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EC MICROBIOLOGY
Review Article

Advances in Management Hyperlipidemia

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Received: December 15, 2021; **Published:** November 30, 2021

Abstract

Introduction: Hyperlipidemia is a modifiable condition where there is an increase in one or more of the plasma lipids such as triglycerides, cholesterol, cholesterol esters, phospholipids, and or plasma lipoproteins such as low-density lipoprotein and very-low-density lipoprotein with reduced high-density lipoprotein levels. This increase in plasma lipids is one of the leading risk factors associated with various cardiovascular diseases. The advancement in research management of hyperlipidemia has led to the new concepts of inverse correlation of low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein (non-HDL) cholesterol. The incidence of lipid disorders is evidently increasing worldwide most commonly in the western region. This is primarily because of unhealthy lifestyle choices or inherited risk factors or secondary causes like other diseases or medication. Cholesterol-lowering drugs are most commonly used for medication but are not fully adequate, the scenario with the current treatment options requires new therapies. Gene therapy is one such advancement employing targeted RNA technology that utilizes small interfering RNAs, antisense oligonucleotides to regulate target protein production whereas viral gene therapy provides functional therapeutic genes.

Aim of the Study: The purpose of the present review is to better understand the recent advances in the management of lipid disorders such as Hyperlipidemia and provide an overview of lipids and their metabolism.

Methodology: The review is a comprehensive research of PUBMED since the year.

Conclusion: With recent advancement and better diagnosis of the cause of increased plasma lipid levels enables appropriate decisions to be taken regarding its management. The treatment may include a variety of options starting from nutritional counseling understanding the risk factors associated with CHD, most commonly smoking and hypertension. Appropriate drug choices should be made based on the particular lipid abnormality associated with it. Patients with clinical vascular disease are treated more aggressively than others. The current advancement in the treatment of hyperlipidemia fills some of the gaps caused by drawbacks of old treatment modalities and provides better knowledge for the same condition.

Keywords: *Hyperlipidemia; Dyslipidemia; Pharmacological Management; Recent Advances*

Introduction

Hyperlipidemia is a medical condition characterized by an increase in one or more plasma lipids such as triglycerides, cholesterol, cholesterol esters, and phospholipids and or plasma lipoproteins such as very-low-density lipoprotein and low-density lipoprotein and reduced high-density lipoprotein levels and is one of the major risk factors in various cardiovascular diseases (CVDs) which accounts for one-third of total deaths around the world. CVDs turned out to be the main cause of morbidity and mortality worldwide by the year 2020 [1,2].

Hypertriglyceridemia and hypercholesterolemia are the main causes of atherosclerosis which in turn is strongly associated with ischemic heart disease (IHD). There is a strong correlation between ischemic heart diseases and the high mortality rate [3,4].

Due to the accumulation of cholesterol in the arterial wall which causes narrowing of the arteries, this process of hardening of arteries is known as atherosclerosis. It is very well known that atherosclerosis and associated disorders such as cerebrovascular and peripheral vascular diseases are accelerated by the presence of high plasma lipid [5].

In the state of hyperlipidemia, there is increased oxidative stress causing major production of oxygen free radicals. Oxygen-free radicals cause oxidative modifications in low-density lipoproteins, which in turn causing initiation and progression of atherosclerosis and other associated cardiovascular diseases. These atypical changes in the synthesis, processing, and catabolism of lipoprotein causes severe hypercholesterolemia, hypertriglyceridemia or elevated level of lipid plasma [6].

Lipid metabolism

Plasma lipoproteins

Composition and structure

Lipoproteins are aggregates mainly composed of lipids and proteins. This basic structure allows lipids compatibility with the aqueous body fluids [7].

Lipoproteins composed of

1. Non-polar lipids (cholesteryl esters and triglycerides).
2. Polar lipids (phospholipids and un-esterified cholesterol).
3. Specific proteins known as apolipoproteins are amphiphilic proteins that bind to both lipids and the plasma.

Cholesteryl ester and triglyceride are centered in the core which increases the size of lipoprotein, its density also increases proportionally to the protein content present [7].

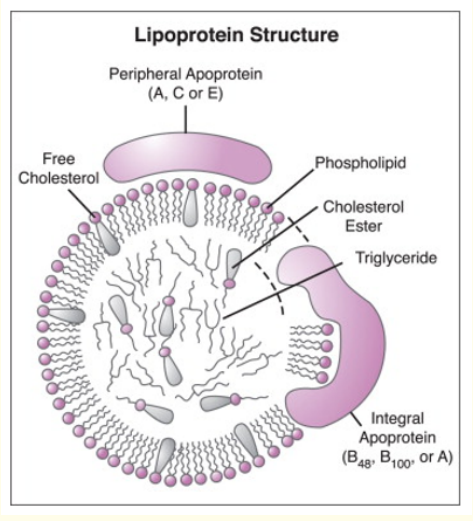

Figure 1: *Showing basic structure of lipoprotein [8].*

Classification of lipoprotein

1. Chylomicrons (CM)
2. Very low-density lipoproteins (VLDL)
3. Low-density lipoproteins (LDL)
4. Intermediate-density lipoproteins (IDL)
5. High-density lipoproteins (HDL).

Function of lipoprotein

Plasma lipoproteins are essential for lipid solubilization so as to transport triglycerides which are an important source of energy, synthesized and absorbed to all those places of utilization and storage. It also aids in the transport of cholesterol between different places of absorption, synthesis, catabolism, and elimination [9].

Enzymes involved in lipoprotein metabolism [7]

Enzymes	Function
Lipoprotein lipase (LPL)	Hydrolysis of triglyceride (TG) into two free fatty acids and mono-acyl-glycerol [11].
Hepatic lipase (HL)	Hydrolyzes phospholipids and triglycerides of plasma lipoproteins and facilitating lipoprotein absorption by cell surface receptors [12].
Lecithin cholesterol acyl-transferase (LCAT)	Converts free cholesterol into cholesteryl esters [13].
Cholesteryl ester transfer protein (CETP)	Accelerates the transferring of esterified cholesterol esters (CE) from HDLs to chylomicrons, VLDL, and LDL, in exchange for triglyceride [14].
Microsomal triglyceride protein (MTP)	Protein 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 [15].
Acyl Co-A transferase (ACAT)	Cellular cholesterol homeostasis in various tissues and prevents the toxic accumulation of excess cholesterol in a cell [16].

Lipid metabolism

Most dietary fats are absorbed from the lumen of the intestine into the lymph of the intestine and packed into chylomicrons. Later lipoproteins move into the bloodstream where the enzyme endothelial lipoprotein lipase hydrolyzes the triglycerides into glycerol and non-esterified fatty acids. The remnant of chylomicrons is absorbed in the liver and packaged with cholesterol, cholesteryl esters, and ApoB100 to form very-low-density lipoprotein (VLDL). When releasing VLDL into the bloodstream it will be converted into low-density lipoprotein (IDL) by the enzyme lipoprotein lipase and hepatic lipase, where apolipoproteins and phospholipids are transferred back to HDL. By cholesterol transport pathway, the peripheral cholesterol is returned to the liver using HDLs which are originally manufactured by the liver and released into the blood. In the blood, HDL cholesterol is esterified by the enzyme LCAT to cholesteryl ester which is later hydrolyzed to cholesterol and extracted from the body as bile acid [10].

Hyperlipidemia classification

Hyperlipidemia can be classified as shown in below table [11].

Primary	Secondary
• Familial Hyperlipidemia occurs due to genetic defects. • Either monogenic i.e. a single gene defect or polygenic i.e. multiple gene defects. • It can be resolved into one of the following lipoprotein patterns such as: 1. Familial hyperchylomicronemia (Type- I) 2. Familial hypercholesterolemia Or Polygenic hypercholesterolemia (Type- IIa) 3. Familial combined hyperlipidemia (Type- IIb) 4. Familial dysbetalipoproteinemia (Type- III) 5. Familial hypertriglyceridemia (Type- IV) 6. Endogenous hypertriglyceridemia (Type-V)	• It is an acquired disorder because it is secondary to other diseases such as diabetes, nephritic syndrome, chronic alcoholism, hypothyroidism, and with use of drugs like corticosteroids, beta-blockers, and oral contraceptives. • It is very well known that secondary hyperlipidemia along with hypertriglyceridemia can cause pancreatitis. • The main risk factors and causative factors include changes in lifestyle habits, poor dietary habits which contain intake of more saturated fat and cholesterol, exceeding to be more than 40% of total calorie uptake.

Diagnosis

After a significant increase in plasma lipid is detected, it is important to diagnose the causative factor, whether the condition is secondary to primary abnormality. The major secondary causes are hormonal factors such as pregnancy, hypothyroidism, diabetes; liver diseases (biliary obstruction), nutritional factors such as obesity, anorexia, alcohol abuse; renal dysfunction; iatrogenic causes such as high dose thiazide diuretics, P-Adrenergic receptor antagonists* which lack a-blocking effects, etc [12].

Diagnosis can be made by identifying clinical symptoms and signs and investigations may include tests such as blood glucose, thyroid function, renal and liver function, to be performed routinely. Only after excluding secondary causes, it is presumed that primary hyperlipidemia is present. Metabolic and genetic abnormalities underlying these conditions should be ruled out [12].

Treatment and advances

Pharmacological treatment for hyperlipidemia

Since hyperlipidemia is strongly associated with a high risk of cardiovascular disorder, drug therapy along with modifying lifestyle is necessary. Monotherapy is usually effective and combination therapy needed a better approach. Following major classes for drugs is recommended along with new approaches [11].

Class of Drug	Mechanism	Side Effects
1. Statins - 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors E.g. Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Atorvastatin and Rosuvastatin [13].	They are structural analogs of HMG-coenzyme- A reductase and act by inhibiting the rate-limiting enzyme (HMG-coenzyme-A reductase)	Transient gastrointestinal symptoms, headache, myalgia, dizziness, myopathy, rhabdomyolysis, and increase serum transaminase often cause kidney damage, cardiomyopathy
2. Bile acid sequestrants - it is the main pathway of cholesterol catabolism in the liver. E.g. cholestyramine, colestipol, colestimide and colesevelam [14].	They are positively charged resins that bind to the negatively charged bile acids in the intestine to form an insoluble complex that is not absorbed and hence excreted.	Poor patient tolerance, gastrointestinal disturbances- constipation, nausea, indigestion, bloating and flatulence, osteoporosis due to calcium loss (long term therapy)

3. Fibrates: Fabric acid derivatives - play an important role in slowing the progression of coronary atherosclerosis disease E.g. clofibrate, gemfibrozil, fenofibrate, and bezafibrate [15].	4 mechanisms are known: • Stimulation of lipoprotein lipolysis • Increase hepatic fatty acid uptake and reduction of hepatic triglyceride production. • Increase in HDL production and stimulation of reverse cholesterol transport. • Increase removal of LDL particles	Gastrointestinal symptoms, myopathy, arrhythmia, skin rashes, and gallstones. Fibrates are contraindicated in patients with liver and renal dysfunction.
4. Niacin: Nicotinic acid derivatives - is a water-soluble vitamin of type B and one of the oldest lipid-lowering agents [16].	It inhibits hormone-sensitive lipase which decreases triglycerides lipolysis.	Cutaneous flush, itching, headache, nausea, and abdominal discomfort
5. Ezetimibe - Selective cholesterol absorption inhibitor [17].	Block the Niemann-Pick C1-Like 1 protein (NPC1L1) by inhibiting the absorption of cholesterol in the small intestine, causing a decrease in the delivery of intestinal cholesterol to the liver.	headache, abdominal pain, and diarrhea, etc.
New potential targets and treatments [7]		
Acyl-CoA cholesterol acyltransferase inhibitors (ACAT)	Catalyzes the conversion of intracellular cholesterol into cholesteryl esters. It has two isomers - ACAT1(foam cell formation in the arterial wall and the development of atherosclerosis- have an anti-atherogenic effect) and ACAT2 (reduce cholesterol absorption in the intestine.)	
Microsomal triglyceride transfer protein (MTP) inhibitors	Performs by multiple functions such as: Transferring neutral lipids between membrane vesicles, antigen-presenting molecules, the biosynthesis of CD1, and the regulation of cholesterol ester biosynthesis	
Cholesteryl ester transfer protein (CETP) inhibitors	In the liver, it facilitates the transfer of cholesteryl esters from anti-atherogenic HDLs to pro-atherogenic lipoprotein B, by involving reverse cholesterol. E.g. Dalcetrapib and anacetrapib	
Squalene synthase inhibitors	Catalyzes farnesyl pyrophosphate to form squalene, needed for the synthesis of sterol (cholesterol)	
ATP citrate lyase inhibitors (ACL)	ATP citrate lyase (ACL)is an enzyme that synthesizes cytosolic acetyl-CoA and oxaloacetate, represent an important step in the synthesis of fatty acids and cholesterol. Hence inhibition of ACL is a promising strategy in the treatment of hyperlipidemia.	
Acyl coenzyme-A: diacylglycerol acyltransferase (DGAT)	It is an enzyme that joins Acyl CoA to 1,2-diacylglycerol in the last step of the synthesis of triglyceride. Two forms of DGAT enzymes are recognized - DGAT-1 and DGAT-2. DGAT-1 inhibition is known to be a good treatment option in hyperlipidemia. The compound which is a potent inhibitor of DGAT-1 is T863.	

PCSK9 inhibitors

PCSK9 is an enzyme controlled by the PCSK9 gene found on chromosome 1 in the human body. Liver cells produce PCSK9. It is a new approach in the management of hyperlipidemia. The mechanism of action is by the release of proprotein convertase subtilisin/Kexin. There are various methods by which PCSK9 can be inhibited such as small interfering RNA (siRNA), vaccines, monoclonal antibodies, antisense oligonucleotides, small molecules, mimetic peptides, and adiponectin. Most of these methods are in their phase-1 trials with an exception of monoclonal antibodies and small interfering RNA which are currently in phase-3 trials. Among all the current approaches,

monoclonal antibodies are the most effective approach in inhibiting PCSK9 and reduce LDL levels in the drugs belong to this class include bococizumab, alirocumab (Praluent), and evolocumab (Repatha) [18].

Another approach is the use of siRNAs which constitute 20-30 nucleotides in an RNA molecule. The inhibition is achieved by interfering with the specific genes' appearances that are complemented by nucleotide series. Adnectins/monobodies have also shown promising results in inhibition of PCSK9 to reduce the 48% chance of LDL-C in the body in hyperlipidemic patients because of their small size compared to monoclonal antibodies. The absence of PCSK9 can cause a person to have LDLC levels of about 15 mg/dL [18].

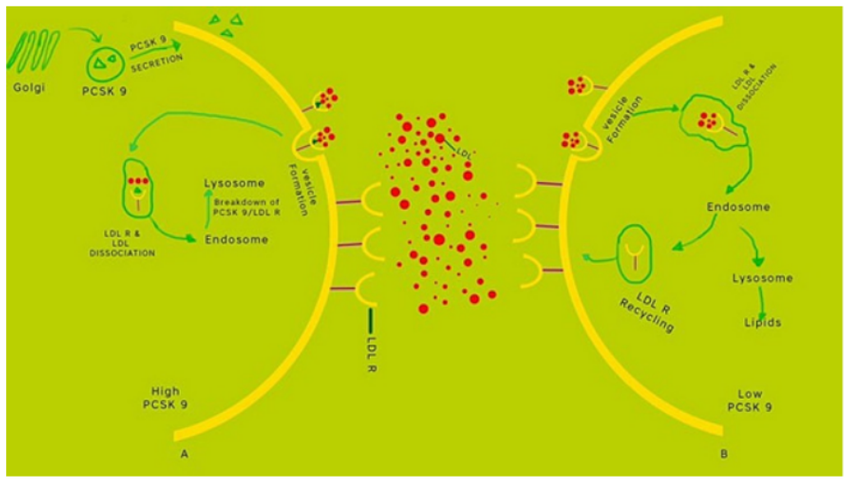

Figure 2: *Mechanism of PCSK9 PCSK9: proprotein convertase subtilisin/Kexin type [18].*

Small interfering RNAs

Small interfering RNAs (siRNA) are double-stranded RNAs that inhibit the target protein production by cleaving the target mRNA. It incorporates into a cytoplasmic RNA-induced silencing complex (RISC) to complementary bind target mRNA and activates its cleavage. In this way the mRNA is degraded and not available for protein translation, resulting in the decreased levels of a particular target protein synthesis. siRNAs when conjugated with a ligand such as N-acetylgalactosamine (GalNac) resulting in better hepatic cellular. One such drug is Inclisiran, which targets PCSK9 and causes its inhibition [19].

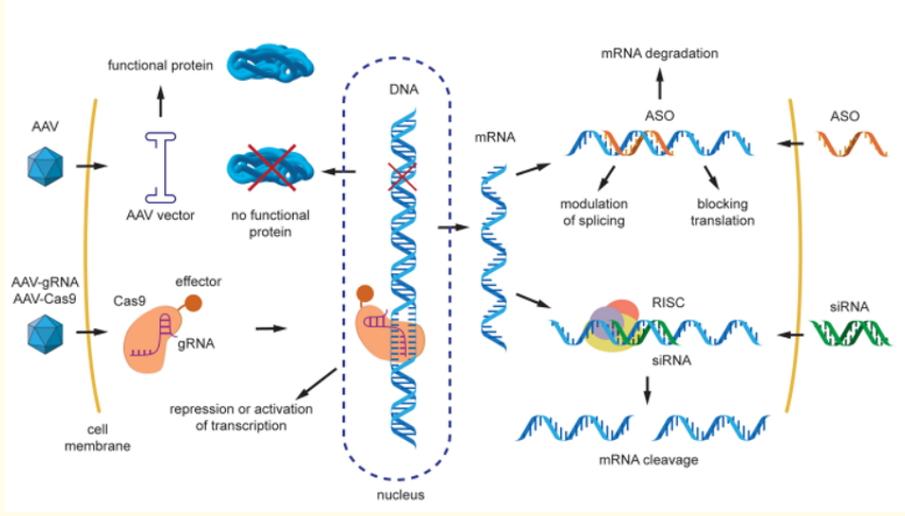

Figure 3: *RNA therapeutics relies on targeting mRNA with siRNAs or ASOs for degradation hence reducing the targeted protein and subsequently affecting circulating lipoprotein levels [19].*

Antisense oligonucleotides

Another approach to target RNA is antisense oligonucleotides (ASO). The short single-stranded nucleic acid bind to target mRNA by Watson Crick interaction and causing changes in process of translation. ASO can cleave target mRNA enzymatically, may change the splicing pattern or alter the function of rRNA. ASO when modified can cause effective cell delivery and distribution (GalNac). The drug available is Mipomersen (administered subcutaneously at 200 mg weekly) (KYNAMRO®, Kastle Therapeutics), an FDA-approved *ApoB* targeting drug, IONIS-APOCIIILrx is another *ApoC3* targeting drug that is effective in Hypertriglyceridemia [19].

Conclusion

Cardiovascular diseases remain one of the key causes of death, especially in the western world and hyperlipidemia is one of the key risk factors. Hence along with conventional drug therapy, new novel approaches and gene modifying agents are essential in better control of hyperlipidemia and its management. The development of novel RNA-based therapeutics and viral gene therapy is providing more specific and potent therapies, which might provide powerful treatment for patients that have not benefitted from the traditional therapies.

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Volume 17 Issue 12 December 2021