



CODEN [USA]: IAJPBB

ISSN : 2349-7750

INDO AMERICAN JOURNAL OF PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

Available online at: <http://www.iajps.com>

Review Article

AN INTRODUCTION TO HYPERLIPIDEMIA AND CURRENT TRENDS IN MANAGEMENT OF HYPERLIPIDEMIA – A REVIEW ARTICLE

J S Venkatesh¹, Upendra N², A S Gayathri Lakshmi³, Anandhu RS⁴, Alby Sunny⁵,
Anju Jayan⁶

¹Head of Department, Department of Pharmacy Practice, S.C.S College of pharmacy,
Harapanahalli, Karnataka, India., ²Assistant Professor, Department of Pharmacy Practice, S.C.S
College of Pharmacy, Harapanahalli, Karnataka, India., ³Pharm D Interns, CG Hospital,
Davangere, Department of Pharmacy Practice, S.C.S College of Pharmacy, Harapanahalli,
Karnataka, India.

Article Received: December 2022

Accepted: December 2022

Published: January 2023

Abstract:

Hyperlipidemia is a condition characterized by an elevation in one or more plasma lipids, such as triglycerides, cholesterol, cholesterol esters, phospholipids, and/or plasma lipoproteins, such as very low-density lipoprotein and low-density lipoprotein, along with a decline in high-density lipoprotein levels. Although excessive levels of low density lipoprotein (LDL) are regarded to be the greatest predictors of an increased risk of developing atherosclerosis, dyslipidemia can also refer to raised levels of total cholesterol (TC) or triglycerides, or low level of high density lipoprotein cholesterol (HDL). Hyperlipidemia is also the major precursor of lipid related ailment such as atherosclerosis, coronary artery disease and also involved in sudden death syndrome. Introduction, categories for hyperlipidemia, signs, complications, pathophysiology, and therapy.

Key words : Hyperlipidemia, Fibrates, Statins, Squalene epoxidase inhibitors, Lanosterol synthase inhibitors, Diacyl glycerol acyl transferase inhibitors.

Corresponding author:

J S Venkatesh,

Head of Department, Department of Pharmacy Practice,
S.C.S College of pharmacy, Harapanahalli, Karnataka, India.

QR code



Please cite this article in press J S Venkatesh et al, *An Introduction To Hyperlipidemia And Current Trends In Management Of Hyperlipidemia – A Review Article.*, Indo Am. J. P. Sci, 2023; 10(01).

INTRODUCTION:

Hyperlipidemia is characterized by abnormally high lipids (fats) in the blood. These lipids comprises of cholesterol, cholesterol esters, phospholipids and triglycerides. Increased level of these lipids are related to the development of atherosclerosis and cardiovascular disease including coronary heart disease (CHDs), cerebral stroke, myocardial infarction and renal failure^[1,2,3].

Atherosclerosis is the process through which arteries harden as a result of cholesterol buildup in the arterial wall, which results in artery narrowing. The presence of hyperlipidemia accelerates atherosclerosis and atherosclerosis-related disorders include coronary, cerebrovascular, and peripheral vascular diseases^[4]. Atherosclerosis is mostly brought on by hypercholesterolemia and hypertriglyceridemia, which are closely associated to ischemic heart disease (IHD)^[5]. IHD and the high death rate are strongly correlated. Over four million fatalities are brought on by plasma cholesterol levels that are even higher each year^[6].

Classification of hyperlipidemia:**Lipid type:**

Hypercholesterolemia-In this the level of cholesterol is elevated.

Hypertriglyceridemia-It is outlined as level of triglycerides elevated.

Causing factor:

1. Primary (Familial: hyperlipidemia) it is also called familial due to a genetic defect, it may be monogenic: a single gene defect or polygenic: multiple gene defects.

Type I–Raised cholesterol with high triglyceride levels.

Type II–High cholesterol with normal triglyceride levels.

Type III–Raised cholesterol and triglycerides.

Type IV–Raised triglycerides, atheroma and uric acid.

Type V–Raised triglycerides.

2. Secondary (Acquired hyperlipidemia) It is acquired because other conditions like diabetes, glomerular syndrome, persistent alcohol use, hypothyroidism, and the use of medications like corticosteroids, beta blockers, and oral contraceptives are what cause it. Pancreatitis can develop when secondary hyperlipidemia and severe hypertriglyceridemia coexist^[7].

Symptoms:

Generally, hyperlipidemia does not have any overt symptoms; instead, signs are typically found during ro

utine physicals or when a stroke or heart attack is imminent.

- Patients who have familial variants of the disease or high blood cholesterol levels may develop xanthomas, which are deposits of cholesterol under the skin, particularly around the eyes.
- Patients with high triglyceride levels may experience a variety of pimple-like lesions across their bodies [8].

Complications:

Atherosclerosis: Hyperlipidemia is the modifiable risk factor of atherosclerosis, which is one of the major cause of cardiovascular disease. In the walls of the large and medium arteries, atherosclerosis is a pathologic process marked by the buildup of lipids, cholesterol, and calcium as well as the creation of fibrous plaques^[9].

Coronary artery disease (CAD): The primary cause of coronary artery disease is atherosclerosis, it is characterized by lipid buildup and the development of fibrous plaques within the artery wall. As a result, the arteries that supply blood to the myocardium get narrower, which limits blood flow and leaves the heart with insufficient oxygen levels. Coronary atherosclerosis has been associated with an elevated lipid profile^[10].

Myocardial Infarction (MI): When one or more cardiac arteries are entirely or partially stopped from the flow of blood and oxygen, it can cause MI, which can harm or kill heart cells. Possible causes of the blockage include burst atherosclerotic plaque. According to research, nearly one-fourth of myocardial infarction survivors had high cholesterol^[11].

Ischemic Stroke : The fourth most common cause of mortality is a stroke. Strokes typically result from a blood clot blocking an artery or an atherosclerotic plaque fragment rupturing in a tiny brain conduit. Numerous clinical studies showed that reducing total cholesterol and low-density lipoprotein by 15% greatly decreased the chance of having the first stroke^[12].

Pathogenesis of hyperlipidemia:

Blood platelets and monocytes adhere to a vascular wall at the locations of endothelial injury in the early stages of hyperlipidemia. The proliferation of smooth cells in the intimal and medial lining of the vessel, collagen synthesis, cholesterol uptake, and the initial formation of the hyperlipidemic plaque are all caused by the release of mediators such as platelet-derived

growth factors. The acute syndromes of unstable angina, myocardial infarction, and sudden cardiac death are brought on by plaque ruptures^[13].

MANAGEMENT:

HMG- CoA -Reductase Inhibitors:

The first class of hypolipidemic medications is HMG-CoA-Reductase Inhibitors. The amount of cholesterol in the cell transcriptionally controls the production of the HMG enzyme and of the LDL receptors. The most popular medications used to prevent cardiovascular diseases (CVD) are these enzyme inhibitors, or statins, because it is widely recognised that elevated cholesterol levels are associated with CVD^[14,15]. The dose-based classification of statins for the prevention of atherosclerotic cardiovascular disease now separates them into two groups: high intensity statins, which drop LDL cholesterol by 50% of the baseline, and low intensity statins, which lower LDL cholesterol by 30%, only a 20% difference^[16].

Mechanism of Action:

These are HMG-coenzyme A reductase structural mimics. They work by slowing down the rate-limiting enzyme (HMG-coenzyme A reductase) involved in the liver's production of cholesterol. Statins considerably lower plasma levels of total cholesterol (TC), LDL, and ApoB by blocking this enzyme. In the meantime, statins also result in a slight reduction in plasma triglycerides and a slight rise in plasma HDL levels^[17].

Side Effects:

The most frequent side effects of statins are temporary gastrointestinal symptoms, headache, myalgia, and dizziness. Statins are typically tolerated well. Higher doses make these symptoms more prevalent, and switching to a different statin may alleviate them^[18].

Statins can cause myopathy, rhabdomyolysis, and a rise in serum transaminase. These toxins injure the kidney frequently and are hazardous to it. Furthermore, statins may result in cardiac cardiomyopathy^[19]. Recent clinical studies revealed a connection between statin use and a rise in type 2 diabetes^[20].

Fibric Acid Derivatives(Fibrates):

Fibrates, which include clofibrate, gemfibrozil, fenofibrate, and bezafibrate, are an antihyperlipidemic drug class that is often used. They significantly lower plasma triglycerides while very slightly lowering LDL sterols. The level of HDL cholesterol rises somewhat. The results of an experimental angiography revealed that fibrates have the greatest impact on reducing the

incidence of coronary artery disease and decreasing the progression of coronary atherosclerosis.

Mechanism of Action:

Fibrates primarily reduce triglycerides while also, though less significantly, raising HDL cholesterol levels. It affects the PPAR- receptor, causing the liver's -oxidation to production of triglycerides to decrease. Additionally, it enhances the activity of lipoprotein lipase, which results in a decrease in VLDL levels, an increase in HDL levels, and an increase in the clearance of residual particles^[21].

Side Effects:

Fibrates are typically thought to be well tolerated. gastrointestinal issues, myopathy, arrhythmia, skin rashes, and gallstones are possible side effects. In patients with liver and renal impairment, fibrates should be avoided^[22].

Nicotinic Acid derivatives(Niacin):

The oldest lipid-lowering medication used to treat hyperlipidemia is niacin, a water-soluble vitamin of type B, which has been shown to reduce cardiovascular morbidity and overall mortality. It lowers triglycerides, LDL cholesterol, and total cholesterol.

Mechanism of Action:

The main source of circulating free fatty acids, triglycerides lipid lysis, is decreased by niacin's inhibition of hormone-sensitive lipase. The liver often plays a significant lead role in the synthesis of triacylglycerol from these circulating fatty acids. Niacin prevents VLDL secretion as a result, which lowers LDL synthesis^[23].

Side Effects:

Low patient compliance rates have plagued niacin treatments. More than 75 percent of patients have an acute cutaneous flush, itching, headache, and some patients also experience nausea and abdominal pain as side effects. Niacin increases liver enzymes as well^[24].

Cholesterol Absorption Inhibitor (Ezetimibe):

The invention of ezetimibe, the first medicine in a class that blocks the absorption of cholesterol and phytosterols in the intestine, has improved the management of hypercholesterolemia. It has no impact on the plasma concentrations of the vitamins ADEK but hinders the absorption of sterol from the small intestine.

Mechanism of Action:

By blocking the Niemann-Pick C1-like 1 protein (NPC1L1), a human sterol transport protein, ezetimibe specifically reduces intestinal cholesterol absorption. This results in a reduction in the transportation of intestinal cholesterol to the liver. As a result, there is an improvement in the removal of cholesterol from the circulation^[25].

Side Effects

The most frequent side effects of ezetimibe, which is typically well tolerated, include headache, abdominal pain, and diarrhea. The liver enzymes alanine transaminase and aspartate transaminase appear to be affected by ezetimibe and to be elevated^[26].

Bile Acid Sequestrants:

Cholestyramine
Colestipol
Colesevelam

Mechanism of Action:

These drugs interfere with enterohepatic circulation by attaching to bile components in the digestive system and preventing their absorption from the gut^[27]. It causes a nearly ten-fold increase in bile acid production, which increases the conversion of cholesterol to bile. It somewhat raises HDL levels as well^[28]. Second-generation bile acid sequestrants like colesevelam and colestimide have been shown to also have a glucose-lowering impact, making them useful for those with diabetes mellitus^[29].

Side Effects:

The bile acid sequestrants have few systemic side effects because they are not absorbed in the gastrointestinal tract. Constipation, stomach pain, bloating, vomiting, heartburn, loss of appetite, indigestion, and upset stomach are some of the most typical gastrointestinal side effects.

New potential targets and treatments:**Acyl-CoA cholesterol acyl transferase inhibitors:**

The enzyme known as acyl-CoA cholesterol acyl transferase (ACAT) is responsible for converting intracellular cholesterol into cholesteryl esters. There are two isomers of ACAT, known as ACAT1 and ACAT2.

Microsomal triglycerides transfer protein (MTP) inhibitors:

The multifunctional microsomal triglyceride transfer protein (MTP) is involved in the regulation of cholesterol ester production, the transfer of neutral lipids between membrane vesicles, the creation of

CD1 antigen-presenting molecules, and other processes.

Cholesteryl ester transfer protein (CETP) Inhibitors:

The liver's CETP makes it easier for cholesteryl esters to move from proatherogenic apo lipoprotein B-containing lipoproteins like VLDLs and LDLs to anti-atherogenic HDLs. Additionally, the majority of research supported the notion that inhibiting CETP slows the development of atherosclerosis and provided evidence that CETP may have a proatherogenic role by participating in reverse cholesterol transport^[26].

Squalene synthase inhibitors:

Squalene synthase (SqS) catalyses the conversion of farnesyl pyrophosphate to squalene, which is the first committed step in the synthesis of sterols, one of which being cholesterol^[23].

Hydroxymethylglutaryl-CoA synthase Inhibitors:

HMG synthase catalyzes the chemical reaction that turn acetyl-CoA and acetoacetyl CoA to 3-hydroxy-3-methylglutaryl-CoA

ATP citrate lyase Inhibitors:

The main enzyme responsible for producing cytosolic acetyl-CoA and oxaloacetate is ATP citrate lyase (ACL). An essential stage in the production of fatty acids and cholesterol is the synthesis of cytosolic acetyl-CoA and oxaloacetate. Because of this, inhibiting ACL offers hope for the therapy of dyslipidemia.

Acyl coenzyme A: diacyl glycerol acyltransferase(DGAT):

DGAT is a microsomal enzyme that joins Acyl CoA to 1,2- diacylglycerol in the final step in triglyceride bio synthesis.

Lanosterol synthase Inhibitors:

The enzyme lanosterol synthase (LSS) catalyses the conversion of (S)- 2, 3-oxidosqualene to lanosterol, the first sterol in the pathway for making cholesterol^[26].

Recent Drugs For Hyperlipidemias:

Two novel non-statin medications that have shown promise in clinical trials to lower high cholesterol have received FDA approval . Nexletol and Nexlizet are used when combined with statins that have low or no side effects. The two new medications have some negative effects that are distinct from statin-related side effects^[30].

CONCLUSION:

According to the studies mentioned above, hyperlipidemia is a significant risk factor for cardiac disease. Modern medications, a diet food plan, home treatments, and regular exercise can all be used to treat hyperlipidemia. If diet management and exercise are carefully adhered to, the risk of hyperlipidemia, CVD, and many other diseases may be decreased.

REFERENCES:

- Xu QY, Liu YH, Zhang Q, Ma B, Yang ZD, et al. (2014) Metabolomic analysis of simvastatin and fenofibrate intervention in high-lipid diet-induced hyperlipidemia rats. *Acta Pharmacologica Sinica* 35: 1265.
- Smith SC, Jackson R, Pearson TA, Fuster V, Yusuf S, et al. (2004) Principles for national and regional guidelines on cardiovascular disease prevention: A scientific statement from the World Heart and Stroke Forum. *Circulation* 109: 3112-3121.
- Jacobson MS (1998) Heart healthy diets for all children: No longer controversial. *J Pediatr* 133: 1-2.
- Wells, G. B., D'ipiro, J., Schwinghammer, T., Hamilton, C. *Pharmacotherapy Handbook*, 7th edn, USA, The McGraw Hill Companies, 2007; pp98-108.
- Brouwers, M. C., Van Greevenbroek, M. M., Stehouwer, C. D., de Graaf, J., Stalenhoef, A. F. The genetics of familial combined hyperlipidaemia. *Nat. Rev. Endocrinol.*, 8(6): 352-62 (2012).
- 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.*, 2(2): 909-913 (2012).
- Joseph, D. *Pharmacotherapy, A pathophysiological approach*, 8th edn, The McGraw Hill companies, Inc. 2011; pp370.
- Tripathi, K. D. *Essentials of Medical Pharmacology*, 6th edn, India: JP brothers medical publishers, pp613-614 (2008).
- Wouters, K., Shiri-Sverdlov, R., van Gorp, P. J., van Bilsen, M., Hofker, M.H. Understanding hyperlipidemia and atherosclerosis: lessons from genetically modified apoe and ldlr mice. *Clin. Chem. Lab. Med.*, 43(5):470-9 (2005).
- 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 miR370 are increased in patients with hyperlipidemia and associated with coronary artery disease. *Lipids Health Dis.*, (11): 55 (2012).
- Nickolas, T.L., Radhakrishnan, J., Appel, G.B. Hyperlipidemia and thrombotic complications in patients with membranous nephropathy. *Semin. Nephrol.*; 23(4):406-11 (2003).
- Amarenco, P., Labreuche, J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol.*, 8 (5): 453 – 463 (2009).
- Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. *Natl Vital Stat Rep.* 2013 May 8;61(4):1-117. PMID: 24979972.
- Ray KK, Seshasai SR, Erqou S. Statins and all-cause mortality in high-risk primary prevention: a meta analysis of 11 randomized controlled trials involving 65,229 participants. *Arch Intern Med*, 2010, 170(12), 1024-31.
- Stone NJ, Robinson J, Lichtenstein AH, et al. ACC/AHA guideline on the treatment of blood cholesterol to reduce athero-sclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force 1.
- Hansen KE, Hildebrand JP, Ferguson EE, Stein JH. Outcomes in 45 patients with statin-associated myopathy. *Arch Intern Med* 2005;165:2671-6.
- Eiland, L. S., Luttrell, P. L. Use of statins for dyslipidemia in the pediatric population. *J. Pediatr. Pharmacol. Therap.*, 15(3): 160–172 (2010).
- 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*. 10th edn, New York: McGraw Hill, 2001; pp971–1002.
- Bellosta, S., Paoletti, R., Corsini, A. Atherosclerosis: Evolving vascular biology and clinical implications, safety of statins: focus on clinical pharmacokinetics and drug interactions. *Circulation.*, (109): 50-57 (2004).
- 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.*, 104(2):109-124 (2011).
- Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P, Pilote L, Genest J, Eisenberg MJ. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. *Am J Med*, 2009, 122(10), 962-962.

22. Kishor, S., Kathiravan, M., Somani, R., Shishoo, C.H. The biology and chemistry of hyperlipidemia. *Bioorg. Med. Chem.*, 15(14): 4674-4699 (2007).
23. Singh R, Nain S. A Mini-Review on Hyperlipidemia: Common Clinical Problem. *Interv Cardiol J* 2018;Vol.4 No.3:11. doi:10.21767/2471-8157.100081.
24. . Safeer RS, Lacivita CL. Choosing drug therapy for patients with hyperlipidemia. *Am Fam Physician*. 2000 Jun 1;61(11):3371-82. PMID: 10865931.
25. Altmann, S. W., Davis, H. R., Zhu, L. J. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science.*, 303(5661): 1201–1204 (2004).
26. Shattat GF. A review article on hyperlipidemia: types, treatments and new drug targets. *Biomedical and pharmacology journal*. 2015 May 3;7(1):399-409. Doi: <https://dx.doi.org/10.13005/bpj/504> .
27. Wong NN. Colesevelam: a new bile acid sequestrants. *Heart disease*, 2001, 3(1), 63-70
28. 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(1).
29. MD, PhD Franklin J. Zieve et al. Results of the glucose-lowering effect of WelChol study (GLOWS): A randomized, double-blind, placebo-controlled pilot study evaluating the effect of colesevelam hydrochloride on glycemic control in subjects with type 2 diabetes. *clinthera*.2007.01.003.
30. Pattis P, Wiedermann CJ. Ezetimibe-associated immune thrombocytopenia. *Ann Pharmacother*. 2008 Mar;42(3):430-3. doi: 10.1345/aph.1K614. Epub 2008 Feb 5. PMID: 18252832.