. Agrawal[7], Pratik D. Dhokne[8], Swapnil Tirmanwar[9]
[1]*Research scholar, Gurunanak College of Pharmacy, Nagpur*
[2]*Student, Priyadarshini J.L College of Pharmacy, Nagpur*
[3]*Lecturer, KDK College of Pharmacy & Research Institute, Nagpur*
[4]*Student, Priyadarshini J.L College of Pharmacy, Nagpur*
[5]*Student, Priyadarshini J.L College of Pharmacy, Nagpur*
[6]*Student, Priyadarshini J.L College of Pharmacy, Nagpur*
[7]*Student, Priyadarshini J.L college of Pharmacy, Nagpur*
[8]*Research scholar Priyadarshini J.L college of Pharmacy, Nagpur*
[9]*Research scholar*

**Abstract: An increase in one or more of the plasma lipids, such as triglycerides, cholesterol, cholesterol esters, phospholipids, and/or plasma lipoproteins, such as very low-density lipoprotein and low-density lipoprotein, combined with a decrease in high-density lipoprotein levels, is known as hyperlipidemia. One of the main risk factors for cardiovascular illnesses is this increase in plasma lipids. At the expense of serious liver and muscle adverse effects, statins and fibrates continue to be the principal anti-hyperlipidemic medications for the treatment of increased plasma cholesterol and triglycerides, respectively. The forms of hyperlipidemias, lipid metabolism, therapies, and novel therapeutic targets for managing high lipid profiles are the primary topics of this review. Numerous substances, including diacyl glycerol, squalene epoxidase inhibitors, and lanosterol synthase inhibitors**

**Keywords: Cholesterol, Hyperlipidemia, Medications, Therapies**

## INTRODUCTION

One of the main risk factors for cardiovascular diseases (CVDs) is thought to be hyperlipidemia. One-third of all fatalities worldwide are attributed to CVDs, and by 2030. It is predicted that CVDs will overtake all other causes of mortality and disability globally. [1,2]

Increases in one or more plasma lipids, such as triglycerides, cholesterol, cholesterol esters, and phospholipids, as well as plasma lipoproteins, such as very low-density lipoprotein and low-density lipoprotein, and decreased levels of high-density lipoprotein, are referred to as hyperlipidemia. [3,4]

The primary cause of atherosclerosis, which is closely linked to ischemic heart disease (IHD), is hypercholesterolemia and hypertriglyceridemia. The high mortality rate and IHD are strongly correlated. Moreover, about four million fatalities annually are attributed to increased plasma cholesterol levels. [5,6]

Atherosclerosis is a process of arteries hardening due to the deposition of cholesterol in the arterial wall, which causes the narrowing of the arteries. Atherosclerosis and atherosclerosis-associated disorders like coronary, cerebrovascular, and peripheral vascular diseases are accelerated by the presence of hyperlipidemia. [7]

Hyperlipidemiarelates to increased oxidative stress, causing significant production of oxygen free radicals. This may lead to oxidative modifications in low-density lipoproteins, which present a significant function in the initiation and progression of atherosclerosis and associated cardiovascular diseases. [3]

Plasma lipoproteins

Composition and structure

Lipoproteins are macromolecule aggregates composed of lipids and proteins; this structure facilitates lipids compatibility with the aqueous body fluids.

Lipoproteinscomposed of non-polar lipids (triglycerides and cholesteryl esters), polar lipids(phospholipids and unesterified cholesterol),

and specific proteins known as apolipoproteins. Apolipoproteins are amphiphilic proteins that bind to both lipids and the plasma[8].

Lipoprotein classification

Chylomicrons (CM), very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), intermediate-density lipoproteins (IDL), and high-density lipoproteins (HDL) are the five classes of lipoproteins present in plasma. These classes are heterogeneous; they have different compositions, sizes, and densities. [8]

As the triglyceride and cholesteryl ester contents of the core increase, the lipoprotein size increases, and the density of lipoproteins increases proportionally to their protein contents and contrariwise to their lipid contents. [9]

Lipoprote in Function

Plasma lipoproteins are important for lipid solubilization to transport triglycerides, an important energy source, which synthesized and absorbed places of utilization and storage, and to transport cholesterol between different places of absorption, synthesis, catabolism, and elimination.[10]

Enzymes involved in lipoprotein metabolism

*Lipoprotein lipase (LPL)*

LPL is a multifunctional enzyme expressed on endothelial cells in the heart, muscle, adipose tissue, macrophages, and lactating mammary glands. LPL plays a critical role in the hydrolysis of triglyceride (TG) into two free fatty acids and monoacylglycerol. Besides, LPL helps in the receptor-mediated lipoprotein uptake of chylomicron remnants, cholesterol-rich lipoproteins, and free fatty acids. [11]

*Hepatic lipase (HL)*

HL is a multifunctional protein that regulates lipoprotein metabolism. It is synthesized by hepatocytes and found in the adrenal gland and ovary. HL hydrolyzes phospholipids and triglycerides of plasma lipoproteins. In addition, HL affects cellular lipid delivery by facilitating lipoprotein absorption by cell surface receptors and proteoglycans. [12]

*Lecithin cholesterol acyl transferase (LCAT)*

Lecithin cholesterol acyltransferase is a crucial enzyme in the metabolism of HDL. It converts free cholesterol into cholesteryl esters, which are then sequestered into the core of lipoprotein and finally make mature HDL. [13]

*Cholesteryl ester transfer protein (CETP)*

Cholesteryl ester transfer protein (CETP), also called plasma lipid transfer protein, is a hydrophobic plasma glycoprotein that accelerates the transfer of esterified cholesterol esters (CE) from HDLs to chylomicrons, VLDL, and LDL in exchange for triglyceride. ACETP deficiency is linked to increased HDL levels and decreased LDL levels. [14]

*Microsomal triglyceride protein (MTP)*

Microsomal triglyceride protein (MTP) is a lipid transfer protein that catalyzes the transfer of neutral lipids, triglycerides, and cholesterol esters between the membrane of the lumen of microsomes isolated from the liver and intestinal mucosa. Microsomal triglyceride protein is an essential protein in the assembly of apo B containing lipoproteins. Now, it is known that MTP is important in the biosynthesis of glycolipid-presenting molecules and the regulation of cholesterol ester biosynthesis. [15]

*Acyl Co-A transferase (ACAT)*

Acyl Co-A transferase (ACAT) is a membrane-bound protein that uses long-chain fatty acyl-CoA and cholesterol as substrates to produce cholesteryl esters. ACAT plays a significant role in cellular cholesterol homeostasis in various tissues and prevents the toxic accumulation of excess cholesterol in a cell. Furthermore, the importance of ACAT arises from its crucial role in the assembly along with the secretion of apolipoprotein-B-containing lipoproteins in the liver and intestines. [16]

Lipid metabolism

Almost all the dietary fats are absorbed from the intestinal lumen into the intestinal lymph and packed into chylomicrons. These lipoproteins move into the bloodstream, where they are hydrolyzed by endothelial lipoprotein lipase, which hydrolyzes the triglyceride into glycerol and non-esterified fatty acids. After this, the chylomicron remnants are absorbed in the liver and packaged with cholesterol, cholesteryl esters, and ApoB100 to form VLDL. After the release of VLDL into the bloodstream, it will be converted into IDL by the action of lipoprotein lipase and hepatic lipase, where phospholipids and apolipoproteins are transferred back to HDL. Furthermore, after the hydrolysis by

hepatic lipase, IDL will be converted to LDL and lose more apolipoproteins. [17]

Peripheral cholesterol is returned to the liver by a reverse cholesterol transport pathway using HDLs, which are originally synthesized by the liver and released into the blood. In the blood, HDL cholesterol is esterified by LCAT to cholesteryl ester and transferred to VLDL and chylomicrons to return to the liver through the LDL receptor. Cholesteryl esters are transferred to LDL particles by CETP and then subjected to LDL-receptors-mediated endocytosis. Finally, cholesteryl esters are hydrolyzed to cholesterol and extracted from the body as bile acid. [18]

Hyperlipidemia classification

Hyperlipidemia, in general, can be classified into:

Primary

It is also called familial due to a genetic defect; it may be

Monogenic: a single gene defect or

Polygenic: multiple gene defects. Primary hyperlipidemia can usually be resolved by one of the abnormal lipoprotein patterns summarized in Table 1. [19]

Secondary

it is acquired because another disorder like diabetes, nephritic syndrome, chronic alcoholism, hypothyroidism, and the use of drugs like corticosteroids, beta-blockers, and oral contraceptives causes it. Secondary hyperlipidemia, together with significant hypertriglyceridemia, can cause pancreatitis.[20]

The main cause of hyperlipidemia includes changes in lifestyle habits The risk factor is mainly a poor diet in which fat intake from saturated fat and cholesterol exceeds 40 percent of the total calorie uptake. [20]

Table 1: Fredrickson classification of primary hyperlipidemia.

| Type | Disorder | Cause | Occurrence | Elevated plasma lipoprotein |
|---|---|---|---|---|
| I | Familial hyperchylomicronemia Or Primary hyperlipoproteinemia | Lipoprotein lipase deficiency or Altered ApoC2 | Very rare | Chylomicrons |
| IIa | Familial hypercholesterolemia Or Polygenic hypercholesterolemia | LDL receptor deficiency | Less common | LDL |
| IIb | Familial combined hyperlipidemia | Decreased LDL receptor and increased ApoB | Commonest | LDL and VLDL |
| III | Familial dysbetalipoprotenemia | Defect in Apo E- 2 synthesis | Rare | IDL |
| IV | Familial hypertriglyceridemia | Increased VLDL production and decreased excretion | common | LDL |
| V | Endogenous hypertriglyceridemia | Increased VLDL production and decreased LPL. | Less common | VLDL and chylomicrons |

Symptoms of hyperlipidemia

Generally, hyperlipidemia does not have any obvious symptoms, but they are usually discovered during a routine examination or until it reaches the danger stage of a stroke or heart attack. Patients with high blood cholesterol levels or patients with familial forms of the disorder can develop xanthomas, which are deposits of cholesterol that may form under the skin, especially under the eyes. At the same time, patients with elevated levels of triglycerides may develop numerous pimple-like lesions at different sites in their bodies. [19]

Complications of hyperlipidemia

*1. Atherosclerosis*

Hyperlipidemia is the most important risk factor for atherosclerosis, which is the major cause of cardiovascular disease. Atherosclerosis is a pathologic process characterized by the accumulation of lipids, cholesterol, and calcium and the development of fibrous plaques within the walls of large and medium arteries. [21]

*2. Coronary Artery Disease (CAD)*

Atherosclerosis, the major cause of coronary artery disease, is characterized by the accumulation of lipids and the formation of fibrous plaques within the wall of the arteries, resulting in the narrowing of the arteries that supply blood to the myocardium and results in limiting blood flow and insufficient amounts of oxygen to meet the needs of the heart. Elevated lipid profile has been connected to the development of coronary atherosclerosis. [22]

*3. Myocardial Infarction (MI)*

MI is a condition that occurs when blood and oxygen supplies are partially or completely blocked from flowing in one or more cardiac arteries, resulting in damage or death of heart cells. The occlusion may be due to ruptured atherosclerotic plaque. The studies show that about one-fourth of survivors of myocardial infarction were hyperlipidemic. [23]

*4. Ischemic stroke*

stroke is the fourth leading cause of death. Usually, strokes occur due to blockage of an artery by a blood clot or a piece of atherosclerotic plaque that breaks loose in a small vessel within the brain. Many clinical trials revealed that lowering low-density lipoprotein and total cholesterol by 15% significantly reduced the risk of the first stroke. [24]

Drugs classes for hyperlipidemia

Since LDL is the major atherogenic lipoprotein, reduction of this lipoprotein would be expected to reduce atherosclerosis and, therefore, reduce cardiovascular adverse effects. In addition to high LDL, the presence of risk factors and CHD should qualify to initiate drug therapy along with lifestyle changes. Monotherapy is effective in treating hyperlipidemia, but combination therapy may be required for a comprehensive approach. Antihyperlipidemic drugs currently contain five major classes (Table 2): statins, fibric acid derivatives, bile acid binding resins, nicotinic acid derivatives, and drugs that inhibit cholesterol absorption. [20]

Table 2: Drug therapy for hyperlipidemia

| Drugs | Effects on lipids |
|---|---|
| *Statins:*<br>Lovastatin (10-80 mg)<br>Simvastatin (5-40 mg)<br>Atorvastatin (10-80 mg) | Decrease TG<br>Decrease LDL<br>Increase HDL |
| *Bile acid binding resins:*<br>Cholestyramine (4-16 mg)<br>Colestipol(5-30 mg) | TG is generally not affected.<br>Decrease LDL<br>Increase HDL |
| *Fabric acid derivatives:*<br>Gemfibrozil (1200 mg)<br>Bezafibrate (600 )mg<br>Fenofibrate(200 mg) | Decrease TG<br>Decrease LDL<br>Increase HDL |

| | |
|---|---|
| *Nicotinic acid derivatives*<br>Niacin(2-6 gm) | Decrease TG<br>Decrease LDL<br>Increase HDL |
| *Cholesterol absorption inhibitors:*<br>Ezetimibe ( 10 mg ) | Decrease LDL<br>Decrease cholesterol |

A. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins).

This class includes (Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Atorvastatin, and Rosuvastatin). Statins are broadly prescribed in the treatment of hypercholesterolemia, can achieve 20%–50% reductions in cholesterol levels, and have been linked to the reduced incidence of coronary morbidity and mortality in high-risk adults. [25]

Mechanism of action

These drugs are structural analogs of HMG-coenzyme A reductase. They act by inhibiting the rate-limiting enzyme (HMG-coenzyme Areductase) in the biosynthesis of cholesterol in the liver. By inhibiting this enzyme, statins significantly reduce plasma levels of total cholesterol (TC), LDL, and ApoB. Meanwhile, statins also cause a modest decrease in plasma triglycerides and a small increase in plasma levels of HDL. [26]

Other HMG-CoA reductase inhibitors include diallyl disulfide (DADS) anddiallylthiosulfinate. DADS, an organosulfur compound derived from garlic, has been shown to reduce cholesterol synthesis by 10–25% at low concentrations. Diallylthiosulfinate, a metabolite of allicin, blocks the formation of 7-dehydrocholesterol and reduces the production of cholesterol. Bis-(3-(4-nitrophenyl) prop-2-ene) disulfide, a new derivative of diallyl disulfide, is effective in reducing plasma total cholesterol. [27]

Side effects

Statins are frequently well tolerated, with the most common adverse effects being transient gastrointestinal symptoms, headache, myalgia, and dizziness. These symptoms are more common with higher doses and may be solved if a different statin is used. [20]

Statins also cause myopathy, rhabdomyolysis, and an increase in serum transaminase. These substances are harmful to the kidneys and often cause kidney damage. Additionally, statins may cause cardiomyopathy[29]. Recent clinical trials showed that statin use has been linked to an increase in type 2 diabetes. [30]

B. Bile acid sequestrants

Bile acid synthesis is the main pathway of cholesterol catabolism in the liver; it has been estimated that about 500 mg of cholesterol is converted daily into bile acids in the adult human liver. Bile acids are secreted into the intestine and have an important role in facilitating the absorption of fats from food. [31]

Bile acid sequestrantsincludecholestyramine, colestipol, colestimide, and colesevelam. Cholestyramine and colestipol are the two bile acid sequestrants currently available. Cholestyramine is a quaternary amine composed of styrene and divinylbenzene polymers. Colestipol is a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane. [32]

Mechanism of action

Bile acid sequestrants are positively charged resins that bind to the negatively charged bile acids in the intestine to form a large insoluble complex that is not absorbed, and so excreted in the feces. Excretion is increased up to tenfold when resins are given, resulting in greater conversion of cholesterol to bile acids. Furthermore, bile acid sequestrants increase HDL levels. [33]

Side effects

Bile acid sequestrants are rarely used as initial therapy because of poor patient tolerance. Gastrointestinal disturbances are the most common complaints of the bile acid sequestrants, including constipation, nausea, indigestion, bloating, and flatulence[34].

On long-term therapy, bile acid sequestering agents may cause osteoporosis due to calcium loss. They may aggravate hypertriglyceridemia by an unknown

mechanism. Some vitamin mineral deficiencies may occur. [32]

C. Fibric acid derivatives (Fibrates)

Fibratesinclude clofibrate, gemfibrozil, fenofibrate, and bezafibrate, are widely used class of antihyperlipidemic agents, resulting in a significant reduction in plasma triglycerides and a modest reduction in LDL cholesterol. HDL cholesterol level increases moderately. Angiographictrial results showed that fibrates play an important role in slowing the progression of coronary atherosclerosis and decreasing the incidence of coronary artery disease.

Mechanism of action

Data from studies in rodents and humans imply four main mechanisms of fibrates:

1. Stimulation of lipoprotein lipolysis.

Fibrates function primarily as ligands for the nuclear transcription receptor PPAR-α. They increased the expression of lipoprotein lipase, apo, and down-regulate apo C-III, an inhibitor of lipolysis. Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI and apo AII. [35]

2. Increase hepatic fatty acid (FA) uptake and reduction of hepatic triglyceride production.

Fibrates enhance the production of fatty acid transport protein and acyl-CoA synthetase, which contribute to the increased uptake of fatty acid by the liver and, as a result, to a lower availability of fatty acids for triglyceride production. [36]

3. Increase removal of LDL particles.

Fibrate appears to enhance LDL catabolism via the receptor-mediated pathway; LDL particles became larger and more lipid-rich and, therefore, had more affinity for receptors. Fibrates also inhibit the formation of slowly metabolized, potentially atherogenic LDL particles. [37]

4. Increase in HDL production and stimulation of reverse cholesterol transport.

Fibrates increase apo A-I production in the liver, which leads to the observed elevation in plasma levels of apo A4 and HDL-cholesterol and a more effective reverse cholesterol transport. [38]

Side effects

Generally, fibrates are considered to be well tolerated. Side effects may include gastrointestinal symptoms, myopathy, arrhythmia, skin rashes, and gallstones. Fibrates should be avoided in patients with liver and renal dysfunction. [32]

D. Nicotinic acid derivatives (Niacin)

Niacin, a water-soluble vitamin of type B, is the oldest lipid-lowering agent used to treat hyperlipidemia and has been proven to decrease cardiovascular morbidity and total mortality. It decreases total cholesterol, LDL cholesterol, and triglycerides.

Besides, niacin is the most effective therapy available for the treatment of low HDL levels when used in a dose of (≈1 gm per day). [39]

Mechanism of action

Niacin inhibits hormone-sensitive lipase, which decreases triglycerides lipolysis, the main producer of circulating free fatty acids. The liver usually uses these circulating fatty acids as a major precursor for triacylglycerol synthesis. Therefore, niacin inhibits VLDL secretion, in turn decreasing the production of LDL.

Furthermore, niacin treatment elevates HDL cholesterol concentrations by reducing the fractional clearance of apo A-1 and increasing HDL synthesis. [32]

Side effects

Niacin treatment has been plagued by low compliance rates. The most common side effects are intense cutaneous flush, which affects more than three-quarters of patients, itching, headache, and some patients experience nausea and abdominal discomfort. Niacin also elevates liver enzymes.

Administering statins in combination with niacin increases the incidence of rhabdomyolysis. Niacin also promotes glucose intolerance and hyperuricemia, which precipitate a gout attack. [34]

E. Selective cholesterol absorption inhibitor (Ezetimibe)

The discovery and development of ezetimibe, the first member of a group of drugs that inhibit intestinal absorption of phytosterols and cholesterol, has improved the treatment of hypercholesterolemia. It inhibits the absorption of cholesterol from the small

intestine without any effect on the plasma concentrations of the fat-soluble vitamins. [40]

A combination of statins and ezetimibe can achieve a reduction in LDL cholesterol levels by 25%, compared to 6% attained by doubling the statin dose. [41]

Mechanism of action

Ezetimibe selectively inhibits the absorption of cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver by blocking the Niemann–Pick C1-like 1 protein (NPC1L1), a human sterol transport protein. This causes an increase in the clearance of cholesterol from the blood. [42]

Side effects

Ezetimibe is usually well tolerated; the most common side effects include headache, abdominal pain, and diarrhea. Ezetimibe appears to cause elevations in liver function tests, including elevations in alanine transaminase and aspartate transaminase. [43]

New potential targets and treatments

Recently, many clinical trials revealed new potential agents with promising antihyperlipidemic activity. In this section, some of these agents will be reviewed.

1. *Acyl-CoA cholesterol acyl transferase inhibitors (ACAT)*

Acyl-CoA cholesterol acyl transferase (ACAT) is the enzyme that catalyzes the conversion of intracellular cholesterol into cholesteryl esters. ACAT has two isomers, termed ACAT1 and ACAT2.

ACAT1 contributes to foam cell formation in the arterial wall and the development of atherosclerosis, so ACAT-1 inhibitors may have an antiatherogenic effect, and ACAT-2 inhibitors may play an important role in reducing cholesterol absorption in the intestine.

Avasimibe and Eflucimibe act by inhibiting ACAT, decreasing plasma cholesterol levels, and slowing the development of atherosclerosis[44,45]. Some of the potent ACAT inhibitors which are currently in clinical development are naphthoquinone derivatives. [46]

*Microsomal triglyceride transfer protein (MTP) inhibitors*

Microsomal triglyceride transfer protein (MTP) has multiple functions, including transferring neutral lipids between membrane vesicles, the biosynthesis of CD1, antigen-presenting molecules, as well as in the regulation of cholesterol ester biosynthesis. Therefore, inhibiting MTP causes significant reductions in plasma triglycerides, LDL, and VLDL cholesterol. These findings suggest that inhibitors of MTP might be useful for reducing atherogenic lipoprotein levels. [15]

A series of newly synthesized phosphonate esters were evaluated for their effects on MTP activity, and they exhibit potent inhibition both in vitro and in vivo. Data also suggest the potency of lomitapide (AEGR-733, formerly BMS-201038), a novel drug for hypercholesterolemia. [47]

2. *Cholesteryl ester transfer protein (CETP) inhibitors*

CETP in the liver facilitates the transfer of cholesteryl esters from anti-atherogenic HDLs to proatherogenic apolipoprotein B-containing lipoproteins, including VLDLs and LDLs. Furthermore, most studies showed that there is evidence that CETP may play a proatherogenic role by involving in reverse cholesterol transport and support the idea that inhibition of CETP slows the progression of atherosclerosis. [48]

Dalcetrapib and anacetrapib are novel compounds in Phase III of clinical trials. Dalcetrapib reduced CETP activity by 50% and elevated HDL cholesterol levels by 31% without affecting LDL cholesterol levels. [49]

3. *Squalene synthase inhibitors*

Squalene synthase (SqS) catalyzes farnesyl pyrophosphate to form squalene. Catalysis by SqS is the first committed step in sterol synthesis, and one of these sterols is cholesterol. Pharmacologists regard SqS inhibitors as promising lead compounds in the development of potential agents to treat hyperlipoproteinemia. [50]

It has been reported that after oral administration of BMS-188, 494, a potential inhibitor of SqS, the plasma levels of cholesterol were reduced in experimental rats. Concurrently, YM-53601, another inhibitor of SqS, reduces plasma cholesterol and triglyceride levels. [51,52]

4. *Hydroxymethylglutaryl-CoA synthase inhibitors*

HMG synthase catalyzes the chemical reaction that converts acetyl-CoA and acetoacetyl-CoA to 3-hydroxy-3-methylglutaryl-CoA. L-659,699 is one of the compounds that have shown a potential HMG synthase inhibitor activity. [52]

5. *ATP citrate lyase inhibitors*

ATP citrate lyase (ACL)is the primary enzyme accountable for the synthesis of cytosolic acetyl-CoA and oxaloacetate. The synthesis of cytosolic acetyl-CoA and oxaloacetate represents an important step in the synthesis of fatty acids and cholesterol. For this reason, inhibition of ACL is a promising strategy in the treatment of dyslipidemia.[53]

Recently, Li et al. described that a chronic administration of BMS-303141, the leading inhibitor of the enzyme ACL in the2-hydroxy-N-arylbenzenesulfonamides class, in high-fat–fed mice reduced weight gain and decreased plasma cholesterol, triglycerides, and glucose. [54]

6. *Acyl coenzyme A: diacylglycerol acyltransferase (DGAT)*

DGAT is a microsomal enzyme that joins Acyl CoA to 1,2-diacylglycerol in the final step in triglyceride biosynthesis. Two forms of DGAT (DGAT-1 and 2) have been identified. Several studies showed that inhibition of DGAT1 is a good target in the treatment of hyperlipidemia.

The compound T863 is a potent inhibitor for DGAT1 in vitro; it was shown that a two-week treatment with compound T863 decreased serum and liver triglycerides and decreased serum cholesterol in mice [55]

7. *Squaleneepoxidase inhibitors*

Squaleneepoxidaseis one of the rate-limiting enzymes for the first oxygenation step in sterol biosynthesis. NB-598 competitively inhibits squalene epoxidase and inhibits cholesterol synthesis. [56]

8. *Lanosterol synthase inhibitors*

lanosterol synthase (LSS)Catalyzes the cyclization of (S)-2,3 oxidosqualene to lanosterol, the initial sterol intermediate in the cholesterol synthesis pathway.LSS inhibitors such as U18666A and Ro 48-8071 have the potential to decrease plasma LDL cholesterol levels. [57]

## CONCLUSION

In conclusion, hyperlipidemia, characterized by increased plasma lipids and lipoproteins, is a significant risk factor for cardiovascular diseases. While statins and fibrates remain the primary treatment options, their adverse effects on the liver and muscles necessitate the exploration of alternative therapies. This review highlights different forms of hyperlipidemia, lipid metabolism, existing treatments, and emerging therapeutic targets, including diacyl glycerol, squalene epoxidase inhibitors, and lanosterol synthase inhibitors, which may offer promising approaches for managing high lipid levels.

## REFERENCES

[1] Ginghina, C., Bejan, I., Ceck, C. D. Modern risk stratification in coronary heart disease.*J. Med. Life.*, 2011; 4(4): 377-86.

[2] Jorgensen, T., Capewell, S., Prescott, E., Allender, S., Sans, S., Zdrojewski, T. Population-level changes to promote cardiovascular health. *Eur. J. Prev. Cardiol*., 2013; 20(3):409-21.

[3] Mishra, P. R., Panda, P. K., Apanna, K.C., Panigrahi, S. Evaluation of acute hypolipidemic activity of different plant extracts in Triton WR-1339 induced hyperlipidemia in albino rats. *Pharmacologyonline.,*2011;3: 925-934.

[4] Jeyabalan, S., Palayan, M. Antihyperlipidemic activity of Sapindusemarginatus in Triton WR-1339 induced albino rats. *Res. J. Pharm. Tech.,* 2009; 2(2):319-323.

[5] Brouwers, M. C., VanGreevenbroek, M. M., Stehouwer, C. D., de Graaf, J., Stalenhoef, A. F. The genetics of familial combined hyperlipidemia.*Nat. Rev. Endocrinol.,*2012; 8(6): 352-62.

[6] Kumar, D., Parcha, V., Maithani, A., Dhulia, I. Effect and evaluation of antihyperlipidemic activity guided isolated fraction from total methanol extract of *Bauhinia variegata* (Linn.) in Triton WR–1339 induced hyperlipidemic rats.*Asian Pac. J. Trop. Dis.,*2012;2(2): 909-913.

[7] Wells, G. B., Dipiro, J., Schwinghammer, T., Hamilton, C. Pharmacotherapy Handbook, 7thedn, USA, The McGraw Hill Companies, 2007; pp98-108.

[8] Scapa, E. F.,Kanno, K., Cohen, D.E. Lipoprotein metabolism In: Rodés,J.; Benhamou, J. P.; Blei, A. T.; JürgReichen, J. and Mario Rizzetto, M.,Hepatology: From

Basic Science to Clinical Practice, 3rdedn, U.K: Blackwell Publishing Ltd, 2007; pp133-134.

[9] Jonas, A. Lipoprotein structure In: (Vance DE, Vance JE), Biochemistry of Lipids, Lipoproteins, and Membranes, 4thedn, Amsterdam: Elsevier, 2002; pp483–504.

[10] Harvey, R. A., Ferrier, D. R. Cholesterol and steroid metabolism In: (Rhyner, S.), Biochemistry, 5th ed, USA: Lippincott Williams & Wilkins, 2011; pp227-237.

[11] Wang, H., Eckel, R. H. Lipoprotein lipase: from gene to obesity. *Am. J. Physiol. Endocrinol. Metab* .,2009; 297 (2): 271-288.

[12] Santamarina-Fojo, S.,González-Navarro, H., Freeman, L., Wagner, E.,Nong, Z. Hepatic lipase, lipoprotein metabolism, and atherogenesis.*Arterioscler.Thromb.Vasc.Biol.,*2004; 24(10): 1750-1754.

[13] Nakhjavani, M., Morteza, A., Karimi, R., Banihashmi, Z., Esteghamati, A. Diabetes induces gender gap on LCAT levels and activity.*life Sci.*, 2013; 92(1): 51–54.

[14] Durrington, P. N. Cholesteryl ester transfer protein (CETP) inhibitors. *Br. J. Cardiolo.,*2012; 19(3):126–133.

[15] Hussain, M., Rava, P., Walsh, M., Rana, M., Jahangir Iqbal, J. Multiple functions of microsomal triglyceride transfer protein. *Nutr. Metab.,*2012; (9):14-30.

[16] Chang, T. Y., Li, B. L., Chang, C. Y., Urano, Y. Acyl-coenzyme A: cholesterol acyltransferases. *Am. J. Physiol- Endoc. M.,*2009; 297(1): E1-E9.

[17] McLaren J. E., Michael D. R., Ashlin T. G., Ramji D. P. Cytokines, macrophage lipid metabolism and foam cells: Implications for cardiovascular disease therapy.*Prog. Lipid Res.,*2011; 50(4):331–347.

[18] Hegele, A. R. Plasma lipoproteins: genetic influences and clinical implications.*Nat. Rev. Genet.,*2009; (10): 109-121.

[19] Tripathi, K. D. Essentials of Medical Pharmacology, 6thedn, India: JP brothers medical publishers, 2008; pp613-614.

[20] Joseph, D. Pharmacotherapy, A pathophysiological approach, 8thedn, The McGraw Hill Companies, Inc. 2011; pp370.

[21] Wouters, K., Shiri-Sverdlov, R., van Gorp, P. J., van Bilsen, M., Hofker, M.H. Understanding hyperlipidemia and atherosclerosis: lessons from genetically modified ape and older mice.*Clin. Chem. Lab. Med.,* 2005; 43(5):470-9.

[22] Gao, W., He, H. W, Wang, Z. M., Zhao, H., Xiao-Qing Lian, X. Q., Wang, Y. S., Zhu, J., Jian-Jun Yan, J. J., Zhang, D. G., Zhi-Jian Yang, Z. J., Wang, L. S. Plasma levels of lipometabolism-related miR-122 and miR-370 are increased in patients with hyperlipidemia and associated with coronary artery disease. *Lipids Health Dis.,*2012; (11): 55.

[23] Nickolas, T.L., Radhakrishnan, J., Appel, G.B. Hyperlipidemia and thrombotic complications in patients with membranous nephropathy.*Semin.Nephrol*.; 2003; 23(4):406-11.

[24] Amarenco, P., Labreuche, J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol.,* 2009; 8 (5): 453 – 463.

[25] Belay, B., Belamarich, P. F., Tom-Revzon, C. The use of statins in pediatrics: knowledge base, limitations, and future directions. *Pediatrics*.,2006; 119(2): 370–380.

[26] Eiland, L. S., Luttrell, P. L. Use of statins for dyslipidemia in the pediatric population.*J. Pediatr. Pharmacol. Therap.,*2010; 15(3): 160–172.

[27] Sharma, M., Tiwari, M., Chandra, R. Bis [3-(4′-substituted phenyl) prop-2-ene] disulfides as a new class of antihyperlipidemic compounds.*Bioorg. Med. Chem. Lett.,* 2004; 14(21); 5347-5350.

[28] Mahley, R. W., Bersot, T. P. Drug therapy for hypercholesterolemia and dyslipidemia, In: Hardman, J.G.; Limbird, L. E. and Gilman, A. G., Goodman & Gilman's, The Pharmacological Basis of Therapeutics. 10thedn, New York: McGraw Hill, 2001; pp971–1002.

[29] Bellosta, S., Paoletti, R., Corsini, A. Atherosclerosis: Evolving vascular biology and clinical implications, safety of statins: focus on clinical pharmacokinetics and drug interactions. *Circulation.*,2004; (109): 50-57.

[30] Mills, E. J., Wu, P., Chong, G., Ghement, I., Singh, S., Akl. E. A., Eyawo, O., Guyatt, G., Berwanger, O., Briel, M. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials.*QJM*.,2011; 104(2):109-124.

[31] Russell, D. W. The enzymes, regulation, and genetics of bile acid synthesis, *Annu. Rev. Bioch.,*2003; (72): 137–174.

[32] Kishor, S., Kathiravan, M., Somani, R., Shishoo, C.H. The biology and chemistry of hyperlipidemia.*Bioorg. Med. Chem.,*2007; 15(14): 4674-4699.

[33] Arnold, M.A., Swanson, B.J., Crowder, C.D., Frankel, W.L., Lam-Himlin, D., Singhi, A.D., Stanich, P.P., Arnold, C.A. Colesevelam and colestipol: novel medication resins in the gastrointestinal tract. *Am. J. Surg. Pathol.;* 2014; 38(11):1530-7.

[34] Safeer, R. S., Lacivita, C.L. Choosing drug therapy for patients with hyperlipidemia. *Am. Fam. Physician.,* 2000; 61(11): 3371-82.

[35] Fruchart, J-C., Staels, B., Dallongeville, J., Auwerx, J., Schoonjans, K., Leitersdorf, E. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation,*1998; 98(19): 2088-2093

[36] Martin, G., Schoonjans, K., Lefebvre, A., Staels, B., Auwerx, J. Coordinate regulation of the expression of the fatty acid transporter protein (FATP) and acyl CoA synthetase (ACS) genes by PPARα and PPARγ activators. *J.Biol. Chem*., 1997;272:28210–28217.

[37] Caslake, M., Packard, C., Gaw, E., Murray, E., Griffin, B., Vallance, B., Shepherd, J. Fenofibrate and LDL metabolic heterogeneity in hypercholesterolemia.*Arterioscler.Thromb. Vasc. Biol*., 1993; (13): 702–711.

[38] Berthou, L., Duverger, N., Emmanuel, F., Langoue¨t, S., Auwerx, J., Guillouzo, A., Fruchart, J-C., Rubin, E., Dene`fle, P., Staels, B., Branellec, D. Opposite regulation of human versus mouse apolipoprotein A-I by fibrates in human apo A-I transgenic mice.*J. Clin. Invest*., 1996; 97(11): 2408 –2416.

[39] Carlson, L.A. Nicotinic acid: the broad-spectrum lipid drug. A 50th-anniversary review.*J. Intern. Med.,*2005;258(2):94-114.

[40] Nutescu, E. A., Shapiro, N. L. Ezetimibe: a selective cholesterol absorption inhibitor. *Pharmacotherapy*., 2003; 23(11): 1463-74.

[41] Denke, M., Pearson, T., McBride, P. Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome. *Diab. Vasc. Dis. Res.,* 2006; 3(2): 93–102.

[42] Altmann, S. W., Davis, H. R., Zhu, L. J. Niemann-Pick C1 Like one protein is critical for intestinal cholesterol absorption.*Science.,* 2004; 303(5661): 1201–1204.

[43] Pattis, P., Wiedermann, C. J. Ezetimibe-associated immune thrombocytopenia.*Ann. Pharmacother.,* 2008; 42(3): 430-433.

[44] Llaverías, G., Laguna, J. C., Alegret, M. Pharmacology of the ACAT inhibitor avasimibe (CI-1011). *Cardiovasc. Drug Rev.,*2003; 21(1): 33-50.

[45] López-Farré, A. J., Sacristán, D., Zamorano-León, J. J., San-Martín, N., Macaya, C. Inhibition of acyl-CoA cholesterol acyltransferase by F12511 (Eflucimibe): Could it be a new antiatherosclerotic therapeutic?*Cardiovasc. Ther.,*2008; 26(1): 65–74.

[46] Lee, k.,Cho, S. C., Lee, J. H.,Goo, J., Lee, S. Y.,Boovanahalli, S. K.,Koon, S., Yeo, Y. C., Lee, S-J., Kim, Y. K., Kim, D. H., Choi, Y.,Song, G-Y.Synthesis of a novel series of 2-alkylthio substituted naphthoquinones as potent acyl-CoA: Cholesterol acyltransferase (ACAT) inhibitors.*Europ. J. Med. Chem.,* 2013; 62: 515–525.

[47] Magnin, D. R., Biller, S. A., Wetterau, J., Robl, J. A., Dickson, J. K. Jr., Taunk, P., Harrity, T. W., Lawrence, R. M., Sun, C.Q., Wang, T., Logan, J., Fryszman, O., Connolly, F., Jolibois, K., Kunselman, L. Microsomal triglyceride transfer protein inhibitors: discovery and synthesis of alkyl phosphonates as potent MTP inhibitors and cholesterol-lowering agents.*Bioorg. Med. Chem. Lett.,* 2003; 13(7): 1337-1340.

[48] Goldberg, A. S., Hegele, R. A. Cholesteryl ester transfer protein inhibitors for dyslipidemia: focus on dalcetrapib.*Drug Des.Devel.Ther.,*2012; 6: 251–259.

[49] Shinkai, H. Cholesteryl ester transfer-protein modulator and inhibitors and their potential for the treatment of cardiovascular diseases.*Vasc.Health Risk Manag.,* 2012; (8): 323-331.

[50] Liu, C.-I., Jeng, W.-Y., Chang, W.-J., Ko, T.-P., Andrew Wang, A. H.-J. Binding modes of Zaragoza acid A to human squalene synthase and staphylococcal dehydrosqualene synthase.*J. Biol. Chem.,* 2012; 287(22): 18750–18757.

[51] Sharma, A., Slugg, P. H., Hammett, J. L., Jusko, W. J. Clinical pharmacokinetics and pharmacodynamics of a new squalene synthase inhibitor, BMS-188494, in healthy volunteers.*J. Clin. Pharmacol.,*1998; 38(12): 1116-1121.

[52] Ugawa, T., Kakuta, H., Moritani, H., Matsuda, K., Ishihara, T., Yamaguchi, M., Naganuma, S., Iizumi, Y., Shikama, H. YM-53601, a novel squalene synthase inhibitor, reduces plasma cholesterol and triglyceride levels in several animal species. *Br. J. Pharmacol.,*2000; 131(1): 63-70.

[53] Ma, Z., Chu, C.-H., Cheng, D. A novel direct homogeneous assay for ATP citrate lyase.*J. Lipid Res.,* 2009; 50(10): 2131-2135.

[54] Li, J. J., Wang, H., Tino, J. A.,Robl, J. A., Herpin, T. F., Lawrence, R. M., Biller, S.,Jamil, H., Ponticiello, R., Chen, L. 2-hydroxy-*N*-arylbenzenesulfonamides as ATP-citrate lyase inhibitors, *Bioorg. Med. Chem. Lett.,*2007; 17(11): 3208–3211.

[55] Cao, J., Zhou, Y., Peng, H., Huang, X., Stahler, S., Suri, V., Qadri, A., Gareski, T., Jones, J., Hahm, S., Perreault, M., McKew, J., Shi, M., Xu, X., Tobin, J. F., Gimeno, R. E. Targeting Acyl-CoA:diacylglycerolacyltransferase 1 (DGAT1) with small molecule inhibitors for the treatment of metabolic diseases.*J. Biol. Chem.,*2011; 286(48): 41838-41851.

[56] Horie, M., Sawasaki, Y., Fukuzumi, H., Watanabe, K., Lizuka, Y., Tsuchiya, Y., Kamei, T. Hypolipidemic effects of NB-598 in dogs. *Atherosclerosis.,*1991; 88(2-3): 183-192.

[57] Rozman, D., Monostory, K. Perspectives of the non-statin hypolipidemic agents.*Pharmacol. Ther.,*2010; 127(1): 19-40.