

What Causes Elevated Lipoprotein A and How do we Manage It?

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Abstract:

Lipoprotein A (Lp(a)) is a lipid that performs various functions due to its unique structure. Lp(a) is an independent risk factor for Cardiovascular Disease (CVD). Lp(a) testing is recommended for people of all ages because high Lp(a) can lead to CVD. This study explores elevated Lp(a) levels and how to reduce them, providing potential medicines including pharmaceutical interventions or environmental factors. Understanding Lp(a)'s impact on Cardiovascular health is important to minimize health risks. This paper explores the causes of elevated Lp(a), analyzes current pharmacologic and environmental management strategies, and explores emerging therapies, highlighting the importance of regular Lp(a) screening and targeted treatment in controlling cardiovascular risk caused by Lp(a).

Keywords: Lipoprotein A (Lp(a)), Cardiovascular Disease (CVD), Wound Healing, Endothelial Cells, Therapeutic Development, Lifestyle Factors, Inflammation

Introduction:

Lipids, often referred to as fats, are important to human metabolism and physiology. They serve as energy reserves, structural components of cell membranes, signaling molecules, and precursors to vital hormones.¹ These fatty compounds are soluble in organic solvents and consist of fats, oils, steroids, waxes, and phospholipids. For example, prostaglandins are a type of lipid that mediates inflammation, while triglycerides are stored in adipose tissue and act as an energy source during fasting or increased energy demand.

Even though lipids play many beneficial roles, an imbalance—especially when lipids are excessively stored or not sufficiently regulated—can lead to harmful pathological conditions. High lipid levels can damage cells and tissues through disrupting cellular signaling, triggering apoptosis (cell death), and impairing organelle function.¹ These harmful effects are particularly concerning in the context of cardiovascular health, where lipid accumulation in blood vessels is a major contributor to disease.

One of the most well-known lipids is cholesterol. It is synthesized by the liver and is used to produce hormones and aid in digestion. The human body naturally produces cholesterol as needed, consumption of additional cholesterol through diet such as shrimp, eggs, and red meat are not recommended. Excessive dietary intake can lead to hyperlipidemia, a condition characterized by abnormally high lipid levels in the blood. Hyperlipidemia increases the risk of developing cardiovascular disease (CVD) by promoting plaque buildup in arteries, which restricts blood flow and puts additional strain on the heart and vascular system. This can lead to serious complications such as heart attack, stroke, and peripheral artery disease.

	LDL	VLDL	HDL	Triglycerides	Total Cholesterol
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Healthy Range	<100mg/dL	<30mg/dL	>40mg/dL	<150 mg/dL	<200mg/dL
Pathological Range (in	160-189 mg/dL	>39mg/dL	<40mg/dL	>150 mg/dl	>200ng/dL

Table 1: Types of Lipids. Healthy versus Pathological Range.

When studying cholesterol, it is revealed that not all lipoproteins are the same. Low-Density Lipoprotein (LDL) is considered "bad cholesterol" because high LDL-C levels (160–189 mg/dL) leads significantly to plaque formation in the arteries. Similarly, Very Low-Density Lipoprotein (VLDL), carrying triglycerides through the bloodstream, can worsen plaque buildup and obstruct blood flow further. However, High-Density Lipoprotein (HDL) is known as "good cholesterol" because it transports excess cholesterol to the liver for excretion, effectively clearing arteries. HDL levels should remain above 40 mg/dL to reduce cardiovascular risk.

Retaining a healthy lipid profile is necessary for cardiovascular health. The optimal values are: total cholesterol below 200 mg/dL, LDL below 100 mg/dL, and triglycerides below 150 mg/dL.² Routine health checkups, including blood pressure monitoring and lipid panels, play a vital role in early detection and prevention of cardiovascular disease.

In addition to lipoproteins like LDL and HDL, a lesser-known but important lipid is Lipoprotein A (i.e. Lp(a)). Lp(a) has a similar structure to LDL. Lp(a) has distinct biological properties due to the addition of a protein. Unlike LDL or triglycerides, Lp(a) levels are mostly determined by genetics rather than lifestyle changes. Despite this, high Lp(a) has been strongly linked to a higher risk of cardiovascular events, including atherosclerosis, heart attacks, strokes, and aortic valve stenosis. Given its genetic basis, resistance to traditional lifestyle interventions, and role in promoting vascular damage associated with tissue function, Lp(a) is now recognized as an independent risk factor for CVD. Despite the rising prevalence of CVD, it remains underdiagnosed and undertreated. Current biomedical research is focused on developing therapies capable of reducing Lp(a) levels more effectively.

Lp(a) is associated with atherogenesis and is an independent risk factor for CVD. Lp(a) has a unique structure with various functions, including wound healing for endothelial cells and atherogenesis. Due to strong associations between Lp(a) and CVD, testing and therapies are recommended to prevent high levels of Lp(a). This study explores the mechanisms underlying the causes of elevated levels of Lp(a) and current perspectives on disease management through pharmaceutical intervention in addition to other factors such as behavior and environmental factors highlighting various CVD events.

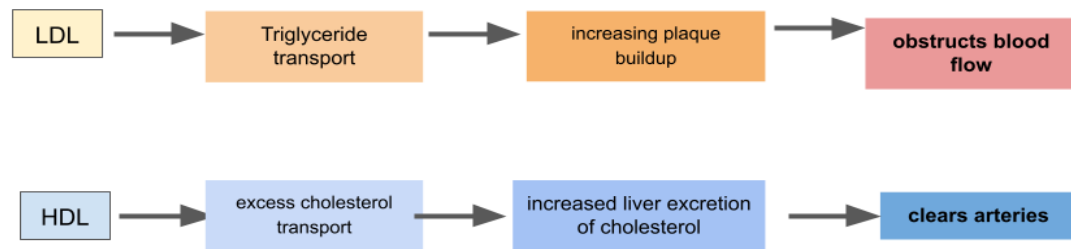


Figure 1: The pathological flow of LDL and HDL.

Methods

Multiple electronic databases were used to find information and research study findings associated with cholesterol, heart disease, and Lp(a). This included PubMed, Google Scholar, and regular search engines like Google. Only English articles were used. The following keywords were used within the databases' search: "lipoprotein a," "Lp(a)," "cardiology," "heart disease," and "lipids." To extract information, main findings were recorded and important themes were summarized within each paper's headings or results sections. To compile the paper, I decided to describe lipids and biochemistry in general before discussing the pathologies associated with lipids. Then, I focused on the specifics of heart disease associated with lipids and biomarkers like Lp(a). Studies included in this review was 11.

Demographics and Risk Factors

CVD is the leading cause of death in the United States, accounting for approximately 30% of all deaths annually.³ It affects nearly 48.6% of adults over the age of 20, making it one of the most prevalent chronic health conditions.³ CVD causes a range of disorders involving the heart and blood vessels, many are driven by atherosclerosis; a condition where plaque builds up in the arteries, restricting blood flow and increasing the risk of blood clots.

A heart attack (or myocardial infarction) is a common CVD event, which occurs when the heart's blood vessels are blocked, preventing adequate oxygen and nutrient delivery to the heart muscle.⁴ Similarly, a stroke, in particular an ischemic stroke, results from a blockage in the blood vessels that supply the brain, leading to potential brain damage or death.⁴ Another CVD event which is a major condition is heart failure, where the heart is unable to pump sufficient blood to meet the requirements for organs to function properly.

Hypertension, also called high blood pressure, is another contributor to CVD. It happens when there is an increase in force of blood against artery walls, ultimately damaging the endothelial lining of blood vessels and lead to conditions such as coronary artery disease.⁵ While blood pressure usually increases gradually with age, sudden spikes can be dangerous and may require medical attention.



Symptoms of cardiovascular disease include chest pain, shortness of breath, nausea, fatigue, dizziness, and cold sweats.⁴ Research suggests that up to 90% of cardiovascular events are preventable through lifestyle changes such as stress reduction, maintaining a healthy weight, and regular exercise.⁴

While many risk factors for CVD such as poor diet, lack of exercise, and smoking are well known, one significant and less frequently discussed contributor is protein levels of Lp(a). This lipoprotein has a structure similar to LDL cholesterol and is found in tissues—including peripheral, liver, and arterial wall tissues—where regeneration and healing occur. However, high Lp(a) levels have been associated with a greater risk of atherosclerosis and cardiovascular events. Despite this, it is still underdiagnosed and undertreated. Globally approximately 20–30% of the population is estimated to have elevated Lp(a) levels.⁶ Given its genetic basis and limited response to traditional lifestyle interventions, Lp(a) represents an important but often overlooked risk factor for cardiovascular disease. In this review, we aim to increase Lp(a) awareness, highlight its role in cardiovascular risk, and discuss strategies for its management.

Lipoprotein(a) Function in Health and Disease

Lp(a) is involved in many roles in the body, and some contribute to the risk of developing cardiovascular events. One of its primary functions results in deposits of cholesterol within arterial walls, forming plaque that obstructs blood flow to vital organs such as the heart and liver. These cholesterol deposits may occur either intact or in fragmented form, increasing the chance of atherosclerosis and other vascular complications. These deposits can lead to heart attacks, strokes, or even gradual narrowing of arteries.

Structurally, Lp(a) consists of two main proteins: apolipoprotein(a) and apolipoproteinB. Elevated levels of apoB are strongly associated with an increased risk of heart disease, as this protein also plays a major role in LDL cholesterol metabolism and plaque formation in common pathologies.

Certain health conditions and demographic factors are associated with higher Lp(a) levels. Individuals with familial hypercholesterolemia (e.g. excessive cholesterol), or chronic kidney disease often exhibit elevated Lp(a), thus increasing their cardiovascular risk. From a genetic standpoint, research findings have indicated that race and ethnicity also influence Lp(a) concentrations and resulting health outcomes. Populations of healthy South Asian and African descent are significantly more likely to have elevated Lp(a) compared to Caucasians. This inconsistency is associated with genetic variations, including differences in the size of the LPA gene and the presence of single nucleotide polymorphisms (SNPs) that affect Lp(a) production.

Interestingly, Lp(a) is not necessary for human survival, as many people have little to no detectable Lp(a) levels with minimal consequences. However, when Lp(a) concentrations rise above 50 mg/dL, the risk of inflammation, thrombosis (clotting), and atherosclerosis increases substantially. This mg/dL level is often used in clinical settings to determine whether intervention or monitoring is necessary.



Targeting Lipoprotein(a) for Diagnostic Criteria and Therapeutics

Testing for Lipoprotein(a) levels is particularly encouraged for individuals under the age of 65 who have a history of heart attack, patients with elevated LDL cholesterol (LDL-C) levels that are unresponsive to statin therapy, or those with a family history of premature CVD. To reduce CVD risk, identifying high Lp(a) as soon as possible is essential. This allows enough time for intervention before any more damage occurs.

At the moment, there are no treatments that can completely eliminate Lp(a) from the blood stream, however, there are many therapeutic choices that are effective at lowering the levels. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were designed to lower LDL-C, but through further research, PCSK9 also decreases Lp(a) concentrations, lowering it by approximately 20-30%.⁷ Other lipid-lowering medicines such as niacin and estrogen also lessen Lp(a) levels.

An emerging treatment is lipoprotein apheresis (LA), a procedure that physically removes excess Lp(a) and LDL-C from the blood. Besides lowering lipid levels, LA can reduce blood viscosity, improve kidney function, and enhance microvascular myocardial perfusion.⁸ Importantly, LA is the only Food and Drug Administration (FDA)-approved therapy specifically for lowering Lp(a). Though it is mostly used in European countries like Germany and the United Kingdom, its slowly being adopted by the United States. its high cost and logistical challenges keeps many from performing this procedure. LA is a multi-step process, with each session lasting 2 to 4 hours and typically performed 1 to 2 times per week. A notable limitation of this therapy is that its effects on Lp(a) levels are temporary, requiring lifelong treatments.

In addition to pharmacologic interventions, non-medical approaches such as aerobic exercise can reduce cardiovascular risk and potentially lower Lp(a) levels overtime. Aerobic activities like running, biking, swimming, increase heart rate, contributing to overall cardiovascular health.⁹ Research by Kokkinos et al. demonstrated that patients who combined statin therapy with regular exercise experienced significantly lower mortality rates compared to those treated with statins alone.⁴ Highly fit people had a 60-70% reduction in mortality risk as compared to sedentary statin users.¹⁰ Similarly, Ekelund et al. reported that individuals who engaged in frequent physical activity had a 12-59% lower mortality rate compared to those who have a sedentary lifestyle.³

Conclusion

Lipids are important in human physiology. There are different types such as LDL, VLDL, and HDL. Lipoprotein(a) (Lp(a)) is a particularly important lipid due to its role in tissue repair and vascular remodeling. Lp(a) testing is recommended especially for individuals under 65 years of age, as elevated levels above 50 mg/dL are associated with an approximately 35% increased risk of cardiovascular disease. Given this heightened risk, it is advisable to pursue interventions aimed at lowering Lp(a) once this threshold is exceeded.

Preventative strategies include stress reduction techniques, limiting caffeine intake, reduction of processed food intake, and achieving approximately 8 hours of sleep nightly can significantly mitigate cardiovascular risk. Pharmacologic options include lipoprotein apheresis



(LA) and PCSK9 inhibitors, both of which have been shown to temporarily reduce Lp(a) levels. Because the effects of these treatments are transient, consistent adherence to medication and therapy schedules is necessary to maintain their cardiovascular benefits.

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