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Hyperlipidemia- A Critical Pathological Condition

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HUMAN

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ABSTRACT

Hyperlipidemia is the condition in which there is an increase in lipid content of the body that probably includes the high-rise in triglycerides and cholesterol levels. The triglycerides and cholesterol have a prominent role in the functioning of the human body. But the excess amount may result in severe critical health issues which can cause disabilities that might be fatal sometimes. The complexes of lipid and proteins known as lipoproteins are transported from cell to cell for the functioning of the body. The three major classes of lipoproteins found in serum are high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). Hyperlipidemia is caused due to various factors such as lifestyle habits or treatable medical conditions, an underactive thyroid gland, pregnancy, alcohol consumption, kidney disorders etc. The treatment approaches for Hyperlipidemia include the Statins, the bile acid sequestrants and the fibric acid derivatives. However, further studies are required in order to provide more information about the safety and efficacy of novel antihyperlipidemic agents.

INTRODUCTION

Cardiovascular diseases are considered to be the leading cause of deaths all over the world. And, it is anticipated that the number of deaths due to CVDs may augment by the year 2020[1, 2]. Though lipids have a prominent role in the functioning of a human body, at certain levels, but if these are in surplus amount, it may result in several critical health issues which can cause disabilities that may be fatal sometimes. Hyperlipidemia is the condition in which there is an increase in lipid content of the body that probably includes the high-rise in triglycerides and cholesterol levels [3, 4]. Lipids are usually the "fats" present in the stream of blood that are often categorized as triglycerides and cholesterol. The cholesterol moves round the stream of blood and it is usually involved in the organization of cells in the body. It is also involved in the functioning of cells as well. While the triglycerides, in general, are either utilized promptly or gets accumulated in the adipose (fat) cells[5, 6]. Moreover, the modifiable risk factor that involves the levels of high cholesterol in the body which is perceptible by certainty that the cholesterol levels of plasma, if found greater than 200mg/dL can lead to 4.4 million deaths per year[7, 8]. Cholesterols are several types that comprise of combined forms which is basically classified as Total Cholesterol (TC), the cholesterol which is good known as High-Density Lipoprotein (HDL), and the one which is considered to be bad cholesterol is the Low-Density Lipoprotein (LDL)[9-10]. Due to various factors such as the factors related to detriment lifestyles like inadequacy of exercise, alcohol consumption or intake of diet containing high fat may result in the unusual raise in the levels of cholesterol [11]. Also, sometimes the other factors including diabetes and insensitive thyroid gland may also result in the raise in levels of cholesterol[12, 13]. Renal diseases, polycystic ovary syndrome or the high-rise in estrogen (female hormone) are basically considered to elevate levels of cholesterol in the body. Other major factors that contribute to the elevation of cholesterol levels in the body are the use of drugs such as beta- blockers, diuretics etc. [14]. The drugs or the class of drugs that play a prominent role in the treatment of hyperlipidemia are Statins, bile acid binding resins, inhibitors of cholesterol absorption, etc.[15-18]

CLASSIFICATION OF LIPID CONCENTRATIONS

Cholesterol, triglycerides and phospholipids are the major lipids in the body and they are transported from cell to cell as complexes of lipid and proteins are known as lipoproteins because they cannot be directly dissolved in blood.

Plasma lipoproteins are spherical particles with surfaces that consist largely of phospholipid, free cholesterol and protein, and cores that consist mostly of triglyceride and cholesterol ester. The three major classes of lipoproteins found in serum are low-density lipoproteins (LDL), high-density lipoproteins (HDL) and very low-density lipoproteins (VLDL).[19]

TOTAL CHOLESTEROL: Total cholesterol reading less than 200mg/dl is said to be desirable blood cholesterol level. Blood cholesterol level of 240mg/dl and above are classified as high blood cholesterol levels. Presence of risk factors along with high blood cholesterol levels and low HDL levels may contribute to the development of coronary heart disease.

In case of children the acceptable range of TC is less than 170mg/dl and elevated TC range is 200mg/dl and above. It is known that atherosclerosis begins in the childhood or adolescent years, hence children with high lipids or lipoprotein levels are at a greater risk of developing atherosclerosis in their lifetime.

TRIGLYCERIDE: The VLDL lipoprotein is a triglyceride-rich carrier of hepatic synthesized triglycerides. 150mg/dl is the normal range whereas greater than 500mg/dl is the elevated level of triglycerides.

Hypertriglyceridemia refers to a fasting plasma triglyceride measurement that is increased above 95 percentile for age and sex although additional quantitative or qualitative lipoprotein abnormalities may also be present. It is of two types, primary hypertriglyceridemia is caused due to genetic abnormalities or mutations whereas secondary hypertriglyceridemia is caused due to higher caloric intake as a result of obesity, alcohol consumption, diabetes mellitus particularly type 2, renal disease, a high-fat diet or a diet rich in high glycemic index content, insufficient physical activity and metabolic syndrome which ultimately causes storage of triglycerides in adipocytes throughout the body. Moderate hypertriglyceridemia is a risk factor for cardiovascular disease and severe hypertriglyceridemia for pancreatitis.[20]

LDL CHOLESTEROL:

LDL cholesterol is considered as the bad cholesterol because it contributes to plaque formation that clogs arteries and leads to atherosclerosis which may further precipitate heart attack, stroke or peripheral artery disease. It carries cholesterol from the liver to muscles, tissues and heart for deposition. Thus when present in high levels in the blood stream than necessary increases the risk of development and progression of CVD.

According to NCEP guidelines, LDL cholesterol concentrations below 100mg/dL are considered optimal, whereas concentrations in the range of 160-189 mg/dL are considered to the higher side. According to the strong heart study, LDL levels even when they are considerably below the NCEP targets, lowering of LDL cholesterol to <100mg/dl in all individuals with diabetes is recommended in order to prevent development of CVD– a recommendation suggested by American Diabetes Association. Thus the risk of CVD decreases with a decrease in LDL levels.

HDL CHOLESTEROL: It is considered good cholesterol because it helps remove LDL cholesterol from arteries and also act as scavenger carrying LDL away from arteries back to the liver where it is broken down and passed out of the body. One-third of the blood cholesterol is carried by the HDL. A healthy level of HDL may also protect against heart attack and stroke, while low levels increase the risk.

However, HDL is often interpreted in context of total cholesterol and LDL concentrations and is of less significance when LDL is low.

Optimal range of HDL cholesterol is less than 40mg/dl and 60mg/dl is considered to be an elevated level. [21]

VLDL CHOLESTEROL: VLDL differs from LDL because it contains very little protein and more amounts of fat. The main purpose of VLDL is to distribute the triglycerides from the liver to various tissues of the body. It is also associated with atherosclerosis and heart disease

CLASSIFICATION OF LIPID LEVELS:

- **LDL CHOLESTEROL**

Optimal range	<100 mg/dl
Near/above optimal	100-129 mg/dl
Borderline high	130-159 mg/dl
High	160-189 mg/dl
Very high	≥190 mg/dl

- **TOTAL CHOLESTEROL**

Desirable	<200 mg/dl
Borderline high	200-239 mg/dl
High	≥240 mg/dl

- **HDL CHOLESTEROL**

Low	<40 mg/dl
High	≥60 mg/dl

- **TRIGLYCERIDES**

Normal	<150mg/dl
Borderline high	150-199 mg/dl
High	200-499 mg/dl
Very high	≥ 500 mg/dl

Hyperlipidemia can basically be divided into two subcategories-

- **Hypercholesterolemia:** A condition where the cholesterol level is high.

- **Hypertriglyceridemia:** A condition where there is high level of triglycerides, which is the most common form of fat.

Lipoproteins are the fat-protein complexes in the blood. LDL (low-density lipoprotein) and HDL (high-density lipoprotein) are the best known lipoproteins. Increased LDL cholesterol promotes to the blockage of arteries, which ultimately leads to heart attack. Population based studies have distinctly shown that the higher the level of LDL cholesterol, the greater is the risk of heart disease. This is true in men and women, in different racial and ethnic groups, and in all adult age groups. Hence, LDL cholesterol has been considered as the bad cholesterol. In contrast the lower the level of HDL cholesterol, the greater the risk of coronary heart disease. As a result, HDL cholesterol is contemplated as the good cholesterol. Low HDL cholesterol levels are characteristically accompanied by an increase in blood triglyceride levels. Studies have shown that high triglyceride levels are associated with an increased risk of coronary heart disease. [22-25]

Although hyperlipidemia does not cause to feel bad, it can significantly increase the risk of developing coronary heart disease, also called coronary artery disease or coronary disease. People with coronary disease develop thickened or hardened arteries in the heart muscle. This can cause chest pain, a heart attack, or both. Because of these risks, treatment is often recommended for people with hyperlipidemia. High lipid levels can speed up a process called atherosclerosis, or hardening of the arteries. Arteries are normally smooth and unobstructed on the inside, but as age goes, a sticky substance called plaque forms in the walls of your arteries. Plaque is made of lipids and other materials circulating in your blood. As more plaque builds up, your arteries can narrow and stiffen. Eventually, enough plaque may build up to reduce blood flow through your arteries. Hyperlipidemia has been implicated in atherosclerosis, which is the primary cause of heart disease and stroke. Atherosclerosis increases your risk of heart disease, stroke, and other vascular diseases. Fortunately, may be able to reduce high lipid levels and therefore prevent or slow the progression of atherosclerosis. Lifestyle changes like exercising and eating a healthy diet can also lower your lipid levels and are often the first step in treatment.[26]

CLASSIFICATION OF HYPERLIPIDEMIA. [18]

According to Fredrickson Classification, Hyperlipidemia can be classified into-

- Familial or Primary type caused due to certain genetic abnormalities.

- Acquired or Secondary type which may be outcome of any other repressed disorder that may lead to variations in the metabolism of lipoprotein and plasma lipids.

Hyperlipidemia may also be without any known cause, i.e. Idiopathic.

FAMILIAL (or) PRIMARY TYPE- It is classified based on the sequence of lipoproteins on Ultracentrifugation or Electrophoresis. Later on, it was embraced by World Health Organization (WHO). It directly doesn't account for the cause of HDL, and also does not discern among the various genes which may be partly accountable for some of these conditions.

According to Fredrickson Classification, there are five types of Hyperlipidemia conditions. They are as follows-

Type-1: In this condition, there is raised cholesterol with elevated triglyceride levels.

Type-2: Increased Cholesterol with normal triglyceride levels.

Type-3: Raised Cholesterol and triglyceride levels.

Type-4: Increased levels of triglycerides, Atheroma and uric acid.

Type-5: Raised triglycerides.

ACQUIRED (or) SECONDARY TYPE-

Acquired hyperlipidemias (also called secondary dyslipoproteinemias) may mimic primary forms of hyperlipidemia and can have similar consequences. They may result in increased risk of premature atherosclerosis or when associated with marked hypertriglyceridemia, may lead to pancreatitis and other complications of the chylomicronemia syndrome. The most common causes of acquired hyperlipidemia are:

• Diabetes Mellitus

• Use of drugs such as diuretics, beta blockers, and estrogens.

Other conditions leading to acquired hyperlipidemia include:

• Hypothyroidism

• Renal Failure

• Nephrotic Syndrome

• Alcohol

• Some rare endocrine disorders and metabolic disorders

According to "Greenspan's Basic & Clinical Endocrinology" by Dr. David Gardner, acquired hyperlipidemia is high fat and cholesterol in the blood due to other conditions or medications. Diabetes, low thyroid hormone levels, kidney disease and some other metabolic disorders cause hyperlipidemia. Some drugs can also cause hyperlipidemia, including alcohol, diuretics, estrogens and beta-blockers.

SIGNS & SYMPTOMS. [27]

Hyperlipidemia usually has no noticeable symptoms and tends to be discovered during routine examination or evaluation for atherosclerotic cardiovascular disease.

1. Xanthoma.
2. Xanthelasma of eyelid.
3. Chest pain.
4. Abdominal pain.
5. Enlarged spleen.
6. Liver enlarged.
7. High cholesterol or triglyceride level.
8. Heart attacks.
9. Higher rate of obesity and glucose intolerance.
10. Pimple like lesions across body.
11. Atheromatous plaques in arteries.
12. Arcus senilis.

CAUSES

1. Lifestyle habits or treatable medical conditions. Lifestyle contributors include obesity, not exercising, and smoking

2. Diabetes (type 2).

3. Kidney disease.

4. Pregnancy.

5. An underactive thyroid gland.

6. Environmental and genetic factors.

7. Alcohol.

8. Monoclonal Gammopathy.

9. Nephrotic Syndrome.

10. Obstructive Jaundice.

11. Hypothyroidism.

12. Cushing's Syndrome.

13. Anorexia Nervosa.

14. Medications-

- Thiazide Diuretics
- Ciclosporin
- Glucocorticoids
- Beta Blockers
- Retinoic Acid

15. High dietary simple carbohydrates.

16. Estrogen therapy.

17. Lipoprotein lipase mutations.

RISK FACTORS

High fat intake is one of the factor which leads to

1. Hypercholesterolemia

2. Type 2 diabetes mellitus

3. Hypothyroidism

4. Chronic renal failure

5. Nephritic syndrome

6. Obesity

7. Alcohol intake

8. Drugs

- Number of drugs can adversely affect the serum lipid and lipoprotein concentrations.
- Antihypertensive agents
- Diuretics
- Oral contraceptives
- Corticosteroids- administration of glucocorticoids increases total cholesterol and TG by elevating LDL-C and to less extent VLDL-C

9. Metabolic syndrome.

PATHOPHYSIOLOGY: The transport of lipoproteins can be categorized into following-

- ***Exogenous Transport:***

Products of fat digestion from the gut (cholesterol, TG) are packaged with intestinal apoB48 to form nascent CMs. This process is mediated by microsomal triglyceride transfer protein (MTP). In the circulation, nascent CMs acquire cholesteryl esters (ChE), apo-C, and apo-E from HDL to form CMs. These CMs come in contact with lipoprotein lipase (LPL) located on the luminal surface of vascular endothelium of skeletal muscle and adipose tissue. LPL breaks down the triglyceride component of CMs into free fatty acids (FFA) and monoglycerides, in the process converting the CMs to smaller particles called CM remnants. The cholesterol-rich CM remnants are taken up by the liver via LDL receptor-like-protein (LRP) receptors or Apo-E receptors. In this way, dietary cholesterol finally reaches the liver.

- ***Endogenous Transport:***

Analogous to the secretion of nascent CMs by the gut, liver synthesizes and secretes nascent VLDL, by complexing TG and apo-B100 under the mediation of MTP. Triglyceride-rich nascent VLDL serves as an efficient acceptor of ChE from HDL. This transfer takes place under the agency of cholesteryl ester transfer protein (CETP) in the plasma and leads to the formation of mature VLDL. During circulation, LPL hydrolyses the TG of VLDL to FFA and

monoglycerides, in the process converting VLDL to smaller lipoproteins called intermediate density lipoproteins (IDL), and further to still smaller ChE-rich LDL. LDL supplies tissues with cholesterol. Thus the liver serves as the major site for both cholesterol synthesis and LDL catabolism. [28-30]

PROGNOSIS:

Hyperlipidemia is a condition characterized by an increased amount of fats (lipids) present in the bloodstream. The prognosis for the condition varies according to a number of different factors.

The prognosis for persons is in direct proportion to their serum cholesterol levels. Persons with hypercholesterolemia are at high risk of dying from heart disease or stroke. Many studies have looked at the relationship between elevated cholesterol levels, increased risk of heart attack and death. In one research investigation of relatively young males who had no known heart disease, cholesterol levels were measured and participants were followed for 6 years. During this time, all heart attacks and deaths that occurred among participants were recorded. As serum cholesterol levels increased, so did the risk of experiencing a fatal heart attack. The risk of a fatal heart attack was approximately five times higher among persons having cholesterol levels of 300 mg/dL or more compared to those with cholesterol levels below 200 mg/dL.

Diet changes, exercise, and medications can lower cholesterol levels for those with the milder form of this disorder, and may significantly delay a heart attack. Men and women with familial hypercholesterolemia typically are at increased risk of early heart attacks. Risk of death varies among patients with familial hypercholesterolemia. Persons who inherit two copies of the defective gene have a poorer outcome. That type of familial hypercholesterolemia causes early heart attacks and is resistant to treatment. [25, 29]

TREATMENT APPROACHES FOR HYPERLIPIDEMIA

Statins:

Statins (or HMG-CoA reductase inhibitors) are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a prominent role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular diseases (CVD), and statins are therefore used in the prevention of these

diseases. Statins have rare but severe adverse effects, particularly muscle damage, and some doctors believe they are overprescribed. The approved statins are Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin, and Pitavastatin.

HMG-CoA Reductase:

This ultimately reduces cholesterol via several mechanisms. Statins block the production of cholesterol in the liver itself. They lower LDL, the "bad" cholesterol, and triglycerides, and have a mild effect in raising HDL, the "good" cholesterol. These drugs are the first line of treatment for most people with high cholesterol. Side effects can include intestinal problems, liver damage, and in a few people, muscle tenderness.

Bile Acid Sequestrants

The bile acid sequestrants are a group of medications used to bind certain components of bile in the gastrointestinal tract. They disrupt the enterohepatic circulation of bile acids by sequestering them and preventing their reabsorption from the gut. In general, they are classified as hypolipidemic agents, although they may be used for purposes other than lowering cholesterol. They are used in the treatment of chronic diarrhea due to bile acid malabsorption. Bile acid sequestering agents (Resins): The liver uses cholesterol to produce bile acids, which are used in the digestive process. The bile acid sequestrants bind to these acids, reducing their supply. In turn, this stimulates the liver to produce more bile acids, which uses more cholesterol. Unfortunately, the resins can increase triglyceride levels. When the statins are not sufficient to lower high cholesterol, these drugs can be added. Their use is often limited by side effects, which are primarily gastrointestinal. They can include nausea, bloating, cramping, and an increase in liver enzymes.

Three drugs are members of this class; all are synthetic polymeric resins:

- Cholestyramine
- Colesevelam
- Colestipol

Fibric Acid Derivatives (Fibrates)

Fibrates are cholesterol-lowering drugs that are primarily effective in lowering triglycerides and to a lesser extent in increasing HDL-cholesterol levels. Fibrates prescribed commonly are

- Bezafibrate
- Ciprofibrate
- Clofibrate
- Gemfibrozil
- Fenofibrate[31]

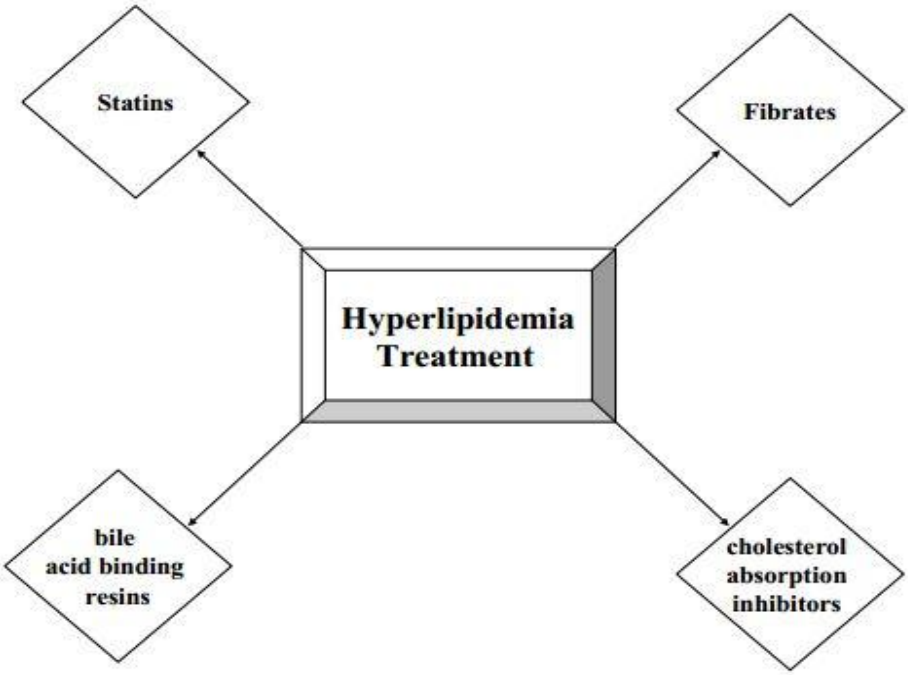

Figure 1- Diagrammatic Representation of some of the treatment Strategies in Hyperlipidemia. [32]

CONCLUSION:

Hyperlipidemia is a critical condition of elevated lipid levels in the body that ultimately lead to the development and progression of various CVDs. The link between hyperlipidemia and occurrence of CVDs has already been established. Various studies have reported the treatment of hyperlipidemia patients with statins, fibrates and nicotinic acid derivatives. Moreover, the focus on dietary management should be done in order to prevent and treat the

patients presented with hyperlipidemia. However, ample studies have provided the evidence for the efficacy of already reported treatments, but further studies are mandatory in order to provide more information about the safety and efficacy of novel antihyperlipidemic agents.

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