A Global Review Article on Hyperlipidemia

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ABSTRACT
Hyperlipidemia is a medical condition characterized by an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters, phospholipids and or plasma lipoproteins including very low-density lipoprotein and low-density lipoprotein along with reduced high-density lipoprotein levels. This elevation of plasma lipids is among the leading risk factors associated with cardiovascular diseases. Introduction, type of lipoprotein, classification of hyperlipidemia, Complications of hyperlipidemia, causes; Symptoms of hyperlipedemia, Pathogenesis of hyperlipidemia, Pathogenesis of hyperlipidemia, diagnosis, prevention, treatments.

Keywords: Hyper lipidemia,cholesterol, Fibrates, statins.

INTRODUCTION

Hyperlipidemia is outlined as an elevation of one or more of the following: cholesterol, cholesterol esters, phospholipids, or triglycerides. Abnormalities of plasma lipids can result in predisposition to coronary, cerebrovascular, and peripheral vascular arterial diseases.1,2 The hyperlipidemia is traditionally defined as conditions in which the concentration of cholesterol or triglyceride-carrying lipoproteins in plasma exceeds an arbitrary normal limit.3,4 Liver is to blame for dominant the content of cholesterol with in the blood stream. In the body, liver produces roughly 80% of the cholesterol whereas rest of the cholesterol is obtained from the food like fish, eggs, meat.5,6 Hyperlipidemia is considered one of the major risk factors causing to cardiovascular diseases (CVDs). CVDs accounts for 1/3 rd of total deaths around the total world, it is believed that Cardiovascular diseases will turn out to be the main cause of death and incapacity worldwide by the year 20207-9. Meanwhile, statins and fibrates stay the many enemy of hyperlipidemic specialists for the treatment of raised plasma sterol and triglycerides individually, with the value of most symptoms on the muscles and also the liver.10

TYPES OF LIPO PROTEINS

Chylomicrons (CM),

Very low-density lipoproteins (VLDL),

Low-density lipoproteins (LDL),

Intermediate-density lipoproteins (IDL)

High-density lipoproteins (HDL)11

Chylomicrons

These are the largest particles both in size as well as in density, and its concentration is directly correlated with dietary triglyceride content.

VLDL:

Very low-density lipoproteins are smaller particles carrying more chylomicrons than triglycerides, and are secreted from the liver. Very low density lipoprotein carries sterol from the liver to organs and tissues in the body. They are formed from the mixture of cholesterol and triglycerides.12

IDL:

VLDL particles after lysis by lipase enzyme in the capillaries of adipose tissue and muscle give rise to intermediate density lipoprotein.

LDL:

According to Lee et al., and Galeano et al., low-density lipoproteins are synthesised partly in intestinal chyle and partly after lipolysis of very low density lipoproteins. It is directly correlative to CHD.

HDL:

HDL is commonly referred as good cholesterol. High-density lipoproteins are synthesized in the liver. It carries cholesterol and other lipids from tissues back to the liver for degradation. HDL plays an antiatherogenic role.13
CLASSIFICATION OF HYPELIPIDEMIA

On the idea of lipid type

Hypercholesterolemia—In this the level of cholesterol is elevated.

Hypertriglyceridemia—It is outlined as level of triglycerides elevated.

On the idea of causing factor (fig.1)

3.1. Primary (Familial) hyperlipidemia

It is also called familial due to a genetic defect, it may be monogenic: a single gene defect or polygenic: multiple gene defects. Primary hyperlipaemia can usually be resolved into one of the abnormal lipoprotein pattern summarized.

Type I—Raised cholesterol with high triglyceride levels.

Type II—High cholesterol with normal triglyceride levels.

Type III—Raised cholesterol and triglycerides.

Type IV—Raised triglycerides, atheroma and uric acid.

Type V—Raised triglycerides

3.2. Secondary (Acquired) hyperlipidemia

It is acquired because it is caused by another disorder like diabetes, glomerular syndrome, chronic alcohol intake, hypothyroidism and with use of drugs like corticosteroids, beta blockers and oral contraceptives. Secondary hyperlipidemia combined with significant hyper triglyceridemia can cause pancreatitis.15

Coronary Artery Disease

Atherosclerosis, the major cause of coronary artery disease, characterized by the accumulation of excess lipid and the formation of fibrous plaques within the wall of the arteries resulting in narrowing of the arteries that supply blood to the myocardium, and results in limiting blood flow and insufficient amounts of oxygen to meet the needs of the heart.17

Myocardial infarction

MI is a condition which occurs when blood and oxygen supplies are partially or completely blocked from flowing in one or more cardiac arteries, leads to damage or death of heart cells. The occlusion may be due to ruptured atherosclerotic plaque.18

Ischemic stroke or cerebrovascular accident

Stroke is the fourth leading cause of death. Usually strokes appear due to blockage of an artery by a blood clot or a piece of atherosclerotic block that breaks loose in a small vessel within the brain. Many clinical trials revealed that reducing of low-density lipoprotein and total cholesterol by 15% significantly reduced the risk of the first stroke19.

CAUSES

Sterol, fatty acids, trans fat in the following food may increase the lipid level in blood:
- Dairy products.
- Ice cream pastries.
- Fried and junk foods.
- Meat etc.

Other disorders like obesity, diabetes mellitus and hypothyroidism is major causes for hyperlipidemia. Smoking and low exercising may lead to hyperlipidemia.21 Excessive use of alcohol also increases the risk of hyperlipidemia. Certain drugs as steroids and β-blockers may cause hyperlipidemia (3) Lipoprotein lipase mutations.

Several other causes of hyperlipidemia
- Obesity.
- Genetic or inheritance.
- Smoking.
- Several drugs such as corticosteroids, estrogen, beta blockers may risk for hypertriglyceridemia.
- Alcohol, steroids, hypothyroidism, kidney failure etc.
- Low exercise 23

SYMPTOMS OF HYPERLIPIDEMIA

Hyperlipidemia usually has no noticeable symptoms and tends to be discovered during routine examination for atherosclerotic cardiovascular disease 24
- chest pain (angina), heart attack or stroke.
• When levels are exceed high, cholesterol may be deposited in tendons or just beneath the skin under the eyes.
• Liver, spleen or pancreas are swelled.
• Blood vessels block in brain and heart.
• Higher rate of obesity and glucose intolerance.
• Pimple like lesions across the body

**PATHOGENESIS OF HYPERLIPIDEMIA**

During the early stages of the hyperlipidemia, blood monocytes and platelets attach to a vessel wall at the sites of endothelial damage. The release of the mediators such as platelet derived from growth factors leads to a growing of smooth cells in the intimad and medial lining of the vessel, collagen synthesis, cholesterol uptake and the initialfor the hyperlipidemic plaque results. Plaque ruptures are resulting in the acute syndromes of unstable angina, myocardial infarction and sudden cardiac death.

**SIGNIFICANCE**

Health care providers are concerned about hyperlipidemia because of the well established association between lipid concentrations and the risk of CVD, the leading cause of death in the United States. A landmark study that helped establish that therapeutic interventions to lower cholesterol levels result in reduced risk of cardiovascular morbidity or mortality was the Lipid Research Clinics Coronary Primary Prevention Trial, which was published in two parts (each using a different statistical analysis) in 1984. A complete history information of the cholesterol controversy can be found in a multi-part review (available on line) which was published over a 3 year span in the Journal of Lipid Research.

**DIAGNOSIS**

No any other specific symptom for Hyperlipidemia it can be only detected by a blood test. Screening for hyperlipidemia is done with a blood test called a lipid profile. Hyperlipidemia may be diagnosed by a regular checkup of LDL, HDL, VLDL and Triglycerides in blood test.

**PREVENTION OF HYPERLIPIDEMIA**

• Low fatty acid and cholesterol diet should be taken.
• Intake of foods high in soluble fiber such as oats, beans and certain fruits.
• Exercise regularly to maintain a healthy weight.

**TREATMENT**

The following lifestyle modification may lower the cholesterol level:

• Proper diet.
• Less weight of the body.
• Regular exercise.
• Having non-oily food.
• Eat pears, apples, bananas etc.
• Have fish twice a week.
• Maximum time the lifelong treatment and medications are required
• Fibrates (fenofibrate), statins may lower the triglyceride levels

**TREATMENTS**

**Therapeutic lifestyle changes**

Diet changes, regular physical exercise, smoking cessation, and weight reducing should be tried as initial treatment, especially in mild cases of hyperlipidemia and in persons without CHD or CHD risk equivalent and<2 risk factors. It should be kept in mind that when dieting, cholesterol intake is reduced. At the same time, production of cholesterol, especially by the liver, increases. It is recommended that the intake should be restricted to 25%-35% of energy intake and that saturated fatty acids make up less than 7% of energy intake and that cholesterol intake should be less than 200 mg daily. The intake of plant sterol esters and soluble fibre is preferred.

**Ayurvedic treatment**

Ayurvedic medicine is one of the world’s earlier medical systems. Ayurvedic therapeutics is based on the “laws” of nature. Its approach to health-care is based on understanding the interrelationship of body, mind and spirit. The aim of ayurveda medicine is to integrate and balance these elements to prevent illness and promote health through diet, nutrition, herbs, yoga, meditation and daily seasonal routines.

**Home medications**

In other hand, pharmacological and ayurvedic treatment, some home remedies are also beneficial in the treatment of hyperlipidemic Nuts; Almonds lower LDL by 4.4%, Walnuts lower LDL by 16%.

- Oatmeal; Drops LDL by 12-24%.
- Orange juice ; Reduce blood cholesterol level.
- Coriander seeds; Lower cholesterol and triglycerides levels.
- Fish oil; Lower triglycerides levels.
- Honey ; Lower cholesterol level.
- Soyabeans ; Lower the production of new cholesterol.
- Indian Gooseberry; decrease the excess cholesterol build-up.
- Brown Rice ; Lower cholesterol level.
- Turmeric ; Lowers LDL cholesterol levels.
- Brinjal ; Lowers LDL cholesterol levels.
- Coconut oil ; Increases HDL and improves the LDL/HDL ratio.
Fenugreek seeds; Lowers cholesterol level by 14%³

**Plants having hypolipidemic activity**

Medicinal plants have always been considered as a healthy source of life for all people due to its rich therapeutic properties and being 100% natural.⁴³ Over the past decade, herbal medicine has become a topic of global significance, making an impact on both world health and international trade. Regular usage of herbal medicine by a large proportion in the developing countries is largely due to the high cost of Western Pharmaceuticals and Healthcare.⁴³

**PHARMACOLOGICAL TREATMENT**

Lot of hypolipidemic drugs are available in the market for the treatment of hyperlipidemia. Drug Project indicating that the drugs are relatively ineffective for preventing myocardial infarction in patients with pre established CHD.⁴⁴

**Drug therapy**

Increase LDL, the presence of risk factors, and documentation of CHD should qualify developing drug therapy along with TLC. Current lipid-lowering drugs include statins, ezetimibe, bile acid sequestrants or bile binding resins, niacin, fibric acid derivatives, and plant sterols. Medication specially designed to lower blood cholesterol levels may be prescribed when dietary modifications prove inadequate.⁴⁵

**Fibrates**

Fibrates include clofibrate, gemfibrozil, fenofibrate, and bezafibrate, are a widely used class of antihyperlipidemic agents, results in a significant reduction in plasma triglycerides and a modest reduction in LDL sterols. HDL cholesterol level increases moderately. Angiographic experimental results showed that fibrates play an maximum role in slowing the development of coronary atherosclerosis and lowering the occurrence of coronary artery disease.

**Mechanism of action**

Data from studies in rodents and in humans imply 4 main mechanisms of fibrates:

**Stimulation of lipoprotein lipolysis**

Fibrates acts primarily as ligands for the nuclear transcription receptor, PPAR-α. They elevate the expression of lipoprotein lipase, apo, and down-regulate apo C-III, an inhibitor of lipolysis. Fibrates also elevated the level of HDL cholesterol by enhancing the expression of apo AI and apo All.⁷

**Enhancing hepatic fatty acid (FA) uptake and reduction of hepatic triglyceride production.**

Fibrates increase the formation of fatty acid transport protein and acyl-CoA synthetase, which contribute to the increase uptake of fatty acid by the liver and also a result in a lower accessible of fatty acids for triglyceride formation.

**Increase removal of LDL particles.**

Fibrates, appears to elevated LDL catabolism via the receptor-mediated pathway; LDL particles became major and more lipid high level and therefore had more affinity for receptors.

**Increase in HDL formation and stimulation of reverse cholesterol transport.**

Fibrates enhance apo A-I formation in the liver which leads to the observed elevation in plasma levels of apo A4 and HDL-cholesterol and a more effective for reverse cholesterol transport.⁵

**Nicotinic acid derivatives (Niacin)**

Niacinis, a water-soluble vitamin of type B, is the earliest lipid reducing agent used to treat hyperlipidemia and proved to decrease cardiovascular morbidity and total mortality. It reduces the total cholesterol, LDL cholesterol, triglycerides⁵

**Mechanism of action**

Niacin inhibits hormone-sensitive lipase which decreases triglycerides lipid lysis the main producer of circulating free fatty acids. The liver usually used for these circulating fatty acids as a major lead role for triacylglycerol formation. Therefore, niacin inhibits VLDL secretion, in turn lower the production of LDL.⁵

**Side effects**

Niacin treatment has been plagued by low patients compliance rates. The most common side effects are intense cutaneous flush which affect more than three quarters of patients, itching, headache and some patients experience nausea and abdominal discomfort. Niacin also elevates liver enzymes.⁵⁵

**Selective cholesterol absorption inhibitor (Ezetimibe)**

The discovery and development of ezetimibe, the first member of a group of drugs that inhibit intestinal absorption of phytosterols and cholesterol, has improved the treatment of hypercholesterolemia. It inhibits the absorption of sterol from the small intestine no any effect on the plasma concentrations of the vitamins ADEK

**Mechanism of action**

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

**Side effects**

Ezetimibe is usually well tolerated drug; the most common side effects include headache, abdominal pain and diarrhea. Ezetimibe appears to cause elevations in liver
function tests include elevations in alanine transaminase and aspartate transaminase.7

NEW POTENTIAL TARGETS AND TREATMENTS

Recently, many clinical trials revealed new potential agents with promising antihyperlipidemic activity.

Acyl-CoA cholesterol acyl transferase inhibitors (ACAT)

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

Microsomal triglyceride transfer protein (MTP) inhibitors

Microsomal triglyceride transfer protein (MTP) has multiple functions including transferring neutral lipids between membrane vesicles, the biosynthesis of CD1, antigen-presenting molecules, as well as in the regulation of cholesterol ester biosynthesis.

Cholestereryl ester transfer protein ( CETP) inhibitors

CETP in liver facilitates the shift of cholestereryl esters from anti-atherogenic HDLs to proatherogenic apo lipoprotein B containing lipoproteins, including VLDLs and LDLs. Furthermore, most studies showed that there is evidence that CETP may play a proatherogenic role by involving in reverse cholesterol transport and support the idea that inhibition of CETP slows the progress of atherosclerosis. 7

Squalene synthase inhibitors

Squalene synthase (SqS) catalyzes farnesyl pyrophosphate to formlation of squalene. Catalysis by SqS is the first committed step in sterol synthesis, and one of these sterols is cholesterol.16

Hydroxymethylglutaryl-CoA synthase inhibitors

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

ATP citrate lyase inhibitors

ATP citrate lyase (ACL) is the primary enzyme accountable for the synthesis of cytosolic acetocetyl-CoA and oxaloacetate. Synthesis of cytosolicacetocetyl-CoA and oxaloacetate represent an important step in the synthesis of fatty acids and cholesterol. For this reason, inhibition of ACL is a promising strategy in the treatment of dyslipidemia.

Acyl coenzyme A: diacyl glycerol acyltransferase (DGAT)

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

Squalene epoxidase inhibitors

Squalene epoxidase is one of the rate controlling enzymes for the first oxygenation step in sterol bio synthesis.

Lanoster synthase inhibitors

lanoster synthase (LSS) Catalyzes the cyclization of (S)-2,3-oxidosqualene to lanosterol, the initial sterol between in the cholesterol synthesis pathway.7

RECENT DRUG FOR HYPERLIPIDEMICS

The FDA has approved two new non-statin drugs that clinical trials indicated can help reduce high cholesterol. Nexletol and Nexlizet can be used with statins that have modulate or minimal side effects. The two new drugs have some side effects different from those associated with statins.46

CONCLUSION

From the above study the hypelipidemia condition is major risk factor for cardiac disease. hypelipidemia can be treated by recent drugs and diet food chart, home remedies, regular physical exercise. If attentive care is given to diet maintenance and fitness may reduce the risk of hyperlipidemic, CVD and many other disease.

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