



## **Hyperlipidemia Condition and Novel-Drug Therapies: A Overall Study**

**CH. K. V. L. S. N. Anjana Male<sup>1</sup>, V. Swathi<sup>1</sup>, D. Sai Kumar<sup>1\*</sup>, Karishma<sup>1</sup>  
and Md. Shuaib Yunus<sup>1</sup>**

<sup>1</sup>Nirmala college of pharmacy, Atmakuru, Mangalagiri-522503, Andhra Pradesh, India.

### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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### **ABSTRACT**

Hyperlipidaemia is an condition that increases the chance of coronary heart disease (CHD) and atherosclerotic disease (ASHD) in blood vessels. Hyperlipidaemia occurs in response to smoking, obesity, sedentary lifestyle, and other risk factors to extend CHD. Cardiovascular disease (CVD) is the reason for death.

Hyperlipidaemia is divided into two broad classifications: Primary (familial) and Secondary (acquired).

Primary hyperlipidemia has been generated by hereditary defects and climatic factors or by undisclosed mechanisms. Secondary hyperlipidemia concern to the metabolic disorders linked with the diabetes mellitus, liver complication, thyroid, and kidney complications. Hyperlipidemia also refers to as elevated levels of lipids within the blood. Circulating lipid are carried in lipoproteins that transport the lipids to varied tissues for energy use, lipid deposition, hormone production, and steroid formation. The lipoprotein consists of esterified and unesterified cholesterol, triglycerides, phospholipids, and protein. The general public who have hyperlipidemia experience no symptoms. Hyperlipidemia is most oftenly correlated with high-fat diets, a stationary lifestyle, obesity and diabetes mellitus. Four different classes of cholesterol-lowering drugs namely, statins, niacin, resins, and fibrates are available to treat hyperlipidemia; however, statins are now considered to be the first line therapy. The preventable causes of hyperlipidemia can include: Smoking, Being

\*Corresponding author: E-mail: [saikumardarsiguntla@gmail.com](mailto:saikumardarsiguntla@gmail.com);

overweight, Physical inactivity, Steroid use, Alcohol consumption & Diet high in saturated fat, & cholesterol such as cheese, meat, fried & processed foods and egg yolk. The treatment of hyperlipidemia includes statins, bile acid sequestrants, fibric acids, niacin, and cholesterol absorption inhibitors.

There are some of the novel drugs which are selected for the treatment of hyperlipidemia which includes: Evolocumab, Alirocumab, Bempedoic acid, Lomitapide, Evinacumab, and Sebelipase alfa.

*Keywords: Hyperlipidemia; coronary cardiopathy; atherosclerotic disease; blood vessels.*

## 1. INTRODUCTION

Hyperlipidemia is an condition that increases the chance of coronary heart disease and atherosclerotic disease (ASHD) in blood vessels. Hyperlipidemia occurs in response to smoking, obesity, sedentary lifestyle, and other risk factors to extend CHD [1].

Hyperlipidemia also refers to as elevated levels of lipids within the blood. Circulating lipid are carried in lipoproteins that transport the lipids to varied tissues for energy use, lipid deposition, hormone production, and steroid formation. The lipoprotein consists of esterified and unesterified cholesterol, triglycerides, phospholipids, and protein. The general public who has hyperlipidemia experience no symptoms [2].

Coronary heart disease is that the leading reason behind morbidity and mortality within the elderly population. Approximately 80% of all deaths caused by CHD occur during this age bracket. Almost of men (25%) and women (42%) older than 65 years have abnormal serum total cholesterol level greater than 240 mg/dL. At menopause, cholesterol increases gradually due to declining oestrogen levels and weight gain [2].

Total cholesterol levels increase in men after the onset of puberty until 50 years old, followed by gradual line until 70 years of age. Serum cholesterol concentration then declines slightly. The foremost important factor for cholesterol could also be weight change [2].

In women, the serum cholesterol concentration is slightly on top of in men before 20 to 25 years old. Between 25 to 55 years of old, the serum cholesterol increases. Cholesterol levels in women are capable those of men between 55 and 60 years old [2].

## 2. EPIDEMIOLOGY

Cardiovascular disease (CVD) is the reason for death. 38% of adults plagued by CVD have risk

factors like elevated serum lipid levels, diabetes, and high pressure level. It known that atherosclerosis starts at a young age, and therefore the number of young individuals developing atherosclerosis are on the increase, especially children with risk factors like familial hypercholesterolemia (FH) [3].

In the past few years, hyperlipidemia in children and adolescents has been increasing, and also the American Heart Association (AHA) identifies these children as being at higher risk of developing premature atherosclerosis. As of now, 13% of adolescents have increased cholesterol levels, up from 10%. FH is an autosomal condition due to mutations within the lipoprotein (LDL) receptor gene, and it occurs in 1 in 274 to 1 in 500 individuals [3].

Familial hypercholesterolemia is further classified into two types, namely, Homozygous familial hypercholesterolemia (HoFH) and Heterozygous familial hypercholesterolemia (HeFH). Patients with FH have an elevated plasma cholesterol level (>140 mg/dL [ $>3.6$  mmol/L]) throughout life and an increased risk of cardiovascular events, including stroke and coronary failure. In these patients, atherosclerosis can start as early as 10 years old and can need treatment with statins to prevent the progression. The incidence of coronary heart disease (CHD) is low during childhood in patients with HeFH, but the danger of early CVD and early events is increased by 50 years old in 50% of men and 25% of women [3].

Familial combined hyperlipidemia (FCHL) is one amongst the genetic causes of hyperlipidemia; it is said to be 3 times more prevalent than FH and occurs in 0.50% to one percent of the population [3].

In children and adolescents aged 12 to 19 years, the prevalence of hypertriglyceridemia (TG level >150 mg/dL [ $>1.7$  mmol/L]) is approximately 10.7%. But 0.2% have severe hypertriglyceridemia (TG level >500 mg/dL [ $>5.7$

mmol/L]). Causes of primary hypertriglyceridemia include lipoprotein lipase (LPL) deficiency. Type V hyperlipoproteinemia is rare and accounts for five of patients with hypertriglyceridemia [3].

### 3. ETIOLOGY

Hyperlipidemia is divided into two broad classifications: Primary (familial) or Secondary (acquired) hyperlipidemia. Primary hyperlipidemia derives from genetic disorders that a patient may inherit through birth, while secondary hyperlipidemia originates from an underlying etiology, such as an unhealthy diet, medications (amiodarone, glucocorticoids), hypothyroidism, uncontrolled diabetes, and/or a poor lifestyle [4].

Familial dyslipidemias, are much rarer, and the reason behind the changes in the blood lipid level and are also responsible for cardiovascular damages at an early possible age [4].

Some causes of hypercholesterolemia and/or elevated triglycerides are diabetes mellitus, renal failure, nephrotic syndrome, hypothyroidism, sedentary lifestyle. Other causes may be the administration of certain drugs like thiazide diuretics, beta-blockers, estrogen-progestin contraceptives, and antiretrovirals [4].

Before starting treatment for any lipid abnormality, consideration of secondary causes of hyperlipidemia is required because these can result in atherogenic lipoprotein with increased risk for coronary heart disease (CHD) or severe hypertriglyceridemia [5].

List of possible causes of secondary hyperlipidemia is given below (Table 1).

### 4. CLASSIFICATION OF HYPERLIPIDEMIA

Classifications of hyperlipidemia are based on abnormalities of lipoproteins (Chart 1). The National Cholesterol Education Panel (NCEP) created a standard using lipid levels in 2001 that is still the most commonly used clinical classification (Table 2) [6].

Hyperlipidemia will be broadly classified as an elevation of cholesterol, isolated elevated TG, or elevation of both. The causes could also be genetic, environmental, or both. (Table 3) may be a list of genetic causes of hyperlipidemia with a short clinical description. In general, to a genetic syndrome include very high cholesterol levels (>300 mg/dL), very high TG levels (>500 mg/dL), xanthomas, strong case history of hyperlipidemia or early CVD, or absence of required reply to most curative doses of lipid-lowering agents [6].

**Table 1. Secondary causes of hyperlipidemia**

Condition	Lipid Abnormality	Change in HDL
Excess alcohol	Hypertriglyceridemia	Elevated HDL
Anabolic steroids	Hypercholesterolemia	Low HDL
Cholestasis	Hypercholesterolemia (Lp-X)	Low HDL
Diabetes	Hypertriglyceridemia	Low HDL in NIDDM
Oestrogen therapy	Hypertriglyceridemia	Increased HDL
Hypothyroidism	Hypercholesterolemia	Low HDL
Nephrotic syndrome	Hypercholesterolemia	Low HDL
Thiazide diuretics	Hypertriglyceridemia	Low HDL
Weight gain	Hypertriglyceridemia	Low HDL
Chronic renal failure	Hypertriglyceridemia	Low HDL

*HDL = High-Density Lipoprotein; NIDDM = Non-Insulin Dependent Diabetes Mellitus; Lp-X – Lipoprotein-X*

**Chart 1. Classes of apolipoproteins**

- Chylomicrons: Triglyceride (TG)-rich carrier of dietary fats.
- Very Low Density Lipoprotein (VLDL): TG-rich carrier of hepatic synthesized TGs.
- Intermediate-Density and Low-Density Lipoprotein (IDL and LDL): Cholesterol-rich remnant particles derived from lipolysis of triglycerides in VLDL.
- High-Density Lipoprotein (HDL): Cholesterol-rich particle that transports cholesterol to liver for disposal or recycling.

**Table 2. Classification of hyperlipidaemias as defined by the NCEP ATP-III**

<b>Low-density lipoprotein cholesterol</b>	
<100	Optimal
100 – 129	Near or above optimal
130 – 159	Borderline high
160 – 189	High
>190	Very high
<b>Total cholesterol</b>	
<200	Desirable
200 – 239	Borderline high
>240	High
<b>High-density lipoprotein cholesterol</b>	
<40	Low
>60	High
<b>Triglycerides</b>	
<150 Normal	
150 – 199	Borderline high
200 – 499	High
>500	Very high

**Table 3. Genetic causes of hyperlipidemia**

<b>Causes</b>	<b>Clinical Features</b>
<b>Isolated cholesterol elevation</b>	
Genetic familial hypercholesterolemia	Relatively common (1 in 500 heterozygote); TC exceeds 300 mg/dL, family history of elevated TC common, associated with tendon xanthomas, premature (20-40 y old) CVD is common. Homozygotes are rare, but have TC >600 and usually die of MI before the age of 20.
Familial defective apolipoprotein B100	Increases LDL and has a phenotype that is different from that of FH, including increased susceptibility to CHD.
Mutations associated with elevated LDL levels	Rare and isolated; suspect if elevated LDL unresponsive to treatment.
Elevated plasma lipoprotein(s)	Relationship to CVD unclear, studies contradictory.
Polygenic hypercholesterolemia	No family history, no physical manifestations such as xanthomas, exact cause is unknown.
Lp (X)	Associated with obstructive hepatic disease, CVD risk of unclear.
Sitosterolemia	Rare; LDL levels normal to high, xanthomas develop in childhood.
<b>Elevated cholesterol and triglycerides</b>	
Combined (familial) hyperlipidemia	May occur with family history of hyperlipidemia and Type 2 diabetes
Hepatic lipase deficiency	Rare disorder with very high cholesterol concentration and triglyceride concentration.
<b>Isolated triglyceride elevations</b>	
LPL deficiency	Results in elevated chylomicrons, and extreme high triglycerides may lead to pancreatitis.
ApoCII deficiency	Apolipoprotein is an activator of LPL. Its absence may cause deficiency to LPL
Familial hypertriglyceridemia	Defect is over production of VLDL triglycerides by the liver.

*Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; FH, familial hypercholesterolemia; LDL, low-density lipoprotein; LPL, Lipoprotein Lipase; TC, total cholesterol; VLDL, very low density lipoprotein*

## 5. TYPES OF HYPERLIPIDEMIA

Hyperlipidemia in young one will be divided into 2 classes: primary and secondary. Primary origin of elevated TG volume involve hereditary defects in lipid synthesis and metabolism, and secondary origin are a result of medical state such as badly curbed diabetes, nephrotic syndrome, obesity, and hepatitis.

Primary causes will be further divided into 4 different disorders: LPL deficiency, familial combined hyperlipidemia, familial hypertriglyceridemia, and dysbeta lipoproteinemia (Table 4) [7]

## 6. COMPLICATIONS

Hyperlipidemia complications occur when there is an untreated or undertreated hyperlipidemic condition. All types of vascular disease which include coronary artery disease, peripheral artery disease, cerebrovascular accidents, aneurysms, type II diabetes, hypertension, and in some cases even death occurs as complication of hyperlipidemia [8].

Myopathy, renal injury, arthralgia, pains, nausea, elevated liver enzymes, diarrhoea occurs as complications of statin therapy [8].

## 7. PATHOGENESIS [8]

Hyperlipidemia is identified by increased amount of lipids that can be begin due to hereditary or acquired disorders. In grown-ups, hyperlipidemia has been appeared to be a vital key factor in developing CVD. Atherosclerotic procedure occur early in youth, with fatty streaks reporting in the aortas and coronary arteries of patients as young as 10 years old [9]

## 8. OVERVIEW OF LIPID METABOLISM

The utilize of lipids as an power source launch with the gulp of dietary fats, which are broken up by bile acids and consumed by the intestinal lumen. In the intestinal cell, free fatty acids are combined with a glycerol molecule to form triglycerides, and cholesterol is made into a cholesterol ester by the enzyme acyl-coenzyme A (Cholesterol Acyltransferase). The TG's and cholesterol esters are then combined with apolipoprotein (apo) B-48 to form chylomicrons. Then the chylomicrons enter the systemic circulation through the lymphatic system and acquire apoCII and apoE from high-density

lipoprotein (HDL), which are first synthesized in the liver cells or the intestines from chylomicron and VLDL leftovers. The chylomicron then binds to LPL, a receptor found on endothelial cells, to hydrolyse TGs and deposit fatty acids in peripheral tissues as a source of energy. Triglycerides and cholesterol esters are combined endogenously to build VLDL, which stick to LDL receptors via exterior apoB-100 and apoE and uses LPL for transforming to median-density lipoprotein.[9]

## 9. PATHOGENIC FACTORS

Hyperlipidemia can be divided into primary and secondary subtypes. Primary hyperlipidemia has been generated by hereditary defects and climatic factors or by undisclosed mechanisms. Secondary hyperlipidemia concern to the metabolic disorders linked with the diabetes mellitus, liver complication, thyroid, and kidney complications.[10]

## 10. GENETIC'S ARE THE MAIN PATHOLOGICAL CAUSE OF CONGENITAL HYPERLIPIDEMIA

There are numerous genes linked to lipid metabolism, involving ApoA, ApoB, ApoC, ApoE, and alike genes; LDL-R (Low-Density Lipoprotein Receptor), lipoprotein esterase gene; and ATP binding cassette transporter gene. When a one gene or various genes are heritable, an independent may be exposed to grow inborn hyperlipidemia. ApoE plays an crucial role in blood lipid metabolism. It is tangled in the synthesis, secretion, metabolism, and transport of lipoprotein [10].

Familial hypercholesterolemia has been occurred by a alteration in the LDL-R gene. LPL is a key enzyme for lipid metabolism, which can hydrolyze the ester bonds of triacylglycerol to produce glycerol and free fatty acids.

ATP binding cassette transporter is an important protein located on the cell membrane to regulate the outflow of cholesterol, and it is the medium for intracellular cholesterol transport to extracellular transport [10].

The shift cholesterol is reversely transferred to the liver via high-density lipoprotein (HDL) to be metabolized into bile acid, and eventually left-out in the form of feces. Therefore, it is commonly believed that mutations in the single or multiple

genes will lead to the occurrence of hyperlipidemia [10].

## **11. METABOLIC DISORDERS – FOR SECONDARY HYPERLIPIDEMIA**

Metabolic diseases often causes the occurrence of hyperlipidemia, such as diabetes, low thyroid gland function, liver disease, kidney disease, hypertension, and obesity. Insulin is also an important factor in regulating fat metabolism, which will reduce lipolysis enzyme activity and HDL metabolism activity, resulting in triglyceride problems. At early stage of diabetes, the plasma insulin level is very high, which leads to the excessive synthesis of fat in body, causing endogenous high blood TC and TG [10].

In the delayed phase of primary acidity cirrhosis, LDL is increased and HDL is decreased. The available action is that the esterification of total cholesterol is inhibited. Nephrotic ailment is a regular nephropathy complication with hyperlipidemia. Hyperlipidemia caused by metabolic disorders has been highly concerned but the inducing mechanism is not clear [10].

## **12. DIAGNOSIS**

The diagnosis of hyperlipidemia mainly involves history, physical, and laboratory screening. In most of the cases the primary causes are more, but occasionally secondary cause is also found. Severe hypercholesterolemias are genetic and mostly consulted by the cholesterol experts, as these severe cases may involve multiple drugs. When genetic case of hyperlipidemia is suspected, then the siblings, children, parents should be screened as well [11].

## **13. HISTORY**

In hyperlipidemia the history plays a major role in determining the laboratory significance and the risk factors that the patient has for CHD. Some of the secondary causes like: alcohol, obesity, diabetes mellitus, nephrotic syndrome are also determined by the use of history. Risk factors for CHD includes the age, greater than 45 in men and 55 in women, having a family history of CHD, cigarette smoking, hypertension etc.[11]

## **14. PHYSICAL**

Findings of physical examinations for hyperlipidemia are not specific. But they are more specific in severe cases of hyperlipidemia. These physical findings are helpful in diseases which are associated like diabetes, hypertension.

In severe cases of hyperlipidemia, tendons, xanthomas, premature arcus (senilus) are present which are noted by the physical findings.[11]

## **15. TREATMENT**

After hyperlipidemia diagnosis is done, dietary treatment may begin immediately. After 6 months of diet, exercise still the lipids levels are elevated, medication therapy will begin. The goal of therapy in patients with CHD or ASHD is to lower LDL to <100 mg/dL. Those patients who are hospitalised, if an elevated cholesterol level is observed on admission and the patient is metabolically stable, the patient may be considered for medication on discharge if LDL >130 mg/dL.[12]

## **16. EFFECT OF DIETARY FACTORS ON SERUM LIPIDS**

Dietary modifications resulted in decreased mortality from CHD even when not associated with changes in levels of cholesterol [12].

Dietary modifications includes step-I diet, step-II diet, step-III diet, saturated fatty acids, monosaturated fatty acids (MUFA), polysaturated fatty acids (PUFA), omega-6 polysaturated fatty acids, omega-3 polysaturated fatty acids, trans fatty acids, vitamin-E, dietary calcium and dietary fiber [12].

Dietary modifications are listed below in the (Table 5).

The NCEP (National Cholesterol Education Project) recommends <300 mg of dietary cholesterol should be consumed daily in its Step 1 diet (Table 6). This can be done by minimizing the consumption of egg to no more than 4 yolks per week, limiting the meat, poultry, and fish intake to 6 ounces per day, and selecting non-fat dairy products. The TC levels should be measured at 4 to 6 weeks and at 3 months [12].

After a 6-month, if the Step 1 diet fails to reduce the cholesterol levels in the patients, then patients are advised to follow the Step 2 diet (<200 mg cholesterol) in this step eggs are limited to no more than 2 yolks per week, non-fat dairy products are restricted to no more than 2 intakes per day, and the consumption of fruits, vegetables, and grains are further elevated to help limit the dietary cholesterol to <7% of total calories. The TC levels should be measured at 3 to 4 weeks and 3 months [12].

**Table 4. Types of hyperlipidemia**

TYPE	INCIDENCE	PRESENTATION	TREATMENT
Heterozygous familial hypercholesterolemia	1 in 200 to 1 in 500	Asymptomatic	Diet and exercise for 6 months, add statins
Homozygous familial hypercholesterolemia	1 in 160,000	Xanthomas	Diet, exercise and statins, bile acids, cholesterol absorption inhibitors
Secondary hypertriglyceridemia	10.7%	Diabetes, renal dysfunction	Fibrates, Nicotinic acid & Omega fatty acids.
Familial combined hyperlipidemia	0.5% to 1%	May be obese	Diet, exercise, statins

### 17. EXERCISE

Exercise is associated with decreased CHD. Exercising for 3 hours a week or 30 minutes five times a week, and combining with diet can improve TC, LDL, TGs, and HDL levels [12].

Improvement in HDL (>80 mg/dL), however require strenuous exercise, for example, running >64 km per week.

A 2000kcal/week or 5 to 6 hours/week of regular physical exercise is required when low ASHD is measured by an angiography [12].

Blood lipid status will improve during the exercise training. Serum lipid and lipoprotein level may changes with change in the weight during the exercise. Weight loss is also associated with the exercise training [13].

### 18. MEDICATIONS FOR HYPERLIPIDEMIA

Four different classes of cholesterol-lowering drugs namely, statins, niacin, resins, and fibrates are available to treat hyperlipidemia; however, statins are now considered to be the first line therapy. The choice of drug should be based on treatment goals, side effects, and their tolerability to the patient.

The AHA suggests selection of drug depends upon the TG, that is, <200 mg/dL – statin, resin, or niacin; 200 to 400 mg/dL – statin or niacin, and >400 consider combined therapy with niacin, fibrates, and statin.[12]

### 19. COMBINATION THERAPY

If LDL cholesterol is not reduced after a 3-month usage of a one drug at an low dose then, combination therapy may be advised. When statins are combined with niacin or fibric acid derivatives there is chance of increased risk of hepatotoxicity and myopathy upon usage. Combining multiple agents may, produce lesser side effects with increased efficacy. Example:

Low-dose lovastatin and low colestipol, when combined together produced a greater reduction in LDL cholesterol than higher doses of lovastatin alone [12]

### 20. MANAGEMENT

Management of hyperlipidemia should be based on the underlying cause of increased cholesterol levels. It should be determined that whether the patients have a primary cause of hyperlipidemia, such as FH, or whether the cause is secondary. It is important to monitor for the secondary causes of hyperlipidemia, like, nephrotic syndrome, hypothyroidism, diabetes, obesity, anorexia nervosa, diet-related (excessive intake of dairy products), or drug-induced (oral contraceptive pills, corticosteroids, cyclosporine, etc) [14]

### 21. PHARMACOLOGICAL MANAGEMENT

The pharmacological treatment for hyperlipidemia mainly involves:

Stains, Bile acids, Fibric acids, Nicotinic acids, Omega-3 fatty acids and Cholesterol absorption inhibitors.

#### 21.1 Statins

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the first-line drugs for the treatment of hyperlipidemia in decreasing LDL-C and TG levels and increasing the HDL-C levels in familial and severe hypercholesterolemia. Statins therapy should start at the low dose, and dosing should be adjusted to get a target LDL-C level of 140 mg/dL or less (<3.6 mmol/L) by increasing the dose, changing to a more strong statin, or adding another lipid-lowering drug, such as ezetimibe and resins [14].

The younger age at which statins can be started is 8 and 10 years of age. Statins have a similar

safety as in adults, and adverse effects include headache, myalgias, hepatotoxicity, myopathy, and, rarely, rhabdomyolysis. Commonly most of the patients may have increase in aspartate aminotransferase/alanine aminotransferase levels. Statins are contraindicated in pregnancy patients due to potential as a teratogen [14].

**21.2 Alternatives to statins**

Even though statins are preferred treatment for the hyperlipidemia, there are few reasons to consider other medications for treatment of hyperlipidemia. Some believes that a combination of low to moderate doses of drugs can produce better LDL-C reduction with less side effects, while other believes a single monotherapy is preferable. In times, statin therapy for hyperlipidemia is maximal, but the goals of the lipid are not met. Some therapeutic options for the treatment of hyperlipidemia which are alternative to statins are listed below in Table 7 [15].

**21.3 Bile Acids Sequestrants**

Bile acid sequestrants (resins) function to decrease LDL-C levels with primary use for familial or severe hypercholesterolemia. The side effects are usually gastrointestinal, including bloating, abdominal discomfort, and constipation. Resins are generally considered to be safe and are approved for patient use, older than 10 years of age. Sequestrants are clearly safe and are effective cholesterol-lowering agents and can interfere with the absorption of fat-soluble vitamins and folic acid, so supplementation may be needed in these cases [14].

**21.4 Cholesterol Absorption Inhibitors**

Cholesterol absorption inhibitors act to decrease the LDL-C levels with primary use for familial or

severe hypercholesterolemia. Adverse effects include gastrointestinal symptoms, hepatotoxicity, and myopathy. It is effective in treating the HeFH. However, it is also used as an adjunct to other medications [14].

**21.5 Fibric Acids**

Fibric acids (fenofibrate and gemfibrozil) are mainly used to decrease the LDL-C and TG levels and increase HDLC levels in hypertriglyceridemia patients (TG levels >600–1,000 mg/dL [>6.8–11.3 mmol/L]). Fibrates are first-line pharmacologic agents for severe hypertriglyceridemia. Fibric acids are generally well tolerated as monotherapy and may be used with caution when combining with a statin [14].

**21.6 Nicotinic Acids**

Nicotinic acid (niacin) is used to decrease LDL-C and TG levels and increase HDL-C levels in familial or severe hypercholesterolemia. The adverse effects associated with niacin are flushing, intolerance in glucose levels, headache, hepatotoxicity, and myopathy. It is not used continuously due to the potential for severe adverse effects. Niacin increases serum homocysteine and uric acid levels in patients. Nicotinamide, although a well-tolerated drug, cannot be replaced with some other drug because it has no lipid-lowering properties [14].

**21.7 Omega-3 Fatty Acids**

Omega-3 fatty acids (fish oils) are used in lowering TG levels. They work by reducing the hepatic secretion of VLDL-C and increasing chylomicron metabolism. It is more effective in adults than in the paediatric patients and these are not suggested as an single therapy but advised with the combined therapy [14].

**Table 5. NCEP step 1 and step 2 diet**

	<b>Step 1 Diet</b>	<b>Step 2 Diet</b>
Total fat	<30% of calories	<30% of calories
Saturated fat	<10% of calories	<7% of calories
Polyunsaturated fat	Up to 10% of calories	Up to 10% of calories
Monounsaturated fat	10 to 15% of calories	10 to 15% of calories
Carbohydrates	>55% of total calories	>55% of total calories
Proteins	~15% of total calories	~15% of total calories
Cholesterol	<300 mg/d	<200 mg/d
Total calories	Maintain IBW	Maintain IBW



**Table 6. Alternatives to statins**

DRUG	EFFECTS	ADVERSE REACTIONS
<b>Bile acid sequestrants</b>		
Cholestyramine (4-16 g)	LDL -15-30%	Gastrointestinal distress, Decreased absorption of other drugs.
Colestipol (5-20 g)	HDL +3-5%	
<b>Nicotinic acid</b>		
Immediate release nicotinic acid (1.5-3 g)	LDL -5-23%	Flushing
Extended release nicotinic acid (1-2 g)	HDL +15-35%	Hyperglycaemia
	TG -20-50%	Hyperuricemia
<b>Fibric acids</b>		
Gemfibrozil (600 mg BID)	LDL -5-20%	Dyspepsia
Fenofibrate (200 mg)	HDL +10-20%	Gallstones
Clofibrate (1000 mg BID)	TG -20-50%	Myopathy
<b>Ezetimibe</b>		
Zetia (10 mg daily)	LDL-C -18%	Diarrhoea
As monotherapy, often combined with statin	HDL-C +3%	Arthralgia
	TG -8%	Sinusitis Nasopharyngitis

**Table 7. Drugs Used To Treat Hyperlipidemia**

Drug	Mechanism	Adverse effects	Monitoring
Statins	Block cholesterol Synthesis	Myopathy	LFT, CK
Bile acids	Bind with cholesterol	Diarrhoea, constipation	None
Cholesterol Absorption Inhibitors	Block absorption	GI effects, Myopathy	None
Fibrates	Decreasing VLDL Production and clearing Triglycerides	GI adverse effects	None
Nicotinic acids	Antilipolytic effect	Flushing, Myopathy	LFT

## 21.8 MONITORING

Upon receiving the drug therapy of hyperlipidemia (Table 8) for 1 month, follow-up of testing serum aspartate aminotransferase, alanine aminotransferase, creatine kinase, and lipid level [14].

## 22. PREVENTION

The Food and Drug Administration (FDA) has approved TG-lowering drugs once the hyperlipidemia has been diagnosed. The preventive approach should include changes in the behaviour and avoidance of fatty foods, promoting a healthy diet and physical activity. The patients should be explained about avoidance of cigarette smoking and adopting healthy lifestyle choices [14].

Prevention of diabetes mellitus and obesity will help in minimising the risk of hyperlipidemia. Physicians can help to motivate the family

members or patients who at risk regarding the behavioural changes for achieving good lifestyle [14].

## 23. INPATIENT MANAGEMENT

Pancreatitis is a complication of severe hypertriglyceridemia occurring in 1% to 4% of individuals, and mild to moderate elevation in serum TG levels are found in one-third of all patients with acute pancreatitis.

Severe hypertriglyceridemia with concentrations of TG's >1,000 mg/dL (11.3 mmol/L) with abdominal pain/pancreatitis requires hospital admission and medical management, which can include treatment of lipid-lowering medications along with IV insulin to ease the clearance of TG's by activation of LPL [14].

Plasmapheresis is typically reticent for severe cases with more findings of lactic acidosis, severe hypocalcaemia, acute respiratory

distress, and/or organ failure, where direct reduction of serum TG levels is necessary.

The feasible causes of secondary hypertriglyceridemia, like diabetes, adverse effects of medication, poor diet or consumption of alcohol, and other comorbidities, should be examined during hospitalization. Discharging of patients from the hospitals can be done when the TG level is less than 1,000 mg/dL (<11.3 mmol/L) or less than 500 mg/dL (<5.7 mmol/L) [14].

## 24. OUTPATIENT MANAGEMENT

### 24.1 Lifestyle Management

The first-line therapy for an elevated lipid profile is an healthy lifestyle, which involves dietary modification, improving body weight, avoiding tobacco smoking or, if smoking, begin smoking cessation, and 30 to 60 minutes of daily physical activity with moderate to dynamic potency.

Decreasing the intake of total saturated fat, trans-fat may result in a lipid lowering effect. Reduction in weight can help lower the risk of CVD [14].

### 24.2 Dietary Factors

A large number of dietary factors may affect lipid levels. These contain restriction of nutritional elements, use of specific foods, utilization of food preservatives and supplements, and vital dietary approaches [16].

Reducing intake of saturated fat to 7% of total calories and limiting cholesterol intake to 200 mg/day helps in reducing LDL cholesterol levels by 9-12% [16].

A Diet chart is developed which consist of four LDL cholesterol-lowering components: soluble fiber, soy protein and other vegetable proteins, plant sterols, and almonds (Table 9).

**Table 8. Diet chart for Lowering LDL Cholesterol Levels**

Almonds	23 g whole almonds per 1,000 kcal consumed
Plant sterols	1 g plant sterols per 1,000 kcal consumed
Soluble fiber consumed	10 g fiber (e.g., from oats, barley, psyllium, okra, eggplant) per 1,000 kcal consumed
Soy protein	22.5 g soy protein (e.g., soy milk, soy meat analogues) per 1,000 kcal consumed
Other legumes; eat 5 to 10 fruit and vegetables daily; try to consume a vegetarian diet without dairy foods, whites; if meat or dairy products are consumed, amounts should be restricted, and foods low in saturated fat should be selected.	Consume additional sources of plant protein and fiber in the form of dried legumes, eggs, or meat; if egg products are used, they should be egg substitutes or egg whites; if meat or dairy products are consumed, amounts should be restricted, and foods low in saturated fat should be selected.

**Table 9. Drug Therapy For Hyperlipidemia**

DRUGS	EFFECT ON LIPIDS
<b>Statins:</b>	
Lovastatin (10 – 80 mg)	Decrease Triglycerides, LDL. Increase High-Density Lipoprotein
Simvastatin ( 5 – 40 mg)	
Atorvastatin (10 – 80 mg)	
<b>Resins:</b>	
Cholestyramine (4 – 16 mg)	Decrease Low-Density Lipoprotein, Increase HDL
Colestipol (5 – 30 mg)	
<b>Fibric Acids:</b>	
Gemfibrozil (1200 mg)	Decrease TG, LDL. Increase HDL
Fenofibrate (200 mg)	
Bezafibrate (600 mg)	
<b>Nicotinic Acid:</b>	
Niacin (2 – 6 gm)	Decrease TG, LDL. Increase HDL
<b>Cholesterol Inhibitors:</b>	
Ezetimibe ( 10 mg)	Decrease Low-Density Lipoprotein, Cholesterol

## 25. DRUG THERAPY FOR HYPERLIPIDEMIA

The drug therapy for hyperlipidemia are listed below in the (Table 10) [17].

## 26. NOVEL DRUGS SELECTED FOR HYPERLIPIDEMIA

Other than the Drug therapies, Diet and Exercise, there are some novel drugs which are selected for the treatment of hyperlipidemia. The novel drugs selected for the hyperlipidemia treatment include: Evolocumab, Alirocumab, Bempedoic acid, Sebelipase, Lomitapide, and Evinacumab.

## 27. EVOLOCUMAB AND ALIROCUMAB

Evolocumab is a fully human monoclonal antibody (IgG2 type) which links to PCSK9 with high affinity. It contains 2 disulphide bonds between the heavy chains and the kappa light chains. In each heavy chain, there is a single N-linked glycosylation site located within the CH<sub>2</sub> domain of the Fc constant region of the molecule. (Chart. 2) The most elimination of circulating free PCSK9 is seen 4hrs after the administration of a single subcutaneous (SC) dose of 140 mg or 420 mg of evolocumab. When evolocumab concentrations are no longer traceable, the level of loose PCSK9 tends to return to the normal [18].

The response is obtained in 1 week, and the maximum responses are generally seen after 14 days of treatment.

Evolocumab acts on the levels of other lipid parameters, such as total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein-β (ApoB), triglycerides (TG) and Lipoprotein (a) [18].

The pharmacokinetics of evolocumab is non-linear over the dose range of 21–140 mg, but it becomes linear from 140 mg to 420 mg dose. Evolocumab is mainly distributed in the circulatory system, and the mean steady-state, volume of distribution after a single intravenous (IV) dose of 420 mg has been estimated to be low.

This drug is eliminated in two phases: at low concentrations it is mainly eliminated through binding to the target protein PCSK9, while at

higher concentrations it is eliminated through a non-saturable proteolytic pathway.

Its half-life is approximately 11–17 days. A 20% increase in evolocumab clearance has been seen in patients taking statins [18].

The pharmacokinetics of evolocumab is independent of weight, age, gender or ethnicity. There is no need of dose adjustment in patients with mild to moderate hepatic or renal impairment. In those with severe renal or hepatic impairment dose adjustment need to be done [18].

Alirocumab is a fully human monoclonal antibody (IgG1 type) which binds PCSK9 with high affinity. It contains two disulphide bonds between the heavy chains and the kappa light chain. In each heavy chain, there is a single N-linked glycosylation site located within the CH<sub>2</sub> domain of the Fc constant region of the molecule (Chart 3).

Alirocumab is responsible for a concentration-dependent reduction of free PCSK9 levels, with a peak effect after 4–8hrs from the 75 or 150 mg SC injection and a maximum reduction of LDL-C at 8–15 days after the administration. When alirocumab concentrations falls, free PCSK9 returns to normal levels [18].

Maximum plasma concentrations of alirocumab occurs about 3–7 days after a single SC injection. Steady-state concentrations are achieved after two or three drug doses. The median half-life of SC doses is 17 to 20 days. There is no need of dosage adjustment according to age, body weight or mild to moderate renal or hepatic impairment [19].

## 28. SEBELIPASE ALFA

Sebelipase alfa is a recombinant form of the human LAL enzyme used for long-term enzyme replacement treatment for LAL deficiency. Sebelipase alfa contains N-linked glycans with terminal N-acetylglucosamine structures and mannose and mannose-6-phosphate moieties. Sebelipase alfa perform action to change the LAL enzyme, catalysing the lysosomal separation of cholesterol esters and triglycerides to free cholesterol, glycerol and free fatty acids [20].

The pharmacokinetics of sebelipase alfa is non-linear, with greater than dose-corresponding

increases in submission observed between 0.35 and 3 mg/kg doses in infants and between 1 and 3 mg/kg doses in adult patients with LAL deficiency. The half-life of sebelipase alfa is 0.1

hr when administered to infants, children or adults with LAL deficiency. Sebelipase alfa will be degraded through peptide hydrolysis, as a protein [20].

**Chart 2. Evolocumab**

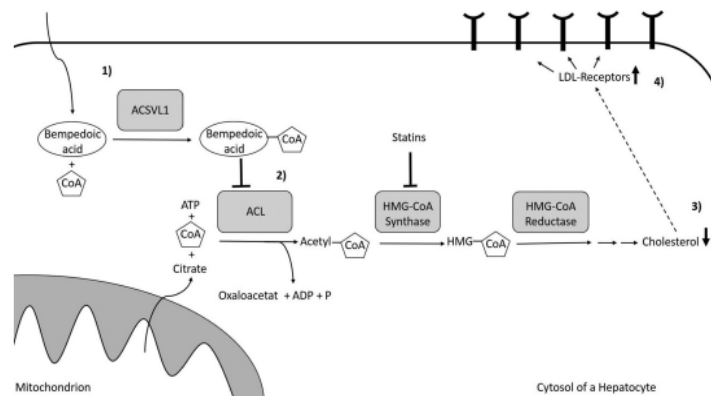
<b>Drug name (generic)</b>	<b>Evolocumab</b>
Indication	Management of primary hyperlipidemia (including familial heterozygous and homozygous hyperlipidemia), atherosclerotic cardiovascular disease
Pharmacology	Protein convertase subtilisin/kexin type 9 (PCSK9)-Inhibitor
Route of administration	Subcutaneous injection
Chemical structure	C <sub>6242</sub> H <sub>9648</sub> N <sub>1668</sub> O <sub>1996</sub> S <sub>56</sub>

**Chart 3. Alirocumab**

<b>Drug name (generic)</b>	<b>Alirocumab</b>
Indication	Management of primary hyperlipidemia (including familial heterozygous hyperlipidemia), atherosclerotic cardiovascular disease
Pharmacology	Protein convertase subtilisin/kexin type 9 (PCSK9)-Inhibitor
Route of administration	Subcutaneous injection
Chemical structure	C <sub>6472</sub> H <sub>9996</sub> N <sub>1736</sub> O <sub>2032</sub> S <sub>42</sub>

**Chart 4. Bempedoic acid**

<b>Drug name (generic)</b>	<b>Bempedoic acid, ETC-1002</b>
Indication	Hypercholesterolemia
Pharmacology	Inhibition of ACL interferes with the cholesterol synthesis pathway
Route of administration	Orally
Chemical structure	Small molecule, 8-hydroxy-2,2,14,14-tetramethyl-pentadecanedioic acid



**Fig. 1. Bempedoic mechanism of action**

(1) After crossing the hepatocyte cell membrane bempedoic acid is activated by binding to Co-A through ACSVL1. (2) Activated bempedoic acid inhibits ACL. (3) Intracellular cholesterol content decreases and stimulates LDL-R synthesis. (4) This increases the amount of LDL-R on the hepatocyte's surface and results in enhanced clearance of LDL-particles from the circulation

**Chart 5. Features of sebelipase alfa**

<b>Drug name</b>	<b>Sebelipase Alfa</b>
Alternate names	Kanuma; lysosomal acid lipase; recombinant human lysosomal
Mechanism of action	Sterol esterase replacement; sterol esterase stimulant
Route of administration	Intravenous infusion
Pharmacodynamics	Acts to replace deficient LAL enzyme activity; catalyses the lysosomal hydrolysis of cholesteryl esters and triglycerides
Chemical name	Human lysosomal acid lipase/cholesteryl ester hydrolase

Sebelipase alfa received its first global approval for long-term enzyme replacement remedy in patients of all ages with LAL deficiency. Features of sebelipase alfa were listed below in the Chart. (Chart.5) [20].

### **LOMITAPIDE**

Lomitapide is a small molecule benzimidazole, developed as an orphan drug for treatment of HoFH (Homozygous familial hypercholesterolemia). It is indicated to low-fat diet and other lipid-lowering agents, with or without LDL apheresis, as an adjunctive treatment for the management of HoFH [21]

Lomitapide is administered orally at a starting dose of 5 mg once daily, generally to be taken 2 hr after the evening meal. Dosing can be increased to a maximum daily dose of 60 mg, based on response and tolerability. Lomitapide is available in the doses of 5, 10, and 20 mg capsules [21].

Lomitapide is an microsomal triglyceride transfer protein (MTP) inhibitor, linking directly to MTP in the lumen of the endoplasmic reticulum. MTP is needed for the hepatic building of very low-density lipoprotein (VLDL) through the transfer of TG to apo B-100-containing lipoproteins, as well as for the production of chylomicrons in enterocytes through the transfer of TG to apo B-48-containing lipoproteins [21].

The major side effect of lomitapide is accumulation of hepatic triglyceride resulting in hepatic steatosis, although likely without inflammation [21].

The bioavailability of oral lomitapide is estimated to be ~7%. It reaches its maximum serum concentrations approximately 6 hr post-ingestion. In circulation, lomitapide is predominantly protein bound. Its elimination half-life is 39.7 hr, with approximately one third excreted renally in

metabolite form, and 53% through faecal elimination. In hepatic impairment patients clearance is reduced. In patients with mild to moderate hepatic impairment lomitapide is contraindicated, and the maximum dose should not exceed 40 mg in the end-stage renal disease patients [21].

Lomitapide is a cytochrome P450 (CYP) 3A4 inhibitor, and coadministration with other moderate to strong CYP3A4 inhibitors is contraindicated in patients taking lomitapide. A 30 mg of lomitapide dose is required when the coadministration is with the weak CYP3A4 inhibitors [21].

Lomitapide dosing should not outreach 30 mg when used in conjunction with atorvastatin, and simvastatin dosing should not outreach 40 mg when used in combination with lomitapide. When lomitapide is given with niacin, fenofibrate, and ezetimibe the dose adjustment is not needed. For bile acid sequestrants, no dose adjustment is required instead these bile acid should be taken separated from lomitapide 4 hr. Lomitapide increased levels of ethinylestradiol and norgestimate in patients taking oral contraceptive pills [21].

The most common side effects of lomitapide are gastrointestinal effects, few patients report diarrhoea, nausea, vomiting, or dyspepsia, and slightly fewer patients report abdominal discomfort, bloating, constipation, and flatulence. Elevated liver aminotransferase levels are common, reported in some patients, measurements of ALT, AST, alkaline phosphatase, and total bilirubin are recommended [21].

Absorption of vitamins A, D, and K were unaffected by lomitapide, but affects the absorption of vitamin E and essential fatty acids.

**Chart 6. Features of Lomitapide**

<b>Drug name</b>	<b>Lomitapide</b>
Alternate names	Juxtapid or Lojuxta
Indication	Homozygous familial hypercholesterolemia
Mechanism of action	Microsomal triglyceride transfer protein inhibitor
Route of administration	Orally
Pharmacodynamics	In vitro of lomitapide suggest IC <sub>50</sub> of 8 nmol/L for MTP inhibition and IC <sub>50</sub> of 0.8 nmol/L for inhibition of apo B secretion
Chemical structure	C <sub>39</sub> H <sub>37</sub> F <sub>6</sub> N <sub>3</sub> O <sub>2</sub>

**Chart 7. Features of Evkeeza**

<b>Drug name</b>	<b>Evkeeza</b>
Alternate name	Evinacumab-dgnb
Indication	Adjuvant to other LDL-C therapy with HoFH
Mechanism of action	Binds and inhibits ANGPTL3, inhibition leads to reduction in LDL-C, HDL-C, and triglycerides (TG).
Route of administration	Intravenous infusion
Pharmacodynamics	Administration resulted in reduction in LDL-C, TC, HDL and TG

The most serious adverse effect is the accumulation of hepatic triglyceride, possibly leading to hepatic fibrosis [21].

Lomitapide should be considered in the treatment HoFH patient who continues to have significantly elevated LDL-C levels and elevated cardiac risk despite with other management, which can diet, statins, ezetimibe, and also the PCSK9 inhibitor, evolocumab which is indicated for the treatment of this condition.

Some of the feature regarding the lomitapide were listed in the Chart. (Chart.6) [21].

## **EVKEEZA**

EVKEEZA is an angiopoietin-like 3 inhibitor designated as an adjuvant to other low-density lipoprotein-cholesterol (LDL-C) lowering for the treatment of patients, aged 12 years and older, with homozygous familial hypercholesterolemia (HoFH). The suggested dose of evkeeza is 15 mg/kg which is administered intravenous infusion, monthly once [22].

Evkeeza is obtained in the form of injections in single dose vials.

Evkeeza is contraindicated in patients who are having a history of serious hypersensitivity reaction to evinacumab-dgnb or to any of the ingredients in Evkeeza. Nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, and

nausea are some common adverse reactions [22] Evinacumab-dgnb which is an recombinant monoclonal antibody that links to and hinder ANGPTL3.

ANGPTL3, it is a member of the angiopoietin-like protein family that is shown primarily in the liver and plays a crucial role in regulating the lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). Inhibition of ANGPTL3 leads to decrease in LDL-C, HDL-C, and triglycerides (TG). Evinacumab-dgnb lowers LDL-C which is independent of the presence of LDL receptor (LDLR) by advancing very low-density lipoprotein (VLDL) activity and clearance of LDL formation. The blockage of ANGPTL3 lowers TG and HDL-C by saving LPL and EL activities, respectively. Some features of Evinacumab are listed below in the Chart. (Chart.7) [22].

## **CONCLUSION**

Hyperlipidemia (High Cholesterol) is a medical term for abnormally high levels of fats (LDL, VLDL) in the blood. The two types of lipids which are found in the blood include: Triglycerides and Cholesterol. Triglycerides are made when the body stores extra calories not needed for energy. They also come directly from the diet (Red meat & Whole fat-dairy). A diet high in refined sugar, fructose & alcohol raises triglycerides. Cholesterol is naturally produced in the liver.

Similar to triglycerides, cholesterol is also found in fatty foods like eggs, red meat & cheese.

Hyperlipidemia does not have any obvious symptoms but usually discovered during routine examination or until the stage of a stroke or heart attack is reached. Patients with high blood cholesterol level or with the familial forms of the disorder can develop Xanthomas which are deposits of cholesterol that may form under the skin, especially under the eyes. Patients with increased levels of triglycerides may grow numerous pimple like lesions at various different sites in their body. Hyperlipidemia is most often correlated with high-fat diets, a stationary lifestyle, obesity and diabetes mellitus. The preventable causes of hyperlipidemia can include : Smoking, Being overweight, Physical inactivity, Steroid use, Alcohol consumption & Diet high in saturated fat, & cholesterol such as cheese, meat, fried & processed foods and egg yolk. The treatment of hyperlipidemia includes statins, bile acid sequestrants, fibric acids, niacin, and cholesterol absorption inhibitors.

There are some of the novel drugs which are selected for the treatment of hyperlipidemia which includes: Evolocumab, Alirocumab, Bempedoic acid, Lomitapide, Evinacumab, and Sebelipase alfa.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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