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Overview about Hyperlipidemia

Ankit Gour[1]*, Dr. Dhanraj Patidar[1], Mukesh Sahu[1], Maneesh Sahu[1], Shobhit Shrivastava[1], Dr. Satish Nayak[1]
[1] Bansal College of Pharmacy, Kokta Anand Nagar, Bhopal
*Corresponding author
Ankit Gour
E-Mail address: ankitgourvds121@gmail.com
Contact No. 9713250292, 7987054168

ABSTRACT
Hyperlipidemia is a path-medical condition determined by an elevation in one or more of the plasma lipids, including cholesterol, triglycerides, cholesterol esters, phospholipids and or plasma lipoproteins including very low-density lipoprotein and low-density lipoprotein along with decreased high-density lipoprotein levels The increase in plasma lipids is one of the primary risk factors linked to cardiovascular diseases. Introduction, type of lipoprotein, classification of hyperlipidemia, Complications of hyperlipidemia, causes; Symptoms of hyperlipidemia, Pathogenesis of hyperlipidemia, Pathogenesis of hyperlipidemia, diagnosis, prevention, treatments.
Keywords: Hyperlipidemia, cholesterol, Fibrates, statins.

1. INTRODUCTION

Hyperlipidemia is described as an excess level of cholesterol, cholesterol esters, phospholipids, or triglycerides in the bloodstream. Irregularities in these plasma lipids can contribute to an increased risk of developing coronary artery disease, cerebrovascular disease, and peripheral vascular arterial diseases [1, 2]. Hyperlipidemia is conventionally described as a state in which the concentration of cholesterol or lipoproteins transporting triglycerides in the bloodstream surpasses a designated threshold considered normal [3, 4]. The liver plays a dominant role in maintaining cholesterol levels within the bloodstream. Roughly 80% of the total cholesterol is synthesized by the liver, while the remaining cholesterol is sourced from dietary intake, including foods like fish, eggs, and meat [5, 6]. Hyperlipidemia, a condition characterized by elevated cholesterol levels, is considered a major risk factor for cardiovascular diseases. These CVDs presently account for approximately one-third of global deaths, and it is anticipated that by the year 2020, they will emerge as the primary cause of death and disability worldwide [7-9]. In the meantime, hyperlipidemic specialists maintain their opposition to statins and fibrates as effective treatments for elevated plasma cholesterol and triglycerides, primarily due to the adverse effects experienced on the muscles and liver [10].

Lipoproteins are classified into various groups:-

Namely, chylomicrons, very low-density lipoproteins, low-density lipoproteins, intermediate-density lipoproteins, and high-density lipoproteins.

Chylomicrons

Chylomicrons are the largest particles in terms of both size and density, and their levels are directly influenced by the amount of dietary triglycerides consumed**.**

Very Low-Density Lipoproteins:

Very low-density lipoproteins are smaller particles that transport a higher proportion of chylomicrons compared to triglycerides, and they are synthesized and released by the liver. VLDL carries cholesterol

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and triglycerides from the liver to organs and tissues throughout the body [12]

Intermediate-Density Lipoprotein:

Following enzymatic breakdown by lipase in the capillaries of adipose tissue and muscle, VLDL particles undergo lysis and give rise to intermediate-density lipoprotein (IDL).

Low-Density Lipoproteins:

Based on the studies by Lee et al. and Galeano et al., LDLs are produced through a combination of synthesis in the intestinal chyle and the lipolysis of very low-density lipoproteins. Furthermore, there is a direct correlation between LDL levels and coronary heart disease.

High-Density Lipoproteins:

HDL is often recognized as "good cholesterol" due to its beneficial effects. Synthesized in the liver, high-density lipoproteins are responsible for transporting cholesterol and other lipids from tissues back to the liver, where they are broken down. HDL actively plays an anti-atherogenic role [13].

The classification of hyperlipidemia is based on the specific lipid type:

Hypercholesterolemia: This condition is marked by elevated cholesterol levels

Hypertriglyceridemia: It is defined by elevated levels of triglycerides.

On the basis of the causing factor

3.1. Primary hyperlipidemia (Familial hyperlipidemia): Also known as familial hyperlipidemia, this type of hyperlipidemia is attributed to genetic defects. It can be categorized as monogenic, involving a single gene defect, or polygenic, resulting from multiple gene defects. Primary hyperlipidemia can be further differentiated based on specific abnormal lipoprotein patterns, summarized as follows:

- Type I: Elevated cholesterol with high triglyceride levels.
- Type II: Hypercholesterolemia with normal triglycerides
- Type III: Elevated cholesterol and triglycerides.
- Type IV: Elevated triglycerides, atheroma, and uric acid.
- Type V: Elevated triglycerides.

3.2 Secondary (Acquired hyperlipidemia)

It is obtained as a result of other conditions such as diabetes, glomerular syndrome, chronic alcohol consumption, hypothyroidism, and the use of medications like corticosteroids, beta-blockers, and oral contraceptives. Pancreatitis can occur when secondary hyperlipidemia and marked hypertriglyceridemia are present. [15]

Complications of Hyperlipidemia:

Atherosclerosis: Hyperlipidemia serves as a primary risk factor for the development of atherosclerosis, a pathological process characterized by the deposition of lipids, cholesterol, and calcium, leading to the formation of Atheromatous plaques in the walls of medium and large arteries. This condition significantly contributes to the occurrence of cardiovascular diseases. [16]

Coronary Artery Disease

Atherosclerosis: Atherosclerosis, the primary underlying factor behind coronary artery disease, is characterized by the buildup of excessive lipids and the formation of fibrous plaques within the arterial walls. This process leads to the constriction of the arteries responsible for supplying blood to the myocardium, resulting in restricted blood flow and an inadequate oxygen supply to meet the demands

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of the heart. [17]

Myocardial Infraction

The occurrence of myocardial infarction is characterized by the obstruction, either partial or complete, of blood and oxygen supply in one or more cardiac arteries. This blockage, often caused by the rupture of an atherosclerotic plaque, results in detrimental effects on heart cells, including damage or death [18].

Ischemic stroke or cerebrovascular accident

Stroke ranks as the fourth highest cause of mortality. Typically, strokes occur when an artery in the brain becomes obstructed by either a blood clot or a fragment from an atherosclerotic plaque that detaches within a small blood vessel. Numerous clinical trials have demonstrated that a 15% reduction in low-density lipoprotein and total cholesterol levels significantly lowers the risk of experiencing the initial stroke [19].

Causes

The lipid level in the bloodstream can be heightened by the presence of sterols, fatty acids, and trans fats found in certain food choices, such as

- Dairy products,
- ice cream
- pastries
- fried foods
- Processed snacks [20].

Hyperlipidemia can arise from various underlying disorders such as obesity, diabetes mellitus, and hypothyroidism. Unhealthy habits like smoking and a lack of regular exercise have also been identified as factors that can lead to hyperlipidemia. Additionally, excessive alcohol consumption and the use of certain medications like steroids and β-blockers have been associated with an increased risk of hyperlipidemia. Furthermore, mutations in lipoprotein lipase can further contribute to the development of hyperlipidemia [22].

Some 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].

- Symptoms such as discomfort in the chest (angina), a myocardial infarction (heart attack), or a cerebrovascular accident (stroke) can occur due to hyperlipidemia
- When cholesterol levels become excessively high, there is a possibility of cholesterol accumulation in tendons or subcutaneously, particularly beneath the skin near the eyes liver, spleen or pancreas are swelled.
- Obstructions can occur within the blood vessels of the brain and heart, causing a disruption or cessation of blood flow.
- There is an increased prevalence of obesity and impaired glucose tolerance in individuals with this

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condition [25].

Pathogenesis of Hyperlipidemia

In the pathogenesis of hyperlipidemia, during its early stages, there is adherence of blood monocytes and platelets to the damaged endothelial wall of blood vessels. This attachment leads to the release of mediators, such as platelet-derived growth factors, which stimulate the growth of smooth muscle cells within the inner and middle layers of the vessel. This process involves collagen synthesis, cholesterol accumulation, and the initiation of hyperlipidemic plaque. Subsequent plaque ruptures can develop acute conditions like unstable angina, myocardial infarction, and sudden cardiac death.[26.]

Significance

Healthcare professionals regard hyperlipidemia with great concern because of the well-established link between lipid concentrations and the risk of developing cardiovascular disease (CVD), which ranks as the primary cause of death in the United States [27-29]. An influential study that played a pivotal role in demonstrating the correlation between reducing cholesterol levels through therapeutic interventions and a decreased risk of cardiovascular morbidity or The Lipid Research Clinics Coronary Primary Prevention Trial examined the impact on illness or death rates. This groundbreaking trial was published in two parts in 1984, utilizing different statistical analyses. [30, 31] In-depth information regarding the cholesterol controversy can be found in a multi-part review series that was published over the course of three years in the Journal of Lipid Research. These articles, accessible online, offer a comprehensive examination of the subject, presenting a thorough historical perspective. [32-38]

Diagnosis

Hyperlipidemia is generally asymptomatic, and its identification requires a blood test. A lipid profile is the standard screening method employed to diagnose hyperlipidemia. [39] A regular blood test that assesses the concentrations of LDL, HDL, VLDL, and triglycerides is commonly employed to diagnose hyperlipidemia. [40]

Prevention of Hyperlipidemia

- Prioritize a balanced dietary approach: Make a conscious effort to maintain a diet that strikes a balance and provides essential nutrients while minimizing the consumption of saturated and trans fats, cholesterol, and refined sugars. Ensure an abundant intake of fruits, vegetables, whole grains, lean proteins, and healthy fats derived from sources like nuts, seeds, and fatty fish.
- Make it a habit to participate in regular physical activities, including aerobic exercises, strength training, or any activity that increases your heart rate. Aim to achieve a minimum of 150 minutes of moderate-intensity exercise or 75 minutes of vigorous exercise per week.
- Weight Maintenance: Sustain a healthy weight by adopting a well-balanced diet and incorporating consistent physical activity into your routine. If carrying excess weight or being classified as obese, shedding pounds can aid in lowering lipid levels.[3]

Treatment

Incorporating the following lifestyle modifications into your routine may help lower cholesterol levels:

- Balanced Diet
- Manage body weight
- Regular workout
- Consuming food that is low in oil or fat content.
- Make it a practice to consume fish twice a week..
- The need for treatment and medication in this situation typically persists throughout one's

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

lifetime.

- Fibrates (fenofibrate) and statins are medications that are commonly prescribed to lower triglyceride levels. [40]

Treatments

Adjustments in daily habits for therapeutic purposes

The initial approach to treating hyperlipidemia, particularly in mild cases and individuals without coronary heart disease (CHD) or CHD risk equivalent and fewer than two risk factors, involves implementing dietary Implementing alterations in daily routine, including consistent physical activity, cessation of smoking, and a dedicated focus on shedding excess weight. It is important to consider that during dietary modifications, cholesterol intake is reduced while acknowledging that cholesterol production, particularly by the liver, may increase. To support a healthy eating pattern, it is advised to restrict dietary fat intake to 25%-35% of total energy intake. It is further recommended to limit saturated fatty acids to less than 7% of energy intake and maintain cholesterol intake below 200 mg per day. Including plant sterol esters and soluble fiber in the diet is a favorable choice. [3]

Ayurvedic therapy:-

Ayurvedic medicine, an ancient healing tradition, holds a prominent position among the early medical systems worldwide. Its therapeutic practices are rooted in the fundamental "laws" of nature. This holistic approach to healthcare revolves around the interconnectedness of the body, mind, and spirit. The core objective of Ayurvedic medicine is to achieve a state of equilibrium and vitality by integrating and balancing these elements. This is accomplished through the implementation of dietary guidelines, nutritional interventions, herbal remedies, yoga, meditation, and the adoption of daily and seasonal routines. [41].

Home Remedies

Additionally, it is worth considering various dietary interventions as part of the overall treatment plan for hyperlipidemia. Incorporating nuts into the diet, such as almonds and walnuts, has been shown to be beneficial, with almonds reducing LDL cholesterol by around 4.4% and walnuts reducing LDL cholesterol by up to 16%.

Oatmeal: Decreases LDL by 12-24%.

Orange juice: Plummets blood cholesterol level.

Coriander seeds: fall cholesterol and triglycerides levels.

Fish oil: Reduce triglycerides levels.

Honey: Reduce cholesterol level.

Soyabeans : Minimize the synthesis of fresh cholesterol

Indian Gooseberry: Drops the excess cholesterol build- up.

Brown Rice: Subside cholesterol level.

Turmeric: Minimize LDL cholesterol levels.

Brinjal: Cut down LDL cholesterol levels.

Coconut oil: Elevated HDL and improves the LDL/HDL ratio.

Fenugreek seeds: Drops cholesterol level by 14% [3]

Plants having hypolipidemic activity

Medicinal plants have always held great importance as a health-enhancing resource, thanks to their abundant therapeutic properties and complete naturalness. The field of herbal medicine has emerged as

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a topic of global significance, leaving a profound impact on worldwide health and international trade. The widespread adoption of herbal medicine in developing countries can be attributed to the high costs associated with Western Pharmaceuticals and Healthcare. [43.]

Pharmacological Treatment

Numerous hypolipidemic drugs are available in the market to address hyperlipidemia. However, research suggests that these medications have limited effectiveness in preventing myocardial infarction in patients with pre-existing coronary heart disease (CHD). [44]

Drug therapy

When LDL levels rise, along with the presence of risk factors and documented CHD, it is advisable to consider drug therapy in conjunction with therapeutic lifestyle changes (TLC). The existing range of lipid-lowering medications comprises statins, ezetimibe, bile acid sequestrants or bile-binding resins, niacin, fibric acid derivatives, and plant sterols. If dietary modifications are insufficient, specialized medications aimed at reducing blood cholesterol levels may be prescribed.[45]

Fibric acid derivatives (Fibrates)

Fibrates, such as clofibrate, gemfibrozil, fenofibrate, and bezafibrate, belong to a commonly prescribed category of antihyperlipidemic agents. They are known to significantly lower plasma triglyceride levels and modestly reduce LDL sterols. Additionally, they moderately increase HDL cholesterol levels. Experimental angiographic findings demonstrate that fibrates have a substantial impact in slowing the progression of coronary atherosclerosis and reducing the incidence of coronary artery disease.

Mechanism of action

Research findings from rodent and human studies indicate four primary mechanisms of action for fibrates Stimulation of lipoprotein lipolysis

Fibrates primarily function as ligands for the nuclear transcription receptor PPAR-α. They enhance the expression of lipoprotein lipase, and apolipoproteins, and suppress the activity of apo C-III, a lipolysis inhibitor. Additionally, fibrates increase HDL cholesterol levels by promoting the expression of apo AI and apo AII.[7]

Boosting hepatic fatty acid uptake and lowering hepatic triglyceride production.

The administration of fibrates leads to an upregulation of fatty acid transport protein and acyl-CoA synthetase, thereby facilitating the uptake of fatty acids by the liver and decreasing their accessibility for triglyceride synthesis.

Enhance the elimination of LDL particles.

Fibrates seem to increase LDL breakdown through the receptor-mediated pathway, causing LDL particles to become larger and richer in lipids, resulting in a heightened receptor affinity.

Enhancement of HDL synthesis and promotion of reverse cholesterol transport.

Fibrates stimulate the synthesis of apo A-I in the liver, resulting in increased levels of apo A4 and HDL-cholesterol in the bloodstream, thereby facilitating reverse cholesterol transport more effectively. [5]

Nicotinic acid derivatives (Niacin)

Niacin, a B-complex vitamin, is the original lipid-lowering agent employed to manage hyperlipidemia. It has been shown to effectively reduce the incidence of cardiovascular morbidity and overall mortality. Niacin accomplishes this by decreasing levels of total cholesterol, LDL cholesterol, and triglycerides.[5]

Mechanism of action

Hormone-sensitive lipase inhibition by niacin leads to a decline in triglyceride breakdown and lipid lysis, which are responsible for generating the majority of circulating free fatty acids.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

As a result, niacin impedes the secretion of VLDL, leading to a decrease in LDL production.[5]

Side effects

The efficacy of Niacin therapy has been compromised by the poor compliance rates exhibited by patients. The most common adverse effects observed include a marked cutaneous flush experienced by more than 75% of patients, as well as itching, headaches, and occasional instances of nausea and abdominal discomfort. It should also be noted that Niacin administration leads to an elevation in liver enzyme levels.[45]

Selective cholesterol absorption inhibitor (Ezetimibe)

The exploration and advancement of ezetimibe, the inaugural drug within a class of medications that obstruct the assimilation of phytosterols and cholesterol in the intestines, have enhanced the management of hypercholesterolemia. It hinders the absorption of sterol from the small intestine without impacting the plasma levels of vitamin ADEK.

Mechanism of action

Ezetimibe specifically targets the absorption of cholesterol in the small intestine, resulting in reduced transportation of intestinal cholesterol to the liver. It achieves this by inhibiting the Niemann–Pick C1-like 1 protein (NPC1L1), which is responsible for transporting sterols in humans. As a consequence, sterol clearance from the bloodstream is enhanced.

Side effects

In general, Ezetimibe is well tolerated by patients; however, there are common side effects that may occur. These include headaches, abdominal pain, and diarrhea. It's important to note that Ezetimibe can also cause increases in liver function tests, including alanine transaminase and aspartate transaminase..[7]

2. NEW POTENTIAL TARGETS AND TREATMENTS

In recent times, several clinical trials have brought to light new candidate substances showing encouraging antihyperlipidemic properties.

Acyl-CoA cholesterol acyl transferase inhibitors(ACAT)

The transformation of intracellular cholesterol into cholesteryl esters is governed by the enzyme Acyl-CoA cholesterol acyl transferase (ACAT). ACAT manifests as two distinct isomers, ACAT1 and ACAT2.

Microsomal triglyceride transfer protein (MTP) inhibitors

The diverse functions of Microsomal triglyceride transfer protein (MTP) include transferring neutral lipids between membrane vesicles, participating in the biosynthesis of CD1 antigen-presenting molecules, and regulating the production of cholesterol esters.

Cholesteryl ester transfer protein (CETP)inhibitors

Cholesteryl ester transfer protein (CETP) present in the liver facilitates the transference of cholesteryl esters from HDLs, which are atheroprotective, to lipoproteins harboring apoB, including VLDLs and LDLs. These observations from various studies underscore the role of CETP in reverse cholesterol transport and substantiate the proposition that restraining CETP activity can decelerate the progression of atherosclerosis.[7]

Squalene synthase inhibitors

SqS initiates the synthesis of squalene by catalyzing the conversion of farnesyl pyrophosphate, and this process is crucial for the production of cholesterol and other sterols.[5]

Hydroxymethylglutaryl-CoA synthase inhibitors

HMG synthase facilitates the conversion of acetyl-CoA and acetoacetyl CoA into 3-hydroxy-3-

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

methylglutaryl-CoA

ATP citrate lyase inhibitors

The primary role of ATP citrate lyase lies in catalyzing the formation of cytosolic acetyl-CoA and oxaloacetate. These compounds are vital intermediates in the biosynthesis of fatty acids and cholesterol. Consequently, inhibiting ACL offers a promising therapeutic approach for dyslipidemia.

Acyl coenzyme A: diacyl glycerol acyltransferase

DGAT is a microsomal enzyme responsible for catalyzing the final step in triglyceride biosynthesis by combining Acyl CoA with 1,2-diacylglycerol.

Squalene epoxidase inhibitors

Squalene epoxidase functions as a key enzyme that controls the rate of the initial oxygenation step in sterol synthesis.

Lanosterol synthase inhibitors

Lanosterol synthase (LSS) facilitates the cyclization of (S)-2,3 oxidosqualene into lanosterol, which serves as the primary sterol in the cholesterol synthesis pathway[7].

Recent Drug For Hyperlipidemia

The Food and Drug Administration (FDA) has granted approval to two novel non-statin medications based on positive results from clinical trials, showing their efficacy in lowering high cholesterol levels. Nexletol and Nexlizet can be combined with statins that exhibit minimal or manageable side effects. Moreover, these newly approved drugs entail certain adverse effects distinct from those typically associated with statins.[46]

3. CONCLUSION

The above-mentioned research highlights hyperlipidemia as a primary risk factor for cardiovascular disease. The implementation of modern pharmaceuticals, a well-balanced diet, home remedies, and a consistent exercise regimen can effectively address this condition. Consequently, by diligently maintaining a healthy diet and engaging in regular physical activity, individuals can potentially mitigate the risks of hyperlipidemia, cardiovascular diseases, and various other ailments.

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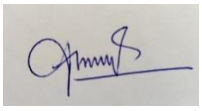
Certificate of Interest:

The review article entitled Overview about Hyperlipidemia is herewith submitted for publication in Journal of cardiovascular disease research. It has not been published before, and it is not under consideration for publication in any other journal (s). I/We certify that I/We have obtained written permission for the use of text, tables, and/or illustrations from any copyrighted source(s), and I/We declare no conflict of interest.



Signature of author(s):
Name(s) and designation: Ankit Gour, Assistant Professor
Name(s) of Institution/Organization: Bansal College Of Pharmacy, Bhopal ,M.P.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

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