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Pharmacological Treatment and Emerging Therapies on Hyperlipidemia

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Abstract

Angiopoietin-like protein 3 (ANGPTL3) and apolipoprotein C-III (Apo C-III) and their functions in cardiovascular health and lipid metabolism. The liver's production of Apo C-III prevents triglyceride-rich lipoproteins from breaking down, which raises triglyceride levels and raises the risk of cardiovascular disease. Those who have mutations that cause the APOC3 gene to malfunction have much lower triglyceride levels and a lower chance of developing ischemic heart disease. In an effort to mimic the protective effects observed in APOC3 deficiency, treatments that target Apo C-III, such as plozasiran, olezarsen, and volanesorsen, have been developed. As a therapeutic target, ANGPTL3 has also been identified, and evinacumab, a monoclonal antibody, is currently being used in clinical settings. To completely comprehend the effectiveness and safety of these novel treatments, further extensive long-term research is necessary.

Keywords: Liver, Cardiovascular disease, Hyperlipidemia

Introduction

Hyperlipidemia, or high cholesterol, is one of the main causes of chronic disease and a persistent global health concern. Nearly 40% of the world's population is affected by heart disease, which is estimated to be responsible for 2.6 million deaths annually and 33.3% of all heart disease globally, according to the World Health Organization (WHO). Furthermore, according to a 2023 American Heart Association (AHA) report, 32.8% of men and 36.2% of women were predicted to meet the diagnostic criteria for hyperlipidemia. Less than one-third of those people are reportedly receiving proper care, according to the same data, which amply illustrates the undertreatment and uncontrollability of chronic illness.

Hyperlipidemia is simply defined as high blood lipid or fat concentrations, including but not limited to triglycerides, total cholesterol (TC), low-density cholesterol (LDL), and high-density cholesterol (HDL).

Recent research has shed light on the molecular basis and genetic origins of dyslipidemias, the role they play in the development of atherosclerosis, and the potential of pharmaceutical agents to reduce the risk of ASCVD in those who are affected. The options for managing dyslipidemias are also growing.

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These include the well-established use of monoclonal antibodies that target proprotein convertase subtilisin/kexin type 9 (PCSK9) to treat hypercholesterolemia, the European approval of volanesorsen, which targets apo C-III, to treat familial chylomicronemia syndrome (FCS), and the recent approvals in North America of bempedoic acid, evinacumab, and inclisiran for a number of indications pertaining to LDL-C reduction. A number of additional substances, such as those targeting the novel targets of Lp(a) and angiopoietin-like protein 3 (ANGPTL3), are undergoing advanced clinical development [1].

Pathophysiology of dyslipidemia

Dyslipidemia is the result of changes in lipid metabolism based on by a combination of environmental and genetic factors. Homozygous familial hypercholesterolemia (HoFH), heterozygous familial hypercholesterolemia (HeFH), and familial chylomicronemia syndrome (FCS) are inherited forms of dyslipidemia.

Lipid homeostasis is made possible by the liver, which regulates the synthesis, absorption, and excretion of TGs and cholesterol. When HDL-C (high-density lipoprotein-cholesterol) levels are low and TG and LDL-C levels are high, dyslipidemia can upset this balance. This imbalance can increase the risk of cardiovascular events by causing atherosclerosis, which is a lipid accumulation in artery walls.

A number of metabolic pathways that impact lipid metabolism as well as genetic, nutritional, and lifestyle variables interact intricately in the pathogenesis of hyperlipidemia.

Lipid Metabolism

Lipid metabolism includes a number of processes, such as consumption, absorption, transportation, and use. Lipoproteins, which are categorized according to their density, carry lipids through the bloodstream after being absorbed in the intestines:

- Chylomicrons: Deliver dietary cholesterol and triglycerides from the intestines to the tissues.
- Very-Low-Density Lipoproteins (VLDL): Deliver cholesterol and endogenous triglycerides from the liver to the tissues around it.
- Low-Density Lipoproteins (LDL): Transport cholesterol to all of the body's cells. An elevated risk of atherosclerosis and cardiovascular disease is linked to high LDL cholesterol levels.
- High-Density Lipoproteins (HDL): Eliminate extra cholesterol from tissues and return it to the liver for elimination.

Genetic Factors

Primary hyperlipidemia may result from genetic abnormalities that alter lipid metabolism. A prevalent hereditary condition known as familial hypercholesterolemia (FH) is defined by mutations in the LDL receptor gene that hinder the removal of LDL from the blood, leading to high levels of LDL cholesterol. Hyperlipidemia may also result from other genetic conditions that impact Apo lipoproteins, lipid metabolism-related enzymes, or receptors.

Lifestyle and Dietary Factors

An important factor in the development of hyperlipidemia is dietary choices. Elevated blood lipid levels can result from diets heavy in cholesterol, trans fats, and saturated fats. Significant contributing factors also include obesity, excessive alcohol use, and physical inactivity.

Insulin Resistance and Metabolic Syndrome

Dyslipidemia is linked to insulin resistance, a defining feature of type 2 diabetes and metabolic syndrome. higher hepatic VLDL synthesis, decreased clearance of triglyceride-rich lipoproteins, and higher release of free fatty acids from adipose tissue are all consequences of insulin resistance. Triglycerides rise as a result, HDL cholesterol falls, and LDL cholesterol levels frequently rise.

Inflammation and Atherosclerosis

The development of atherosclerosis, a serious consequence of hyperlipidemia, is significantly influenced by chronic inflammation. Oxidation of LDL cholesterol, which is brought on by elevated levels, can cause inflammation and the development of atherosclerotic plaques in artery walls. The risk of cardiovascular events like heart attacks and strokes can be raised by these plaques, which can also restrict arteries and decrease blood flow.

Hormonal Influences

Lipid metabolism may be impacted by hormonal variables such as glucocorticoids, sex hormones, and thyroid hormones. For example, decreased LDL receptor activation in hypothyroidism is

linked to higher cholesterol levels. LDL cholesterol can rise and HDL cholesterol can fall in postmenopausal women who are estrogen deficient.

Secondary Causes

Chronic renal illness, diabetes mellitus, hypothyroidism, and liver disorders are among the underlying factors that can cause secondary hyperlipidemia. Additionally, several drugs, such as beta-blockers, thiazide diuretics, and corticosteroids, might raise cholesterol levels [2].

Symptoms of Hyperlipidemia

Hyperlipidemia doesn't show any symptoms until the lipid level reaches a risky level that can lead to a heart attack or stroke. People with familial Hyperlipidemia or high cholesterol get xanthomas, especially under the eyes, while people with high TG levels get pimple-like lesions in several body areas [3].

Diagnosis of Hyperlipidemia

A lipid profile checkup performed as part of a routine medical evaluation or after a CVD incident is responsible for the majority of HL occurrences. They also suggested that all women and men between the ages of 20 and 45 who are at a higher risk of coronary heart disease (CHD) get screened for TC and HDL-c.

- Every adult 20 years of age and older should have a fasting lipoprotein profile that includes TC, TG, HDL-c, and LDL-c tested at least every five years.
- Plasma cholesterol, TG, and HDL levels must be measured after a 12-hour or longer fast because fasting has only a slight impact on TC and non-fasting people may have increased TGs.
- People with consistent diets, weights, and no acute illnesses should have two measures taken one to eight weeks apart in order to minimize variability and produce a solid value. If TC is more than 200 mg/dl, a second measurement is advised; if TC is less than 30 mg/dl, three measures should be averaged.
- Additional investigations, including a family medical history, age, gender, physical examination, and laboratory testing, are conducted if lipid abnormalities are found.
- A comprehensive medical history and physical examination help determine whether there are any-
  - CVD risk factor in persons or to identify those who are at certain risk for CVD.
  - Premature cardiovascular disease or lipid disorders in the family.
  - Medication is one of the secondary causes of HL.
  - xanthomas, pancreatitis, liver or kidney disease, peripheral vascular disease, cerebrovascular disease, or stomach pain.
- Additionally linked to the risk of CHD is diabetes mellitus. Patients with diabetes who have known CHD are therefore at the same risk as those who do not have diabetes.
- If a physical examination and family history are unable to identify any familial disorders, agarose gel lipoprotein electrophoresis is used to identify the afflicted lipoprotein classes. For VLDL and LDL calculation scans, use VLDL = TG/5 and LDL = TC-(VLDL+HDL) if TG < 400 mg/dl and neither chylomicrons nor type III HL are found in electrophoresis.
- TC is made up of LDL, VLDL, and HDL cholesterol. HDL levels are raised by moderate alcohol usage, quitting smoking, exercising, losing weight, using oral contraceptives, etc., whereas they are lowered by β-blocker use, smoking, leading a sedentary lifestyle, etc.
- The diagnosis of LPL deficiency is made based on diminished or low enzyme activity in normal human plasma or Apo C-II, an enzyme cofactor [4].

Lifestyle Modifications

Hyperlipidemia can be avoided in the majority of cases. Low-saturated-fat diets, an active lifestyle, abstinence from smoking, and moderate alcohol use are lifestyle choices that can help prevent hyperlipidemia. Changes in lifestyle have also been demonstrated to control and avoid co-morbid conditions like diabetes, hypertension, and obesity. Evidence-based care for clients' health promotion and treatment of hyperlipidemia can be provided by lifestyle medicine providers, nutrition counselors, exercise physiologists, and behavior therapists for quitting smoking and drinking.

- Diet - Limiting consumption of trans and saturated fats, boosting dietary fiber, and prioritizing fruits, vegetables, and whole grains are all components of a heart-healthy diet. Significant improvements in lowering

cholesterol have been demonstrated by the Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets.

- Exercise - To enhance lipid profiles, regular aerobic exercise (150 minutes per week) lowers LDL and triglycerides while increasing HDL.
- Weight loss - A 5–10% decrease in body weight improves dyslipidemia considerably.
- Alcohol and smoking - Avoiding smoke and drinking alcohol in moderation are important lifestyle choices. [5]

Pharmacological Treatments of Hyperlipidemia

HMG-COA reductase inhibitors (statins)

- Drugs: Atorvastatin, Lovastatin, Simvastatin, Pravastatin, Rosuvastatin, Fluvastatin
- Statins inhibit the primary enzyme necessary for cholesterol production, which is the phase that limits the rate of de novo cholesterol biosynthesis.
- This causes Low-Density to catabolize. The key mechanisms for antihyperlipidemic actions seem to be lipoproteins mediated through LDL receptors.
- Less than 10% of statin-using patients have constipation.

Bile acid resins

- Drug: Cholestyramine, Colestipol
- Bile acid sequestrants, a type of ion exchange resin, swap ions with bile acids.
- This lowers the amount of LDL in the bloodstream by increasing the catabolism of plasma lipoproteins through an increase in LDL receptors on the hepatic cell membrane.

Fibric acid derivatives

- Drug: Clofibrate, Fenofibrate, Gemfibrozil, Benzafibrate, Ciprofibrate
- The presence of fibrates increased the plasma HDL-C content by around 20%, while the fibrates class of medications can lower plasma triglyceride levels by up to 50%.
- The main way fibrates work is by modifying the liver's peroxisome proliferator-activated receptor-α (PPAR-α) activity.
- This causes the liver's fatty acid β-oxidation to rise, lipoprotein lipase activity to increase, and hepatic triglyceride production to decrease.
- Thus, the clearance of HDL, VLDL, and residual particles has increased overall.

Niacin

- Drug: Nicotinic acid
- Nicotinic acid, or niacin, lowers the hepatic synthesis of VLDL. Decreased LDL cholesterol raises HDL's effective plasma levels and dramatically lowers HDL catabolism.

Ezetimibe and colesevelam

- Ezetimibe is used both as a monotherapy and in combination with other medications, such as statins. Ezetimibe interferes with the intestinal brush border's ability to absorb cholesterol, which is a unique mechanism that makes it a good choice for adjuvant therapy.
- It was recently demonstrated that fenofibrate and ezetimibe together are safe and beneficial for patients with high LDL-C and triglyceride levels. One of the adverse effects is gastrointestinal distress [6].

Recent and Emerging Therapies

Anti-PCSK9 Therapies

The treatment of dyslipidemia has changed dramatically since PCSK9 was discovered. PCSK9 is widely expressed, binds to LDL receptors, and breaks them down. In the liver, this activity is particularly significant. By binding to apo B-100, a large protein on the surface of atherogenic lipoproteins, hepatic LDL receptors enable receptor-mediated endocytosis, which removes the lipoproteins from plasma. The LDL particle is the most prevalent apo B-100-containing lipoprotein. Lower plasma clearance of LDL particles occurs when PCSK9 binds to LDL receptors extracellularly and encourages their intracellular destruction. On the other hand, PCSK9 inhibition leads to a greater removal of LDL.

The first description of the connection between PCSK9 and LDL-C was made over 20 years ago. The PCSK9 gene was found to have gain-of-function mutations in 2003, which resulted in autosomal dominant hypercholesterolemia. Subgroup analyses of the Dallas Heart Study subsequently revealed that people with one copy of each of two distinct loss-of-function alleles of PCSK9 had lower LDL-C levels and that these naturally occurring variants were linked to a roughly 80% lifetime reduction in coronary heart

disease events. It was suggested by these genetic research that pharmacologic suppression of PCSK9 could lower LDL-C and stop ASCVD outcomes. [7]

Anti-Lp(a) Therapies

Lipoprotein(a), also known as Lp(a), is a distinct pro-atherogenic particle that shares structural similarities with LDL. The unique apo(a) protein and apo B-100 on an LDL-like particle establish a covalent connection to generate Lp(a). Beyond the cholesterol at its core, the inclusion of apo(a) confers prothrombotic and pro-inflammatory effects. Genetically determined, Lp(a) levels exhibit a skewed distribution, with higher mean levels in Black and South Asian populations and increased Lp(a) (classified as >100–125 nmol/L) in around 20% of the general European population. Independent of apo B-100, which is a measure of the overall amount of atherogenic lipoproteins, elevated Lp(a) levels are linked to an increased risk of ASCVD. Lp(a) levels had no relationship to LDL-C, non-HDL cholesterol, or apo B-100. The Canadian Cardiovascular Society guidelines for clinical practice suggest that Lp(a) be tested at least once during a patient's lifetime and that it be regarded as a non-modifiable risk factor comparable to a positive family history of ASCVD. Statin medication and lifestyle modifications have little effect on Lp(a) levels, in contrast to LDL-C and apo B-100. Niacin lowers Lp(a) levels by about 23%, however outcome studies have not shown that there is a therapeutic benefit in terms of cardiovascular events. Furthermore, when niacin is administered at the recommended therapeutic dosages, many individuals find the side effects unacceptable. Intriguingly, PCSK9 inhibitors reduce Lp(a) levels by 15–30%; however, it is unclear if this lowers the risk of ASCVD due to Lp(a). We address a few that are being studied, but as of right now, no drug has been approved with a specific indication for lowering excessive Lp(a) levels in patients [8].

Anti-Apo C-III Therapies

Apo C-III, a hepatically produced protein that circulates on the surface of TG-rich lipoproteins and serves to block their lipolysis, has been identified as a new therapeutic target for lowering TG levels. People with APOC3 gene disabling variations naturally have lower plasma TG levels and a roughly 40% lower risk of developing ischemic heart disease and ischemic vascular disease. These findings spurred the creation of novel pharmaceutical treatments that target APOC3 mRNA to lower the production of apo C-III protein, simulating the protective effects observed in apo C-III deficiency. Among the substances that are currently on the market or being developed to block apo C-III are plozasira, olezarsen, and volanesorsen [9].

Anti-ANGPTL3 Therapies

Angiopoietin-like 3 belongs to a family of proteins whose effects on plasma lipoprotein metabolism are intricate and not fully understood. ANGPTL3 inhibition was thought to be beneficial for individuals with hypercholesterolemia, HTG, or particularly combination hyperlipidemia, since humans with ANGPTL3 loss-of-function mutations experienced panhypolipidemia. Three ANGPTL3-targeting drugs advanced to the point of development, but two were shelved, leaving just evinacumab for clinical use at this time [10].

Conclusion

The therapeutic potential of targeting apolipoprotein C-III (Apo C-III) and angiopoietin-like protein 3 (ANGPTL3), two key regulators of lipid metabolism, in the treatment of dyslipidemia and cardiovascular disease. Apo C-III, synthesized in the liver, inhibits the lipolysis of triglyceride-rich lipoproteins, contributing to elevated plasma triglyceride (TG) levels. Individuals with loss-of-function mutations in the APOC3 gene demonstrate significantly reduced TG levels and a ~40% decreased risk of ischemic heart disease and other vascular conditions. These findings have driven the development of mRNA-targeting therapies such as plozasiran, olezarsen, and volanesorsen, which aim to lower Apo C-III levels and mimic the cardioprotective effect observed in APOC3-deficient individuals. Similarly, ANGPTL3, another liver-derived protein, plays a pivotal role in regulating TG, LDL-C, and HDL-C. Loss-of-function mutations in ANGPTL3 are associated with panhypolipidemia, indicating its therapeutic value. Evinacumab, a monoclonal antibody against ANGPTL3, has reached clinical application, while other candidates were discontinued. These advances underscore the potential of protein-

specific therapies in lipid management and cardiovascular risk reduction. However, further long-term studies are essential to fully understand their efficacy, safety, and broader clinical impact.

Reference

1. Ghazwani, Mousa, et al. "Prevalence of dyslipidemia and its determinants among the adult population of the Jazan region." *International journal of general medicine* (2023): 4215-4226.
2. Rani, Rapothula Roopa, Zeenath Banu, and Amtul Rahman. "Comprehensive Review of Hyperlipidemia: Pathophysiology, Diagnosis, and Management."
3. Tripathi, K.D., Essentials of Medical Pharmacology. 2008, India: JP brothers medical publishers
4. Dogan, Sengul, and Ibrahim Turkoglu. "Diagnosing hyperlipidemia using association rules." *Mathematical and Computational Applications* 13.3 (2008): 193-202.
5. Giles, L. Amy. "Hyperlipidemia prevention and management utilizing lifestyle changes." *Journal of Midwifery & Women's Health* 69.3 (2024): 361-369.
6. Wells, Barbara G. *Pharmacotherapy handbook seventh edition*. The McGraw-Hill Companies,, 2009.
7. Abifadel, Marianne, et al. "Mutations in PCSK9 cause autosomal dominant hypercholesterolemia." *Nature genetics* 34.2 (2003): 154-156.
8. Jacob, Erin O., et al. "Lipoprotein (a) in familial hypercholesterolemia." *CJC open* 6.1 (2024): 40-46.
9. Tardif, Jean-Claude, et al. "Apolipoprotein C-III reduction in subjects with moderate hypertriglyceridaemia and at high cardiovascular risk." *European heart journal* 43.14 (2022): 1401-1412.
10. Berberich AJ, Hegele RA. A modern approach to dyslipidemia. Endocr Rev. 2022;43:611–3.

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