Review Article

HYPERLIPIDEMIA: AN OVERREVIEW

ABSTRACT

Hyperlipidemia is a medical condition indicated by an increase 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, as well as decreased levels of high-density lipoprotein. This increase in plasma lipids is one of the most important risk factors for cardiovascular disease. In the meanwhile, statins and fibrates remain the most common anti-hyperlipidemic drugs for treating high plasma cholesterol and triglycerides,

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Keywords: hyperlipidemia, lipid transport, cholesterol, dietary plant fibers, Hypolipidemic drugs, statins, fibrate, Atherosclerosis.

Comment [WU2]: Keywords should not be more than 5/6

1. INTRODUCTION

Hyperlipidemia is a term used to describe a group of inherited and acquired illnesses in which the body's lipid levels are abnormally high. Hyperlipidemia is extremely widespread, particularly in the Western hemisphere, but also worldwide. Hyperlipidemia is defined as low-density lipoprotein (LDL), total cholesterol, triglyceride levels, or lipoprotein levels greater than the 90th percentile in comparison to the general population, or an HDL level less than the 10th percentile in comparison to the general population, according to a more objective definition. Elevated levels of LDL cholesterol have regularly been demonstrated to enhance a person's risk of developing atherosclerotic plaques and consequent vascular disease in a variety of trials and research. High-density lipoprotein (HDL) cholesterol, on the other hand, aids in the regulation of cholesterol levels, reducing the risk of atherosclerotic vascular disease. The LDL cholesterol goal for each patient is determined by their overall cardiovascular risk, and medical therapy should be individually customised to each patient. "Primary prevention" refers to the management of risk factors such as hyperlipidemia in order to reduce the risk of atherosclerotic cardiovascular disease. The evidence for lowering LDL cholesterol comes from a large body of epidemiologic evidence that shows a favourable, long-term link between LDL cholesterol levels, cardiovascular events, and patient mortality. Cholesterol levels, lipoproteins, chylomicrons, VLDL, LDL, apolipoproteins, and HDL are all examples of lipids.Elevated levels of LDL cholesterol have regularly been demonstrated to enhance a person's risk of developing atherosclerotic plaques and consequent vascular disease in a variety of trials and research. High-density lipoprotein (HDL) cholesterol, on the other hand, aids in the regulation of cholesterol levels, reducing the risk of atherosclerotic vascular disease. [1,2]

Cholesterol:It is a precursor of steroid hormones and bile acids and is an important component of the mammalian cell membrane in all tissues. It is found in all animal cells, either free or as numerous fatty esters, however it is not found in plant fats [3]. Its structure is depicted in fig. 1

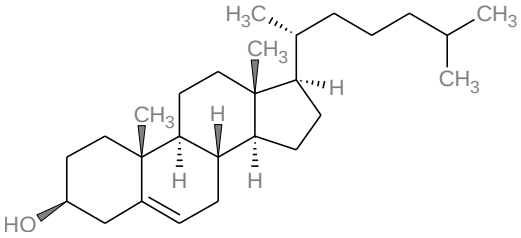

Fig. 1: Structure of cholesterol

Lipoproteins:These are big globular particles with an oily core of nonpolar lipid (cholesteryl esters of triglycerides) and a polar covering of phospholipids free of cholesterol and apoproteins (i.e. unesterified). Lipoproteins are divided into six categories (table 1), each with its own size, density, and triglyceride and cholesterol characteristics.

Table 1: Characteristics of major lipoprotein classes

Lipoprotein class	Density (g/ml)	Diameter (nm)
Chylomicrons	<<1.006	500-80
VLDL	<1.006	80-30
IDL	1.006-1.019	35-25
LDL	1.019-1.063	25-18
HDL	1.063-1.210	5-12
Lp(a)	1.055-1.085	30

***Triglycerides* :**These are the most abundant lipids on the planet. Adipocytes contain a large amount of it. These are important components of plant and animal storage fats. Excess calories, alcohol, and sugar are converted to triglycerides in the body and deposited in fat cells all throughout the body. Triglycerides are glycerol esters with three fatty acid molecules[4].

***Chylomicrons*:** These are the largest particles in terms of both size and density, and their concentration is linked to dietary triglyceride levels.

VLDL: Very low-density lipoproteins are smaller particles released by the liver that have lower triglyceride content than chylomicrons. VLDL transports cholesterol from the liver to the body's organs and tissues. They're made up of a mixture of cholesterol and triglycerides.

IDL: Intermediate density lipoprotein is formed when VLDL particles are degraded by the lipase enzyme in the capillaries of adipose tissue and muscle.

LDL: low-density lipoproteins are made partly in the chyle of the intestine and partly after the lipolysis of VLDL. It has a direct link to coronary heart disease[5,6].

HDL:HDL stands for "high-density lipoprotein," or "healthy cholesterol." The liver is where high-density lipoproteins are made. It transports cholesterol and other lipids from tissues to the liver, where they are degraded. HDL has anti-atherogenic properties[7].

LP (a): It's produced by the liver. Lipoprotein (a) is a cholesterol-rich plasma lipoprotein that is linked to atherosclerosis, according to Berg. A higher Lp(a) plasma concentration level increases the risk of CHD by 2 to 5 times. Females had greater Lp(a) levels than males, and there was a statistically significant increase in Lp(a) plasma level concentration with age. They also discovered that alcohol drinkers had lower Lp(a) plasma levels than non-drinkers.

2. PATHWAY OF LIPOPROTEIN

Cholesterol is absorbed from the intestine and transferred to the liver by chylomicron remnants, which are absorbed by LDL-receptor-related proteins (LRP). After lipoprotein lipase removes the triglyceride, hepatic cholesterol enters the circulation as very low-density lipoprotein (VLDL) and is converted to remnant lipoproteins. LDL receptors (LDL-R) remove the remaining lipoproteins, or they are converted to LDL and then eliminated by these receptors.High-density lipoproteins transfer cholesterol from peripheral cells to the liver (HDL). Cholesterol-ester transport proteins (CETP) recycle cholesterol into LDL and VLDL, whereas hepatic lipase absorbs it in the liver. Bile is where cholesterol is eliminated. Familial hypertriglyceridemia (FHTG), familial combination hyperlipidemia (FCHL), remnant removal disease (RRD) also known as familial dysbetalipoproteinemia, familial hypercholesterolemia (FH), and hypoalphalipoproteinemia are the five primary lipoprotein disorders that influence this process[8-9].

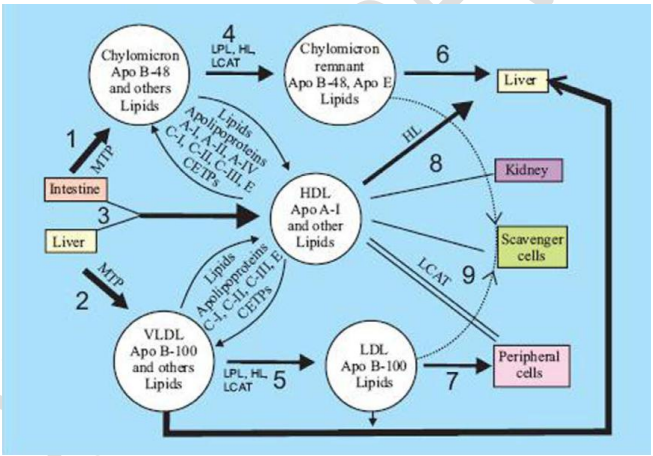

Figure 2. An overview of human apolipoprotein (apo) metabolism.

3. CLASSIFICATION OF HYPERLIPIDEMIA

Depending on the lipid type

- *Hypercholesterolemia* is a condition in which the level of cholesterol in the blood is abnormally high.
- *Hypertriglyceridemia* is characterized as a high level of triglycerides in the blood[10,11].

Depending on the etiology Familial (Primary) hyperlipidemia–

Hyperlipidemia can be classified as primary or secondary depending on the underlying causes. On the basis of the electrophoresis or ultracentrifugation pattern of lipoproteins, Fredrickson divides familial hyperlipidemia into five kinds[12] (table 2).

• Type I–High triglyceride levels and elevated cholesterol.

• Type II–Low triglyceride levels with high cholesterol.

• Type III–Higher triglycerides and cholesterol.

• Type IV–High triglycerides, atheroma, and uric acid levels.

• Type V triglycerides are elevated.

Table 2: Fredrickson classification for hyperlipidemia

Hyperlipoproteinemia	**Synonyms**	**Increased lipoprotein**	**symptoms**
Type I	Familial hyperchylomicronemia familial apoprotein CII deficiency	Chylomicrons	Acute pancreatitis, lipemiaretinalis, xanthomas, hepatosplenomegaly.
Type II	Familial hypercholesterolemia	LDL	Xanthelasma, arcus senilis, tendon xanthomas
Type III	Familial combined hyperlipidemia	LDL and VLDL	Tuboruptivexanthomas
Type IV	Familial dysbetalipoproteinemia	IDL and VLDL	Palmar xanthomas
Type V	Familial hypertriglyceridemia	VLDL and chylomicrons	Cause pancreatitis at high triglycerides levels

Acquired (Secondary) hyperlipidemia: Acquired (secondary) hyperlipidemia is caused by underlying illnesses and results in alterations in lipid and lipoprotein metabolism in the blood. This kind of hyperlipidemia has symptoms that are similar to primary hyperlipidemia. They may increase the risk of early atherosclerosis, pancreatitis, and other complications of the chylomicronemia syndrome. The following are the most common causes of acquired hyperlipidemia[13].

Hyperlipidemia symptoms: Hyperlipidemia normally has no symptoms and is diagnosed during a regular evaluation for atherosclerotic cardiovascular disease[14].

- Chest pain (angina), a heart attack, or a stroke are all possible symptoms.
- When cholesterol levels are really high, it may be deposited in tendons or beneath the skin under the eyes.
- Organs such as the liver, spleen, and pancreas may swell.
- Blood vessel blockage in the brain and heart.
- Obesity and glucose intolerance are more common[15].
- Lesions that resemble pimples all over the body.

Diagnosis of hyperlipidemia: Hyperlipidemia is usually asymptomatic and can only be discovered with a blood test. A blood test called a lipid profile is used to screen for hyperlipidemia. According to the National Cholesterol Education Program (NECP), screening

should begin at age 20 and be repeated at least every five years if the results are normal[16,17].Normal levels for a lipid profile are listed below (table 3).

Table 3: Normal levels for a lipid

Comment [WU3]: Check and correct values as per NECP

Profile of Lipids	Desirable value	Borderline	High risk
Cholesterol	Less than 200 mg/dl	200-239 mg/dl	240 mg/dl
Triglycerides	Less than 140 mg/dl	150-199 mg/dl	200-499 mg/dl
HDL cholesterol	60 mg/dl	40-50 mg/dl	Less than 40 mg/dl
LDL cholesterol	60-130 mg/dl	130-159 mg/dl	160-189 mg/dl
Cholesterol/HDL ratio	4.0	5.0	6.0

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4. CAUSES OF HYPERLIPIDEMIA:

1. Unhealthy lifestyle choices or medical issues that can be treated. Obesity, a lack of exercise, and smoking are all lifestyle factors[18].
2. Diabetic complications (type 2) [19]
3. Kidney disease
4. Pregnancy motherhood
5. A thyroid gland that is underactive

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5. THE RISK FACTORS FOR HYPERLIPIDEMIA

1. One of the factors that contributes to hypercholesterolemia is a high fat diet[20,21].
2. Diabetes mellitus type 2
3.Hypothyroidism is a condition in which the thyroid gland is underactive.
4. Renal failure that is chronic
5.Nephrotic syndrome is a condition that affects the kidneys.

6. COMPLICATIONS OF HYPERLIPIDEMIA:

- Pancreatitis[22]
- Premature coronary artery disease
- Heart attack Stroke[23]
- Atherosclerosis
- myocardial infarction.

7. INFLAMMATORY MARKERS IN HYPERLIPIDEMIA

The prominent involvement of inflammation in several metabolic disorders such as hyperlipidemia, atherogenesis, metabolic syndrome, and obesity has just lately been recognized [24].

7.1 C-Reactive Protein (CRP): CRP is a well-known acute-phase protein generated by the liver in response to pro-inflammatory cytokines including IL-6 and tumor necrosis factor (TNF-α) among others. Despite the fact that it is not an optimal measure, it appears to be substantially linked to cardiovascular risk and the advancement of atherogenesis. CRP levels appear to be linked to lipid levels as well.

7.2 Interleukin 6 (IL-6): IL-6 is a cytokine with established pro-inflammatory properties, but its significance in the pathogenesis of arteriosclerosis and cardiovascular disease is unknown. Its significance in lipid profile has been demonstrated in several recent research. Indeed, an atherogenic diet elevated non HDL cholesterol levels as well as IL-6 levels in LDL receptor null mice.

7.3 Tumor Necrosis Factor alpha (TNF-α): TNF-α has a critical function in the acute-phase response of the host to infection. TNF-α is an important cytokine that starts the inflammatory cascade and causes the secondary secretion of other cytokines like interleukin-1β (IL-1β) and IL-6. It is also linked to atherosclerosis progression.

7.4 Nuclear Factor Kappa-B: Nuclear factor Kappa-B (NF-kB) is a family of structurally related inducible transcription factors that has been linked to atherosclerosis, congestive heart failure, and diabetes. Recent evidence suggests that NF-kB may have a function in lipid metabolism.

7.5 Lipoprotein-Associated Phospholipase A2 (Lp-PLA2): Lp-PLA2 has recently been identified as a novel inflammatory biomarker that is primarily bound to apo-B carrying lipoproteins, has been linked to atherosclerosis and endothelial dysfunction, and can be utilised to predict cardiovascular risk.

7.6 Fibrinogen: Fibrinogen is a key blood glycoprotein that serves as the substrate for thrombin in haemostasis and coagulation mechanisms. It's also known as an acute phase protein, and it plays a role in the atherothrombotic process at all phases.

8. DRUGS USED IN HYPERLIPDEMIA

As LDL is the most atherogenic lipoprotein, lowering it would be expected to reduce atherosclerosis and, as a result, cardiovascular complications. In addition to high LDL, the presence of risk factors and CHD should preclude starting pharmacological therapy and changing one's lifestyle[25].

8.1 3-Hydroxy-3-methylglutaryl coenzyme A (HMGCoA) Reductase inhibitors (statins).

This class consists of (Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Atorvastatin and Rosuvastatin). Statins are commonly used to treat hypercholesterolemia and have been linked to a lower incidence of coronary morbidity and mortality in high-risk adults[26].

Mechanism of action: These medications are HMG-coenzyme A reductase structural mimics. They work by blocking the rate-limiting enzyme in the manufacture of cholesterol in the liver (HMG-coenzyme A reductase). Statins lower total cholesterol (TC), LDL, and ApoB levels in the blood by blocking this enzyme. In the meantime, statins cause a slight decrease in plasma triglycerides and a slight increase in plasma HDL levels. Diallyldisulfide (DADS) and diallylthiosulfinate are two other HMG-CoA reductase inhibitors[27,28].

Side effects: Statins are generally well tolerated, with brief gastrointestinal problems, headache, myalgia, and dizziness being the most common side effects. These symptoms are more common at larger doses and can be alleviated by switching to a different statin. Statins also induce myopathy, rhabdomyolysis and increase serum transaminase. These compounds are toxic to the kidneys and frequently result in renal damage [29].

8.2 Fibric acid derivatives(Fibrates)

Fibrates, which include clofibrate, gemfibrozil, fenofibrate, and bezafibrate, are an antihyperlipidemic drug class that resulted in a large decrease in plasma triglycerides and a minor decrease in LDL cholesterol. The level of HDL cholesterol rises gradually. Fibrates were found to play a major effect in reducing the evolution of coronary atherosclerosis and lowering the incidence of coronary artery disease in angiographic studies[30].

Mechanism of action: Fibrates appear to have four major processes, according on data from rodent and human studies:

Stimulation of lipoprotein lipolysis: Fibrates primarily act as ligands for the PPAR-α nuclear transcription receptor. They boosted the expression of apo, a lipoprotein lipase enzyme, and decreased the expression of apo C-III, a lipolysis inhibitor. Fibrates also boost HDL cholesterol levels by boosting the expression of apo AI and apo AII.

Increase hepatic fatty acid (FA) uptake and reduction of hepatic triglyceride production.: Fibrates stimulate the production of fatty acid transport protein and acyl-CoA synthetase, resulting in increased fatty acid absorption by the liver and reduced fatty acid availability for triglyceride formation.

Increase removal of LDL particles.: Fibrate appears to increase LDL catabolism via the receptor-mediated pathway; LDL particles grew larger and more lipid-rich, resulting in a higher attraction for receptors. Fibrate also prevents the production of LDL particles that are slowly digested and potentially atherogenic.

Increase in HDL production and stimulation of reverse cholesterol transport: Fibrates enhance apo A-I synthesis in the liver, resulting in higher plasma levels of apo A4 and HDL cholesterol, as well as more efficient reverse cholesterol transfer.

Side effects: Fibrates are commonly believed to be well tolerated. GI problems, myopathy, arrhythmia, skin rashes, and gallstones are all possible side effects. Fibrates should be avoided by people who have liver or kidney problems.

8.3 Bile acid sequestrant

The principal pathway of cholesterol catabolism in the liver is bile acid synthesis; it is estimated that the adult human liver converts roughly 500 mg of cholesterol per day into bile acids. Bile acids are secreted into the intestine and play a critical function in the absorption of lipids from diet. Cholestyramine, colestipol, colestimide, and colesevelam are all bile acid sequestrants. The two bile acid sequestrants now available are cholestyramine and colestipol [31].

Mechanism of action: Bile acid sequestrants are positively charged resins that bind to negatively charged bile acids in the intestine, forming a massive insoluble complex that is not absorbed and hence expelled in the faeces. When resins are provided, excretion can rise by tenfold, resulting in a higher conversion of cholesterol to bile acids. Bile acid sequestrants also help to raise HDL levels.

Side effects:Because of low patient tolerability, bile acid sequestrants are rarely utilised as first-line therapy. Constipation, nausea, indigestion, bloating, and flatulence are the most prevalent gastrointestinal side effects of bile acid sequestrants.

8.4 PCSK9 INHIBITORS

Humans regulate blood LDL cholesterol levels primarily through low-density lipoprotein (LDL) receptors on the surface of liver hepatocytes. PCSK9 (proproteinconvertasesubtilisin/kexin type 9) is a proteolytic enzyme that destroys LDL receptors and hence indirectly modulates serum LDL cholesterol (LDL-C). Increased LDL-C in the bloodstream results from fewer LDL receptors, whereas blocking or binding circulating PCSK9 leads in more LDL receptors and a decrease in serum LDL-C. Alirocumab and evolocumab are two PCSK9 inhibitors that have been licenced for use[32].

Mechanism of action:PCSK9 (proproteinconvertasesubtilisin/kexin type 9) is a newly discovered cholesterol metabolism regulator. Increased exercise is linked to greater LDL cholesterol levels, and autosomal dominant familial hypercholesterolemia with very high cholesterol levels, early atherosclerotic vascular disease, and the development of tendon xanthomas is caused by particular gain of function mutations.

Side effects: Mild injection site responses, Nasopharyngitis,No elevated hepatotoxicity signal,When compared to ezetimibe, there was no increase in muscle-related symptoms or muscle enzymes.

8.5 cholesterol absorption inhibitor(Ezetimibe)

The discovery and development of ezetimibe, the first in a class of pharmaceuticals that block phytosterol and cholesterol absorption in the intestine, has improved hypercholesterolemia treatment. It prevents cholesterol from being absorbed from the small intestine while having no effect on the plasma concentrations of fat-soluble vitamins. When statins and ezetimibe are used together, LDL cholesterol levels can be reduced by 25%, compared to only 6% when statin doses are doubled[33].

Mechanism of action: By blocking the Niemann–Pick C1-like 1 protein (NPC1L1), a human sterol transport protein, ezetimibe specifically reduces cholesterol absorption in the small intestine, resulting in a reduction in the transportation of intestinal cholesterol to the liver. The elimination of cholesterol from the blood increases as a result of LDL[34.35].

Side effects: The most common side effects of Ezetimibe are headache, abdominal pain, and diarrhoea. Ezetimibe appears to raise the levels of alanine transaminase and aspartate transaminase in liver function tests.

8.6 Cholesteryl ester transfer protein (CETP) inhibitors

CETP increases the transfer of cholesteryl esters from anti-atherogenic HDLs to pro-atherogenic apolipoprotein B-containing lipoproteins such as VLDLs and LDLs in the liver.Furthermore, the majority of research found evidence that CETP may play a proatherogenic function in reverse cholesterol transfer, supporting the concept that inhibiting CETP slows atherosclerosis progression. Novel chemicals dalcetrapib and anacetrapib are in Phase III clinical studies. Dalcetrapib reduced CETP activity by 50% and increased HDL cholesterol levels by 31% while leaving LDL cholesterol levels unchanged[36].

8.7 APOLIPOPROTEIN B SYNTHESIS INHIBITORS

Apolipoprotein B (apoB) is a component of very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (LDL), and lipoprotein(a) (Lp[a]), with one molecule in each lipoprotein particle. In the liver, ApoB is expressed all of the time. The possibility for hepatic compensation via enhanced beta oxidation of hepatic lipid, as well as steatosis, are unknown effects of pharmacologic inhibition of apoB production[37].

Mechanism of action: Mipomersen is a second-generation antisense oligonucleotide (ASO) that suppresses the manufacture of apolipoprotein B-100 (apoB-100) by producing a substrate for ribonuclease H (RNase H), a ubiquitously expressed nuclease that preferentially hydrolyzes the ribonucleic acid (RNA) strand of a duplex.Second-generation ASOs are synthetic phosphorothioate-modified oligodeoxynucleotides with 20 -O-(2-methoxyelthyl)-D-ribose (20 -MOE) modified nucleotides incorporated into a portion of the ASO for increased affinity toward the target RNA and greater resistance to exonuclease and endonuclease activity, while maintaining a 20 -deoxy domain to support RNase H activity.

Mipomersen binding to apoB mRNA and RNase H activity can happen in the nucleus or in the cytoplasm. VLDL 1/4 very-low-density lipoprotein; LDL-C 1/4 low-density lipoprotein cholesterol.

Side effects: Swelling of the face, lips, tongue, or throat, as well as difficulty breathing.

8.8 MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN INHIBITOR(MPT INHIBITOR)

MTP is an endosomal protein found in hepatocytes and enterocytes of the intestine. MTP catalyses the formation of VLDL, or chylomicrons, from cholesterol, triglycerides, and apo B.MTP-Is (microsomal triglyceride transfer protein inhibitors) are a new class of cholesterol and triglyceride-lowering drugs that can alter lipoprotein synthesis in both the liver and the gut.

Mechanism of action: When microsomal triglyceride transfer protein (MTP) is suppressed, both the hepatic and intestinal production of very low density lipoproteins (VLDL) and chylomicrons are stopped. As a result, this process provides a highly effective pharmacological target for lowering postprandial lipemia and lowering low-density lipoprotein (LDL) cholesterol. A breakthrough in the treatment of atherosclerosis and cardiovascular disease could arise from the combination of these effects.

Side effects: Nausea and vomiting**,** Indigestion**,** Abdominal discomfort**,** Fever**,** Flu-like symptoms**,** Diarrhea**,** Constipation.

8.9 ANGIOPOIETIN-LIKE 3 (ANGPTL3) INHIBITORS

Lipoprotein metabolism is regulated by angiopoietin-related proteins. Lipoprotein lipase (LPL) is the major enzyme involved in the breakdown of triglyceride-rich lipoproteins, and ANGPTL3 is an endogenous inhibitor of LPL. Noncarriers showed 27% lower triglyceride levels, 9% lower LDL cholesterol levels, and 4% lower HDL cholesterol levels than ANGPTL3 variants[38].

Mechanism of action: The availability of triglycerides, which are formed from substrates generated from the supply of free fatty acids from adipocytes, VLDL and chylomicron remnants, and simple sugars via the portal vein, is required for hepatic VLDL synthesis. Insulin signalling inhibits hepatic VLDL synthesis and secretion, as seen by TG-rich VLDL particle lipidation. The amount of TG in each VLDL particle, on the other hand, may be reduced. Reduced lipidation of VLDL in ANGPTL3 deficiency may be due to a decrease in the flow of free fatty acids into the liver from the circulation.

Side effects: Itching, fever, muscle weakness, or nausea during the injection may occur. Dizziness and runny/stuffy nose may also occur.

TABLE 4:Existing hypolipidemic drugs

CLASSIFICATION	DRUGS
3-Hydroxy-3-methylglutaryl coenzyme A (HMGCoA) Reductase inhibitors	Atorvastatin Simvastatin Rosuvastatin Pita vastatin Pravastatin Lovastatin

Fibric acid derivatives (Fibrates**)**	clofibrate gemfibrozil bezafibrate ciprofibrate fenofibrate
Bile acid sequestrants	cholestyramine. colesevelam. Colestid. colestipol. LoCholest. Prevalite. Questran. Questran Light.
PCSK9 Inhibitors	Evolocumab Alirocumab
Cholesterol absorption inhibitor	Ezetimibe
CETP Inhibitors	Anacetrapib Dalcetrapib Evacetrapib Obicetrapib Torcetrapib
Apolipoprotein b-synthesis inhibitors	Mipomersen
Microsomal triglyceride transfer protein inhibitor	Lomitapide
Angiopoietin-like 3 inhibitors	Evinacumab

9. HYPOLIPIDEMIC ACTIVITY OF DIETARY PLANT FIBERS

. Dietary fibre from a variety of plant foods, such as guar gum, oat bran, and wheat bran, has been shown to lower cholesterol levels. To differing degrees, the various components of dietary fibre exert hypolipidemic effects.Pure cellulose has been shown to be more hypocholesterolemic than hemicellulose and pectin[39].

Table 5: Cholesterol reducing herbs

Herbs	**Botanical name**	**Function**
Alfalfa	Medicagosatina	Helps in clearing art congested with cholesterol.
Arjuna	Terminalia arjuna	It dissolves cholesterol in the coronary artery.
Coriander	Coriandrum sativum	It is diuretic in nature and flush out excess cholesterol from the body.
Garlic	Allium cepa	Reduces blood cholesterol level.

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Guggulu	Commiphoramukul	Reduces blood cholesterol level.
Holy Basil	Ocimum sanctum	It dissolves the cholesterol accumulated in the arteries.

Plants having hypolipidemic activity

Because of their therapeutic powers and the fact that they are completely natural, medicinal plants have traditionally been regarded as a healthy source of life for all people. Medicinal plants are widely used by the majority of people to treat a variety of ailments and illnesses, and they have a significant economic influence around the world[40,41,42].

Table 6: Plants having hypolipidemic activity

Plant	Botanical name	Part used	Family
Inca wheat	Amaranthuscaudatus	Leaves	Amaranthaceae
Palash	Buteamonosperma	Leaves	Fabaceae
Amaltas	Cassia fistula	Legume	Fabaceae
Guggul	Commiphoramukul	Gum resin	Burseraceae

DIET AND EXERCISE

Dietary factors that influence lipid levels include the modification of nutritional components, the consumption of specific foods, the use of food additives and supplements, and the primary dietary methods.Reducing saturated and trans fat intake, increasing polyunsaturated and monounsaturated fat intake, fortifying foods with plant stanols or sterols, isocalorically adding tree nuts to the diet and adopting a Portfolio, Mediterranean, low-carbohydrate, or low-fat diet are the most beneficial changes[43.]The Portfolio Diet is a plant-based TLC diet that also includes soluble fibre, soy and other vegetable proteins, plant sterols, and almonds. (Table 7). The Portfolio Diet has been demonstrated in controlled studies to lower LDL cholesterol levels by 29 to 35 percent, which is comparable to a diet low in saturated fats and cholesterol plus 20 mg of lovastatin daily. After one year, 32% of people who ate self-selected Portfolio Diet items saw a drop in LDL cholesterol of more than 20%.

Table 7: The Portfolio Diet for Lowering LDL CholesterolLevels

Component	Recommended amount
Almonds	23 g whole almonds per 1,000 kcal consumed
Plant sterols	1 g plant sterols (e.g., from an enriched spread) per 1,000 kcal Consumed
Soluble fiber	10 g viscous fibers (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	Consume additional sources of plant protein and fiber in the form of dried legumes; eat 5 to 10 daily servings of fruit and vegetables.

Exercise: Exercise's impact on serum lipid levels have been extensively researched. The results of a meta-analysis of published data show that regular aerobic exercise raises HDL cholesterol levels by an average of 1.9 to 2.5 milligrams per deciliter (0.05 to 0.06 mmol per L).Total cholesterol, LDL cholesterol, and triglyceride levels all decreased by an average of 3.9, 3.9, and 7.1 mg per dL (0.10, 0.10, and 0.08 mmol per L), respectively.The minimum quantity of exercise required to raise HDL cholesterol levels is 900 kcal per week, or around 120 minutes of regular aerobic exercise.HDL cholesterol levels rise by 9% (3.7 mg per dL [0.10 mmol per L]) and triglyceride levels fall by 11% (19.3 mg per dL [0.22 mmol per L]) in individuals with cardiovascular disease who exercise aerobically, showing larger advantages in this high-risk group[44].

10. COMBINED THERAPY

Statin monotherapy may not be enough to reach low-density lipoprotein cholesterol objectives, especially in high-risk patients. Furthermore, atherogenic dyslipidemia is seen in several patient subgroups. As a result, combining a statin with other hypolipidemic medicines, especially in the form of a single pill, may provide additional benefits. Furthermore, the combined hypolipidemic medicines' complimentary modes of action may provide additional benefits such as improved glucose metabolism. As a result, fixed-dose combinations of hypolipidemic medicines may be an appealing alternative for successful and safe hypercholesterolemia therapy[45].

Table 8. Emerging Fixed-Dose Drug Combinations.

Fixed-Dose Drug Combination	Main Effects on Lipids
Rosuvastatin/ezetimibe	Further LDL-C reduction compared with rosuvastatin monotherapy
Atorvastatin/fenofibrate	LDL-C and triglycerides reduction
Atorvastatin/hydroxychloroquine	Further LDL-C reduction compared with atorvastatin monotherapy. Modest HbA1c and glucose reduction

11. INTERGRATIVE MEDICINE USED IN HYPERLIPIDEMIA

The importance of complementary and alternative medicine (CAM) in the management of dyslipidemia is the topic of this special issue. Complementary and alternative medicine (CAM), often known as nonconventional medicine, refers to a diverse range of health-care techniques that are not part of a traditional health-care system (such as herbal medicine, acupuncture, yoga, meditation, and homoeopathy[46].

CONCLUSION

Hyperlipidemia, a primary cause of coronary heart disease, is quite common in India. The link between hyperlipidemia and the development of cardiovascular disease has long been known. Antioxidants, fibrates, bile acid binding resins, and other treatments for hyperlipidemia have been described in a number of trials. Diet, physical exercise, and smoking are all controllable risk factors. Age and gender are two non-modifiable characteristics . Non-healthy people cause adiposopathy. Diet and a low active lifestyle are harmful to the environment, and persons who are genetically prone Prior to the event, The majority of patients have physical results that appear to be abnormal. Regardless, Various lipid disorders frequently coexist, Management strategies are determined by the situation.

irregularity of lipids There are several nations or regions that have their own dyslipidaemia guidelines were produced. Dyslipidemia prevention and therapy consists of a large number of operations. These methods involve risk assessment, treatment goal establishment, increased activity level, food change, medical therapy, follow-up, reassessment, and procedure adjustment as needed. Raise awareness of the disease and the actions that must be taken by all family members. Future research is needed to identify the mechanobiological mechanisms that govern the response of lipid profiles to dietary loading.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCE

1. Nirosha K, Divya M, Vamsi S, Mohammed Sadiq, A review on hyperlipidemia, Int. j. novel trends pharm. 2014;2(1): 1-10.
2. Ghassan F.Shattat,A Review Article on Hyperlipidemia: Types, Treatments and New Drug Targets, Biomed Pharmacol J.2014; 7(2), 399-409.
3. Niharikaverma,introduction of hyperlipidmia and its treatment. Int J Curr Pharm Res, 2019 9(1).
4. Carlson LA, Bittiger LE. Ischemic heart disease in relation to fasting values of plasma triglycerides and cholesterol. Lancet 1972;1:865-68.
5. Katcher HI, Hill AM, Lanford JL, Yoo JS, Kris-Etherton PM. Lifestyle approaches and dietary strategies to lower LDL-cholesterol and triglycerides and raise HDL-cholesterol. EndocrinolMetabClin North Am. 2009;38(1):45-78.
6. Nielsen L. Transfer of low density lipoprotein into the arterial wall and risk of atherosclerosis. Atherosclerosis 1996;123:1–15.
7. Heiss G. The epidemiology of plasma high-density lipoprotein cholesterol levels. Circulation 1980;62:116-36.
8. Ginsberg HN, Goldberg IJ. Disorders of intermediary metabolism (Disorders of lipoprotein metabolism). In: Principles of Internal Medicine. 15th edition; 2001.
9. Santamarina-FojoS.,González-Navarro, H., Freeman, L., Wagner, E.,Nong, Z. Hepatic lipase, lipoprotein metabolism,Thromb.Vasc.Biol.,24(10): 1750-1754 (2004).
10. Amanda Brahm and Robert A. Hegele, Hypertriglyceridemia, Nutrients.2013 Mar; 5(3): 981–1001.
11. Bhatnagar D, Soran H, Durrington PN. Hypercholesterolaemia and its management. Br Med J 2008;337:993.
12. Avogaro P, Cazzolato G. Familial hyper-HDL-(α)-cholesterolemia. Atherosclerosis 1975;22:63-7.
13. Grundy SM, Balady GJ, Criqui MH. Primary prevention of coronary heart disease. Circulation 1998;97:1876-7.
14. Stone NJ. Secondary causes of hyperlipidemia. Med Clin North Am 1994;78:117-41.

15. Shantakumari N, Sequeira S, EL deeb R. Effects of a yoga intervention on lipid profiles of diabetic patients with dyslipidemia. Indian Heart J 2013;65:127-31.
16. National cholesterol education program: Second report of the expert panel on detection, evaluation and treatment of high blood cholesterol in adults. Circulation 1994;89:1333-445.
17. AAFP. Endocrine Society releases guidelines on diagnosis and management of hyperglyceridemia. Am Fam Physician 2013;88:142-4.
18. Gupta R, Mohan I, Narula J. Trends in coronary heart disease epidemomiology in India. Ann Global Health 2016;82:307-15.
19. World Health Organization. Quantifying Selected Major Risks to Health. World Health Organization, Geneva; 2002.
20. Albrink MJ, Meiges WJ, Man EB. Serum lipids, hypertension and coronary artery disease. Am J Med 1961;31:4-23.
21. Smith D. Epidemiology of dyslipidemia and economic burden on the healthcare system. American Journal of Managed Care. 2007;13(S3):S68-S71.
22. Ginghina, C., Bejan, I.,Ceck, C. D. Modern risk stratification in coronary heart disease.J.Med. Life. 4(4): 377-86 (2011).
23. Albrink MJ, Meiges WJ, Man EB. Serum lipids, hypertension and coronary artery disease. Am J Med 1961;31:4-23.
24. GerasimosSiasos, DimitrisTousoulis, et al., Inflammatory Markers in Hyperlipidemia: From Experimental Models to ClinicalPractice,Current Pharmaceutical Design, 2011, 17, 4132-4146.
25. Tripathi, K. D. Essentials of Medical Pharmacology, 6thedn, India: JP brothers medical publishers, pp613-614 (2008).
26. Jones PH. Lovastatin and simvastatin prevention studies. Am J Cardiol 1990;66:398-438.
27. Costel P. Molecular pathways and agents for lowering LDL-cholesterol in addition to statins. PharmolTher 2010;126:263-78.
28. Scott J. Trends in the therapy of hyperlipidemia. Drugs Today 1991;27:223-8.
29. Alsheikh-Ali AA, Karas RH. Ezetimibe, and the combination of ezetimibe/simvastatin, and risk of cancer: a post-marketing analysis. J ClinLipidol 2009;3:138-42
30. Fruchart, J-C., Staels, B., Dallongeville, J., Auwerx, J., Schoonjans, K., Leitersdorf, E. Mechanism of action of fibrates on lipid and lipoprotein metabolism.Circulation.,98(19): 2088-2093 (1998).
31. Kishor, S., Kathiravan, M., Somani, R., Shishoo, C.H. The biology and chemistry on hyperlipidemia.Bioorg. Med. Chem., 15(14): 4674-4699 (2007).
32. Fries ED. Hypertension and atherosclerosis. Am J Med 1969;46:735-40.
33. Nutescu, E. A., Shapiro, N. L. Ezetimibe: a selective cholesterol absorption inhibitor.Pharmacotherapy., 23(11): 1463-74 (2003).
34. Goldberg, A. S., Hegele, R. A. Cholesteryl ester transfer protein inhibitors for dyslipidemia: focus on dalcetrapib.Druges.Devel.Ther.,6: 251–259 (2012).
35. Y. Ando, T. Shimizugawa, S. Takeshita, M. Ono, M. Shimamura, R. Koishi, H. Furukawa, A decreased expression of angiopoietinlike 3 is protective against atherosclerosis in apoE-deficient mice. J. Lipid Res. 44(6), 1216–1223 (2003).
36. 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).
37. Anna Tikka, MattiJauhiainen, The role of ANGPTL3 in controlling lipoprotein metabolism, Endocrine (2016) 52:187–193.
38. T. Shimizugawa, M. Ono, M. Shimamura, K. Yoshida, Y. Ando, R. Koishi, K. Ueda, T. Inaba, H. Minekura, T. Kohama, H. Furukawa, ANGPTL3 decreases very low density

lipoprotein triglyceride clearance by inhibition of lipoprotein lipase. J. Biol. Chem. 277(37), 33742–33748 (2002).
39. Giorgio R, Francesco P, Rodalfo P, Duilio P. eds. Therapeutic selectivity and risk/benefit assessment of hypolipidemic drugs. Raven Press: New York; 1982.
40. Llaverías, G., Laguna, J. C., Alegret, M. Pharmacology of the ACAT inhibitor avasimibe (CI-1011).Cardiovasc. Drug Rev., 21(1): 33-50 (2003).
41. Vinteagarwal and B.M.Chauhan, A study on composition and hypolipidemic effect of dietary fibre from some plant foods, Plant Foods for Human. Nutrition 38:189-197 (1988).
42. Cunningliam AB. An investigation of the herbal medicine trade in Natal/Kwa Zulu. Investigational Report No: 29, Institute of Natural Resources, University Natal, Pietermaritzburg; 1988.
43. Page IH, Stamler J. Diet and coronary heart disease. Mod Concepts Cardiovasc Dis 1968;37:119-30.
44. Bauman AE. Updating the evidence that physical activity is good for health: an epidemiological review 2000-2003. J Sci Med Sport 2004;7:6-19.
45. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol 2009;8:453-63.
46. WarisQidwai, FirdousJahan,andKashmiraNanji, Role of Complementary and Alternative Medicine in Controlling Dyslipidemia, Evidence-Based Complementary and Alternative Medicine Volume 2014, Article ID 215731.