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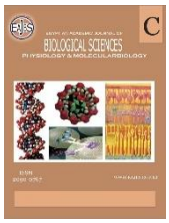

A Quick Guide to the Fundamentals of Lipoprotein(a): Composition, Pathophysiology, and Controversies of Measuring and Treating Elevated Levels of Lipoprotein(a)

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ABSTRACT

Atherosclerosis, a persistent inflammatory condition affecting the arteries, continues to be a major contributor to cardiovascular death globally despite improvements in its treatment. Conventional risk factors such as elevated cholesterol levels, diabetes, and smoking cannot completely account for all instances, emphasizing the need to identify novel treatment targets. Lipoprotein(a) [Lp(a)] is a type of lipoprotein particle that is similar in structure to low-density lipoprotein (LDL-C) but different because it contains apolipoprotein(a) [apo(a)]. Genetic factors, particularly the LPA gene, predominantly determine Lp(a) levels, which vary significantly across populations. Cardiovascular disease (CVD) is strongly associated with high Lp(a) levels. However, researchers are still investigating the precise mechanisms by which Lp(a) contributes to the development of arterial diseases. The metabolism of Lp(a) is complex and includes its synthesis in the liver, its combination with apolipoprotein B_{100} (apo-B_{100}), and its interactions with several receptors for its removal, particularly from the liver and kidneys. In addition to its involvement in atherosclerosis, Lp(a) may also serve physiological purposes such as contributing to wound healing and angiogenesis. Factors that affect Lp(a) levels include genetic composition, acute-phase reactions, and hormonal fluctuations. Despite extensive investigations, the relationship between physical activity and Lp(a) levels remains unclear. This review presents an up-to-date thorough examination of Lp(a) metabolism, pathogenesis, and possible therapeutic approaches.

INTRODUCTION

Atherosclerosis, a persistent inflammatory condition affecting the arteries, continues to be the primary cause of cardiovascular mortality globally despite progress in its management and prevention(Jawi *et al.*, 2024). Although classic risk factors, such as elevated cholesterol levels, diabetes, and smoking, are widely recognized, they do not provide a complete explanation for all instances(Jawi *et al.*, 2024). This emphasizes the need for alternative objectives in future therapies.

Lipoprotein(a) [Lp(a)], a lipoprotein particle discovered several years ago(Berg, 1965), is a highly promising candidate(Jawi *et al.*, 2020). It resembles low-density lipoprotein cholesterol (LDL-C) but possesses distinct structural characteristics(Jawi *et al.*, 2020). It is worth mentioning that there are large variations in Lp(a) levels among different populations and ethnic groups. Notably, even among populations that usually have lower levels of Lp(a), such as Caucasians, individuals with high levels of Lp(a) are at a significantly higher risk of heart disease(Jawi *et al.*, 2020).

Extensive research has established a strong association between elevated Lp(a) levels and various cardiovascular events(Tsimikas, 2017). However, the precise processes that contribute to the development of this disease are still being investigated.

This review provides a comprehensive analysis of the metabolism of Lp(a), the effect of Lp(a) on the body, and promising agents for the management of elevated Lp(a) levels.

The Unique Structural Features of lipoprotein(a):

Lp(a) is a complex lipoprotein differentiated from LDL-C by the inclusion of apolipoprotein(a) (apo[a])(Jawi *et al.*, 2020). Lp(a) also contains a lipid core resembling that of LDL and apolipoprotein B-$_{100}$ (apo-B$_{100}$)(Jawi *et al.*, 2020). In contrast, Lp(a) demonstrates considerable variability in size because of discrepancies in the quantity of kringle type-IV (K-IV) repeats present within apo(a)(Coassin & Kronenberg, 2022). This is in contrast to the greater size uniformity observed in other lipoproteins (Figs. 1 and 2).

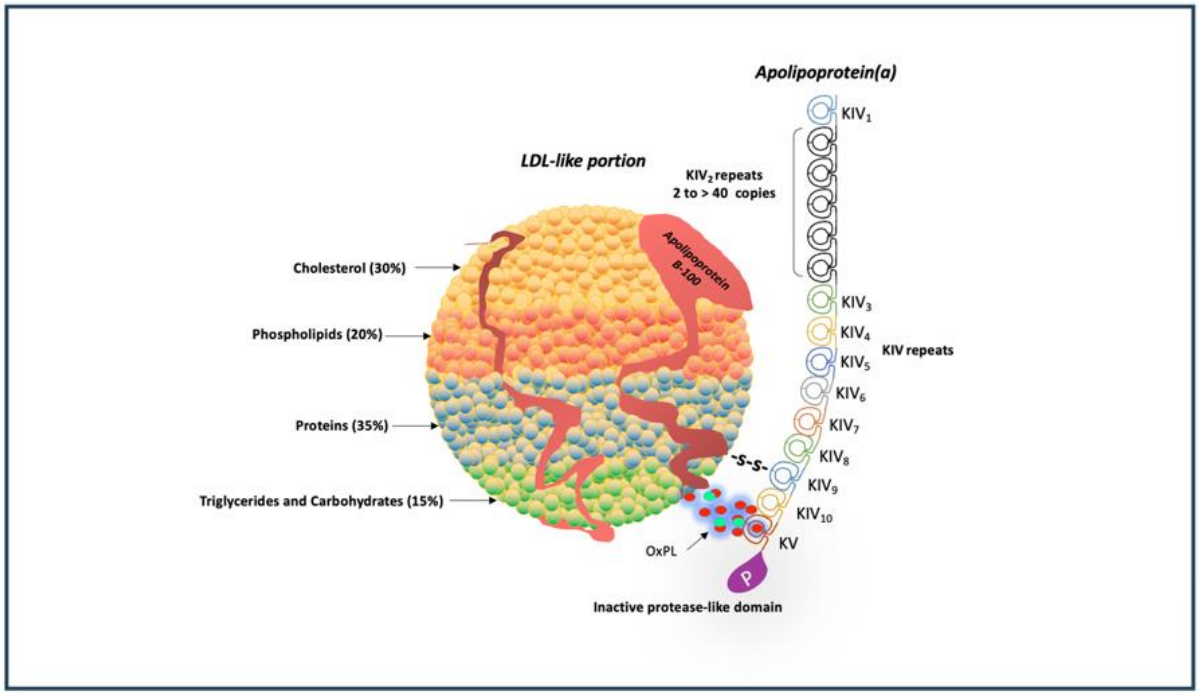

Fig. 1: Apolipoprotein B-$_{100}$ (apo-B$_{100}$) covalently bonds to apolipoprotein (a) to form the Lp(a) molecule. Apo(a) has an unpaired cysteine and forms a disulfide bond with apo-B$_{100}$ to generate the lipoprotein particle Lp(a). Apo(a) consists of 10 subtypes of KIV repeats, including a copy of KIV$_{(\text{subtype 1})}$, multiple copies of KIV$_{(\text{subtype 2})}$, and a single copy of KIV$_{(\text{subtype 3-10})}$, KV, in addition to the inactive protease-like domain. The LDL-like portion of the Lp(a) molecule contains 35 % protein, 30 % cholesterol, 20 % phospholipids, 15 % triglycerides, and carbohydrates. This illustration was constructed by the author.

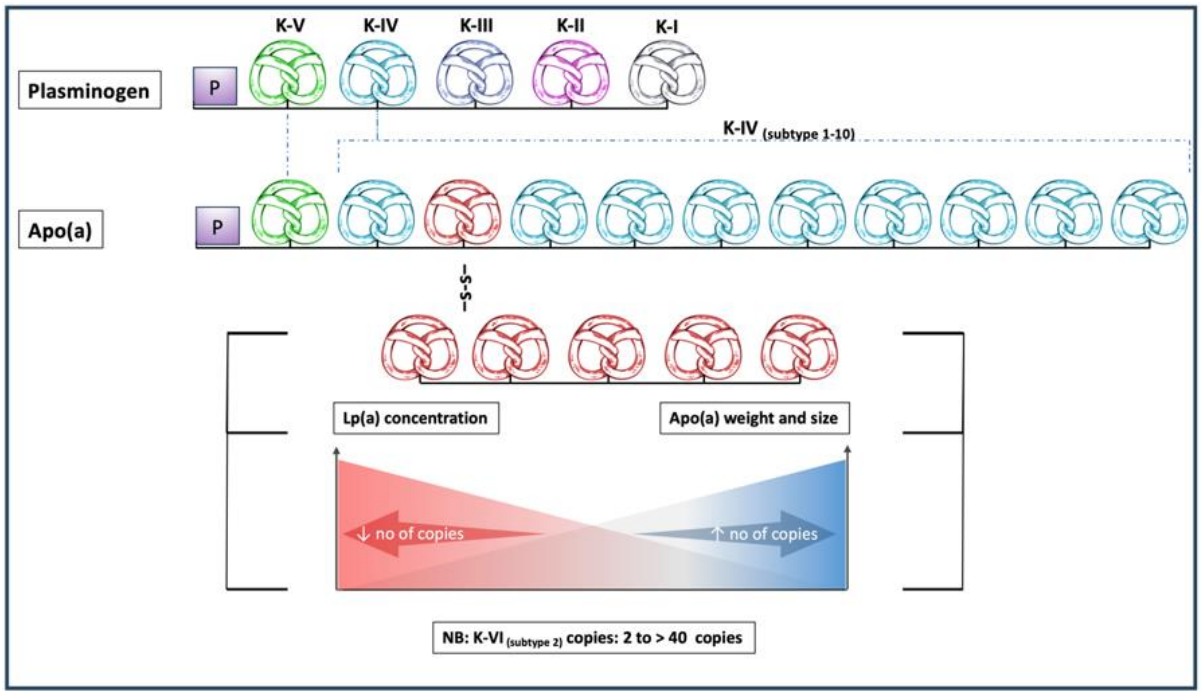

Fig. 2: This demonstration is mostly about how apo(a) has changed over time and how its structure works. It also looks at how K-IV$_{(subtype\ 2)}$ repeats affect the molecular weight and size of apo(a) and how that affects plasma Lp(a) levels. This illustration was constructed by the author.

Apolipoprotein(a): the key to Understanding The Role of Lipoprotein(a) In Cardiovascular Disease:

The structural homology of apo(a), a defining characteristic of Lp(a), has also been observed in plasminogen (PLG), a precursor of fibrinolytic enzymes(Lampsas et al., 2023). Notably, apo(a), which shares a protease domain with PLG, does not exhibit enzymatic activity(M. Jawi *et al.*, 2020). Critical functions are performed by the K domains within apo(a), specifically K-IV repeats. The binding of Lp(a) to cells and fibrin is facilitated by the K-IV$_{(subtype\ 10)}$, which may play a role in atherothrombosis(Cai *et al.*, 2013). In addition, (Cai *et* al., 2013) reported that KIV$_{(subtype\ 6\text{-}7)}$ promotes inflammation and vascular smooth muscle cell proliferation by interacting with scavenger receptors on foam cells(Cai *et al.*, 2013). Angiogenesis or blood vessel formation can also be promoted by KIV$_{(subtype\ 6\text{-}7)}$(Jawi *et al.*, 2020).

The Impact of Genetics on Lipoprotein(a) Levels And Cardiovascular Risk:

Lp(a) levels are predominantly determined by the LPA gene, which is located on chromosome 6 (6q26-27) and accounts for approximately 90 % of the variance(Jacobson, 2013). The size of Lp(a) isoforms is significantly heterogeneous because of the variable number of K-IV$_{(subtype\text{-}2)}$ repeats in this locus, which regulates the size of apo(a)(Coassin & Kronenberg, 2022). Large amounts of K-IV$_{(subtype\ 2)}$ result in the degradation of a significant number of apolipoprotein(a) molecules within liver cells(Jawi et al., 2020). Conversely, low concentrations of K-IV$_{(subtype\ 2)}$ allow the molecules to be freely disseminated, allowing them to bind to LDL particles outside the liver cells and form Lp(a)(Jawi et al., 2020; Reyes-Soffer et al., 2017). Plasma lipoprotein(a) concentrations were inversely correlated with the number of KIV$_{(subtype\ 2)}$ repeats (Fig. 2).

Lipoprotein(a) Metabolism and Its Implications for Cardiovascular Health:

The complex processes involved in Lp(a) metabolism begin with its synthesis in the liver. In contrast to other lipoproteins, the synthesis of Lp(a) is primarily determined by genetic factors as opposed to dietary or

environmental factors. According to Hobbs and White, multiple phases within the liver cells regulate the rate of apo(a) secretion, a critical component of Lp(a)(Hobbs & White, 1999). These phases comprise transcription and maintenance of mRNA stability, translation of apo(a), post-translational modifications within the endoplasmic reticulum (ER), and processing in the Golgi complex(Hobbs & White, 1999). Furthermore, one study has emphasized the importance of apo(a) being efficiently folded before it is transported out of the ER to regulate apo(a) production rates(White *et al.*, 1997).

Following synthesis, Lp(a) is assembled in two steps. First, non-covalent interactions bring the apo(a)-cysteines closer to apo-B_{100}, facilitating their association(Hobbs & White, 1999). The particular domains of apo(a) form a covalent disulfide bridge, which is subsequently formed(M. M. Jawi et al., 2020). Theories differ in terms of the precise location of the assembly; some suggest that it occurs on the surface of liver cells, in Disse, or even extracellularly(Diffenderfer et al., 2016; Hoover-Plow & Huang, 2013). Research utilizing baboon hepatocyte cultures has provided insights into the mechanisms of extracellular assembly, in contrast to in vitro investigations that have proposed potential locations, such as the plasma or interstitial spaces(White & Lanford, 1994).

According to Jawi *et al.*, particles containing apo-B are bound to newly secreted apo(a), resulting in the formation of Lp(a) at diverse densities, such as very low-density lipoprotein (VLDL) and LDL. These particles undergo metabolic processes, including lipolysis, which results in the creation of residual Lp(a) particles that catabolize or recycle in the liver(Jawi *et al.*, 2020). The intricate nature of Lp(a) metabolism is highlighted by the participation of triglyceride synthesis in apo(a) production. Therefore, additional investigation is necessary to clarify the mechanisms underlying apo(a) assembly in hepatocytes or the plasma.

The Clearance of Lipoprotein(a) from The Bloodstream: Key Organs Involved:

Understanding the processes involved in eliminating Lp(a) from the bloodstream is an essential field of study for effectively controlling increased Lp(a) levels. Despite ongoing investigations, the key sites and procedures responsible for Lp(a) removal remain disputed. The liver and kidneys are the primary organs involved, while the spleen and muscles may have secondary involvement(Kostner & Kostner, 2017). The available evidence indicates that changes in Lp(a) plasma concentrations are mostly associated with differences in production rates and size rather than a sluggish rate of clearance(Diffenderfer *et al.*, 2016). The extended duration of apo(a) residency in circulation compared to apo-B_{100}, another constituent of Lp(a), reinforces this concept(Diffenderfer *et al.*, 2016).

The main process by which Lp(a) is eliminated involves intricate interactions with different receptors. First, LDL receptors (LDLR) are believed to majorly influence Lp(a) metabolism. However, data indicate that LDLR has a limited effect on Lp(a) removal because of the interference caused by the apo(a) component(Siekmeier et al., 2008). Although statins, which increase LDLR expression, do not have a substantial impact on Lp(a) levels, PCSK9 inhibitors have proven successful, indicating the presence of alternative routes(Maranhão *et al.*, 2014). Additional liver receptors such as Megalin, LRP-1, and galactose-specific asialoglycoprotein receptor (ASGPR) may also play a role in the removal of Lp(a)(Maranhão *et al.*, 2014). Sharma et al.(Sharma *et al.*, 2016) proposed a new clearance mechanism involving PlgRKTs. They suggested that Lp(a) and apo(a) are metabolized differently in the liver, with apo(a) potentially returning to the bloodstream and LDL being broken down(Sharma *et al.*, 2016). The kidneys play a vital role in Lp(a) metabolism because of their involvement in Lp(a) uptake through receptors present in the liver, such as PlgRKT and Megalin(Kronenberg, 2014). Moreover,

in patients with compromised kidney function, decreased glomerular filtration was associated with higher Lp(a) levels and slower removal rates(Frischmann *et al.,* 2007).

Exploring the Potential Protective Roles of Lipoprotein(a) Beyond Cardiovascular Risk:

Although Lp(a) is commonly associated with cardiovascular risk, it may have specific advantageous functions. Some studies have proposed that Lp(a) may impede the creation of new blood vessels and tumor growth (Kostner & Kostner, 2005). A study by Kim *et al*. (Kim *et al.,* 2003) demonstrated that fragments of K generated from apo(a) can inhibit angiogenesis and tumor growth in animal models, which could be facilitated by disrupting signaling pathways that are essential for angiogenesis(Kim et al., 2003). Nevertheless, there is conflicting evidence indicating that certain individuals with elevated Lp(a) levels have protective effects against cancer(Sawabe *et al.,* 2012).

Lp(a) levels can be elevated because of acute illnesses such as myocardial infarction, inflammatory bowel disease, and gallbladder problems(Pepe *et al.,* 1998). These events trigger an increase in the levels of the acute-phase reactant Lp(a)(Topçiu-Shufta *et al.,* 2010). Studies have demonstrated that inflammatory cytokines have a substantial effect on the increase in Lp(a) levels(Topçiu-Shufta *et al.,* 2010). This emphasizes the significance of considering inflammation when interpreting Lp(a) test findings.

The Relationship Between Oxidized Phospholipids (OxPLs) and lipoprotein(a): Mechanisms of Elimination:

OxPLs play a role in the first phase of atherosclerosis by activating proinflammatory reactions in immune cells(Pirro *et al.,* 2017). These compounds generally develop on oxidized LDL-C and apoptotic cell membranes before entering the bloodstream(Tsimikas & Witztum, 2008). Remarkably, Lp(a) reverses this process by binding and eliminating OxPLs from the bloodstream(Szymanski *et al.,* 1996). The protective mechanism appears to involve the formation of a covalent connection between OxPLs and the KI-V domain of apo(a) within Lp(a)(Oyelola O, 1993). Nevertheless, certain data indicate that this correlation may occur at the cellular level in the liver rather than through direct circulation(Maranhão *et al.,* 2014).

Lipoprotein(a) and Wound Healing: Exploring Its Potential Beneficial Role:

Lp(a) may have beneficial effects on wound healing(Lippi & Guidi, 2000). Yano et al.(Yano *et al.,* 1997) observed a significant presence of Lp(a) in healing tissues, specifically in the fibrous cap, endothelial cells of tiny blood vessels, and extracellular space during the second phase of wound healing(Orsó & Schmitz, 2017). Given the genetically set nature of Lp(a) levels, which are not affected by diet or the environment, this observation implies that Lp(a) could be a beneficial supply of cholesterol for tissue regeneration and repair.

Lipoprotein(a) and Its Influence On Fibrinolysis And Fibrin Breakdown:

Apo(a) isoforms have both structural and functional resemblances to PLG, a crucial constituent of the fibrinolytic pathway responsible for the dissolution of blood clots(Anglés-Cano *et al.,* 2001). This homology enables apo(a) to compete directly with PLG for the fibrin-binding sites. It is worth mentioning that smaller apo(a) isoforms have a higher affinity for fibrin than the larger isoforms(Boffa & Koschinsky, 2016).

Additionally, Lp(a) induces the production of plasminogen activator inhibitor-1 (PAI-1), which blocks the activities of tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). This process helps control the conversion of PLG into plasmin(Boffa & Koschinsky, 2016). This intricate interaction implies a possible function of Lp(a) in the breakdown of fibrin, perhaps providing wounded tissues with sufficient time for healing and regeneration(Boffa & Koschinsky, 2016).

Lipoprotein(a) and Its Role in The Pathogenesis of Atherosclerosis:

Lp(a) has been implicated in atherosclerosis in several ways, with hypotheses mostly concentrating on how early lesions grow into more advanced stages. During the early stages, Lp(a) penetrates the vascular wall and undergoes oxidation with the help of enzymes such as myeloperoxidase (MPO), lipoxygenases (12/15 LO), lipoprotein-associated phospholipase A2 (LPL), and reactive oxygen species such as superoxide anions ($O2^-$), and hydrogen peroxide (H_2O_2)(Tsimikas, 2008). The oxidation of Lp(a) [OxLp(a)] is crucial for subsequent pathophysiological processes.

First, OxLp(a) and OxPLs greatly increase the permeability of the endothelial monolayer, allowing for increased entry of Lp(a) and LDL into the vascular wall (Fig. 3). This inflow contributes to the development and progression of atherosclerotic plaques. In addition, OxLp(a) and OxPLs have affinities for particular receptors such as the E-type prostaglandin receptor (EP2)(Li et al., 2006). This interaction results in the accumulation of connecting segment 1 (CS-1) and the activation of adhesion molecules on endothelial cells(Cole et al., 2003). These molecules, including the intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), and E-selectin, facilitate the attachment and penetration of monocytes into the arterial walls(Jawi *et al.*, 2020; Zhao & Xu, 2000).

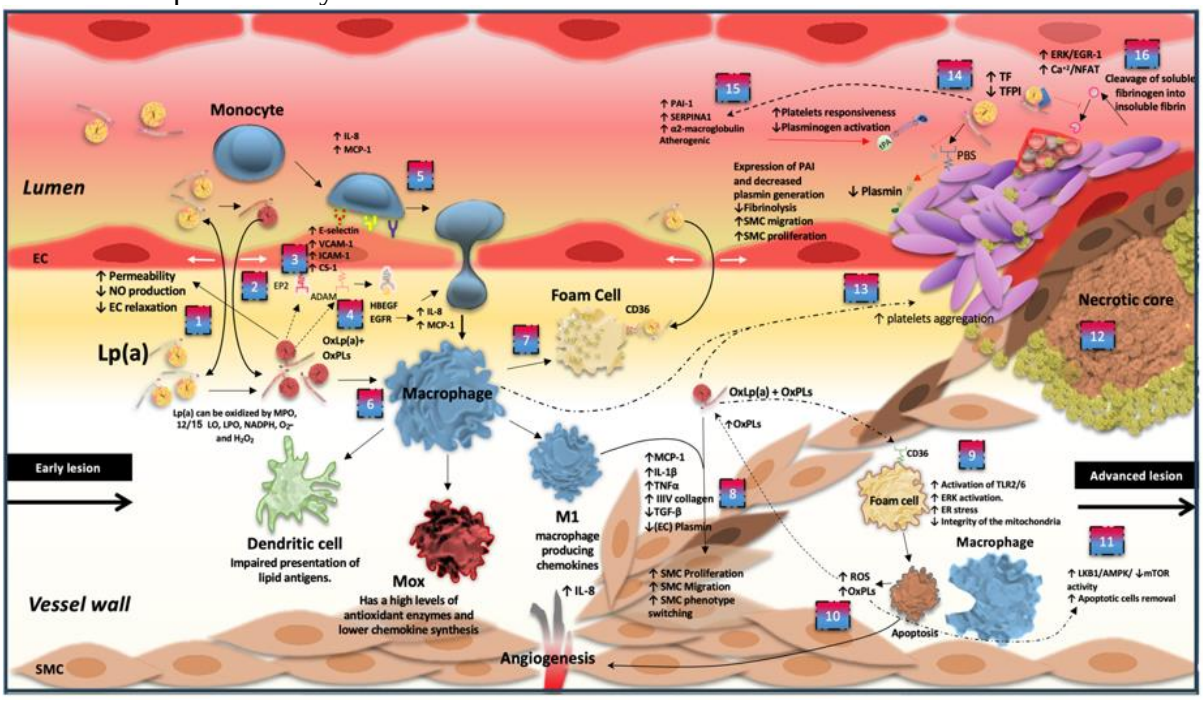

Fig. 3: The proposed summary of different mechanisms for early and late Lp(a) atherosclerotic lesion. This illustration was constructed by the author.

In addition, OxLp(a) can stimulate specific enzymes, such as disintegrins and metalloproteinases (ADAMs), which in turn initiate the release of growth factors, such as heparin-binding epidermal growth factor (HB-EGF), and activate receptors, such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor 2 (VEGFR2)(Lee *et al.*, 2012). This sequence of events results in the synthesis of chemokines, such as interleukin-8 (IL-8) and monocyte chemotactic protein-1 (MCP-1), which in turn attract monocytes to the arterial wall and facilitate their transformation into foam cells, dendritic cells, and pro-inflammatory M1 macrophages(Sotiriou *et al.*, 2006; Subbanagounder *et al.*, 2002).

As the lesions advance, macrophages take in OxLp(a) by binding to scavenger receptors, such as CD36, resulting in the

formation of foam cells that are characteristic of advanced atherosclerotic plaques(Rahaman *et al.,* 2011). Furthermore, OxLp(a) and Lp(a) cause atypical growth, movement, and alterations in the characteristics of smooth muscle cells (SMCs), which leads to the instability of plaque. OxLp(a) further increases CD36 expression, which in turn activates Toll-like receptor 2/6 (TLR2/6)(Seimon et al., 2010). This activation triggers signaling pathways such as ERK and leads to the induction of ER stress, mitochondrial malfunction, and ultimately cell apoptosis(Komai *et al.,* 2002).

The accumulation of apoptotic cells intensifies inflammation and oxidative stress, leading to the formation of necrotic cores and the rupture of vessel walls. In addition, macrophages and OxLp(a) enhance platelet aggregation, whereas the interaction between apo(a) and PLG-binding sites hinders fibrinolysis, resulting in thrombotic events. Moreover, Lp(a) stimulated the production of PAI-1, suppressed tissue factor pathway inhibitor (TFPI) expression, and amplified tissue factor (TF) expression(Noel M. & Panetta, 2001). These actions collectively contribute to the development of blood clots and the advancement of plaques in atherosclerosis.

Factors Influencing Lipoprotein(a) Levels In The Blood:

Genetic makeup is the primary determinant of bloodstream Lp(a) levels. However, other circumstances can influence these levels, leading to either an increase or a decrease, as detailed in numerous reviews(Jawi *et al.,* 2020). Chronic liver and renal diseases are recognized to affect the levels of Lp(a) in the plasma(Barbagallo *et al.,* 2021). In addition, increased levels of Lp(a) may arise as a result of the acute-phase response to variables, such as inflammation, pregnancy, myocardial infarction, and other stimuli(Kostner & Kostner, 2004). These elevated levels typically stabilize once the acute-phase signals cause them to diminish. Studies have investigated the correlation between Lp(a) concentration and long-term alcohol intake and observed a substantial reduction in Lp(a) levels of up to 60 % depending on the dosage, regardless of the distribution of apo(a) isoform sizes(Catena et al., 2003). Similarly, tobacco smoking has been linked to a decrease in plasma Lp(a) by up to 20 % despite its established function as a significant risk factor for cardiovascular disease, affecting plasma triglyceride and HDL cholesterol levels(Scott, 1994).

Underlying disorders and therapeutic administration of hormones can also influence the levels of Lp(a) in the blood, partially because of their effect on other lipoproteins. Hormones, such as adrenocorticotrophic hormone (ACTH), can reduce Lp(a) levels by 40 %(Kostner & Kostner, 2004). Other hormones such as growth hormone (HGH) and insulin-like growth factor (IGF) have opposing effects on plasma Lp(a) levels(Hammerman. & Miller., 1997). HGH notably increases the levels by as much as 120 %, whereas IGF-I reduces them by up to 60 %(Kostner & Kostner, 2004). The effect of insulin on Lp(a) levels varies. Sex hormones, including male and female steroids, affect several elements of lipid metabolism(Kostner & Kostner, 2004). In particular, anabolic steroids can significantly reduce Lp(a) levels by up to 70 %(Saeedi *et al.,* 2014). During pregnancy, Lp(a) levels usually increase by one to two-fold or higher and then return to normal levels after childbirth(Wild & Feingold, 2000).

The Relationship Between Physical Activity and lipoprotein(a) Levels And Its Cardiovascular Risk:

Extensive research has explored the relationship between physical activity (PA) and Lp(a) (Mackinnon *et al.,* 1997). Although moderate exercise positively affects different lipoproteins, its effect on Lp(a) levels remains unclear. Research often indicates a limited or nonexistent connection between PA and Lp(a) levels in adults, whereas there is some indication of an opposite association in young individuals(Jawi, 2021). Elevated levels of both LDL-C and Lp(a) significantly increase the risk of cardiovascular disease (CVD), highlighting the importance of addressing modifiable risk factors through lifestyle

modifications(Jawi, 2021).

Studies examining the effect of PA on Lp(a) levels have yielded inconsistent results. Extensive research has consistently shown that there is no association between moderate PA and Lp(a) levels(Jawi, 2021). Engaging in intense exercise may modestly increase Lp(a) levels, but they will remain within the normal range. A study investigating the immediate effects of endurance exercise found no significant alterations in Lp(a) levels(Jawi *et al.*, 2020). This suggests that the blood concentration of Lp(a) is regulated independently of the PA levels, body weight, and other lipids in the bloodstream. These findings emphasize the significance of addressing other adjustable factors while managing high Lp(a) levels.

Additional studies have investigated the relationship between Lp(a) levels, resting heart rate (RHR), and blood pressure, revealing a notable correlation between increased Lp(a) levels and heightened RHR(Jawi, 2021). PA has a limited effect on Lp(a) levels, and it is possible to lower the risk of CVD in individuals with high Lp(a) levels by lowering the RHR and blood pressure through PA and other lifestyle modifications(Jawi, 2021). Furthermore, studies on carotid artery intima-media thickness (cIMT) have suggested that increased levels of PA are associated with decreased progression of cIMT, even in individuals with high levels of Lp(a)(Jawi, 2021). This finding supports the idea that PA plays a protective role against the development of atherosclerosis.

Challenges in Measuring Lipoprotein(a) Across Different Countries:

Countries that have not yet started measuring Lp(a) have many substantial obstacles because of the intricate characteristics of Lp(a)(Jawi *et al.*, 2024). An important challenge lies in the structural variability of Lp(a), specifically the heterogeneity of KIV_2 repeats. The heterogeneity of Lp(a) levels makes it difficult to standardize the immunological tests employed for their measurement(Marcovina & Albers, 2016). There are two primary classifications of assays: isoform-dependent and isoform-independent. Assays that depend on isoforms that quantify the overall protein mass of Lp(a) are prone to errors, as they have the potential to either overestimate or underestimate Lp(a) levels depending on the size of the apo(a) isoform(Jawi et al., 2020; Marcovina & Albers, 2016). This can result in disparate findings across studies and impede the precise evaluation of cardiovascular risk.

Another major obstacle is the implementation of isoform-independent assays, which quantify Lp(a) in nanomoles per liter (nmol/L) and are regarded as the highest standards by international organizations, such as the IFCC and WHO(Jawi et al., 2020). Although these assays have numerous benefits, they are not yet widely utilized and many earlier investigations have relied on less precise isoform-dependent assays(Marcovina & Albers, 2016). The adoption of isoform-independent assays necessitates significant changes in laboratory procedures, including the creation of new reference materials and calibrators. This transition is crucial for guaranteeing precise and standardized Lp(a) measurements but also requires substantial investment in infrastructure and training(Dati *et al.*, 2004).

Furthermore, translating Lp(a) data from mass-based measurements (mg/dL) into molar concentrations (nmol/L) poses an additional barrier. The conventional conversion factor (2.4 nmol/L to 1 mg/dL) is inaccurate as it fails to consider the variation in apo(a) isoform size(Mcconnell *et al.*, 2014). The lack of precision in measuring Lp(a) can result in substantial inaccuracies, making it challenging to establish consistent measurement standards across various laboratories and populations. To enhance the precision of the Lp(a) evaluations, it is crucial to reassess and modify this conversion factor.

Ultimately, the management and preservation of samples for Lp(a) analysis present difficulties. For optimal accuracy, it is preferable to measure Lp(a) in plasma, which has recently been isolated(Marcovina *et al.*,

2003). Nevertheless, several laboratories depend on frozen samples, which may deteriorate over time, resulting in errors(Marcovina et al., 2003). Countries seeking to incorporate Lp(a) measurements must develop standardized procedures for the collection and storage of samples to mitigate these problems(Marcovina *et al.,* 2003). It is essential to ensure the precise measurement of Lp(a) as new medicines that lower Lp(a) are developed. Therefore, it is necessary for countries to address these problems by offering dependable and standardized Lp(a) data to assess cardiovascular risk.

Desirable and High Lipoprotein(a) Levels: The Key Values:

The effectiveness of using a single Lp(a) threshold to evaluate the risk of atherosclerotic cardiovascular disease (ASCVD) has been questioned by recent discoveries from the UK Biobank, which has a diverse multi-ethnic population(Reyes-Soffer *et al.,* 2024). Evidence indicates that the risk of ASCVD increases linearly and consistently across all ethnic and racial groups as Lp(a) levels increase, with the risk being evident even at levels below the previously established thresholds(Reyes-Soffer *et al.,* 2024). This finding implies that a fixed Lp(a) criterion may not accurately represent true risk profiles across various populations(Reyes-Soffer *et al.,* 2024).

The European Atherosclerosis Society (EAS) and the National Lipid Association (NLA) have suggested that the cardiovascular risk associated with Lp(a) should be viewed as a continuum in response to these findings(Koschinsky *et al.,* 2024; Reyes-Soffer *et al.,* 2024). They suggested that Lp(a) levels should be categorized as follows: levels below 75 nmol/L (approximately 30 mg/dL) are generally regarded as desirable, levels of 125 nmol/L (approximately 50 mg/dL) or higher are classified as very high risk, and levels between 75 and 125 nmol/L (approximately 30–50 mg/dL) are considered to be in a gray zone(Koschinsky *et al.,* 2024; Reyes-Soffer *et al.,* 2024). This approach is spectrum-based, which allows clinicians to more accurately evaluate whether an individual's Lp(a) level indicates a clinically significant increase in risk compared to their overall risk profile(Koschinsky *et al.,* 2024; Reyes-Soffer *et al.,* 2024).

Guidelines for Lipoprotein(a) Screening: Identifying High-Risk Individuals:

Individuals at intermediate or high risk of cardiovascular disease (CVD) or coronary heart disease (CHD), particularly those who exhibit specific risk factors, should have their Lp(a) measured at least once(M. Jawi *et al.,* 2024). These include individuals with familial hypercholesterolemia, recurrent CVD despite statin treatment, or a significant family history of premature CVD or elevated Lp(a) levels ≥50 mg/dL(Jawi et al., 2020). Those with recurrent CVD despite optimal lipid-lowering therapy, those with a ≥5 % 10-year risk of fatal CVD according to European guidelines, or a ≥10 % 10-year risk based on U.S. guidelines, are also advised to undergo screening(Jawi *et al.,* 2020). Repeated Lp(a) measurements are required only when treatment for elevated Lp(a) levels is initiated to monitor the therapeutic response. Finally, Lp(a) assessment should be provided to the biological parents, siblings, and offspring of individuals with familial hypercholesterolemia.

Evaluating the Effectiveness of Current Therapies for Managing Elevated Lipoprotein(a) Levels:

Statins, which are frequently used to treat atherosclerosis, significantly affect Lp(a) levels. While several studies indicate a potentially modest decrease in Lp(a) levels with the use of statins, other studies, such as the JUPITER study, have demonstrated that statins can lead to an increase in Lp(a) by 10–20 %(Lippi & Targher, 2012). This variability may account for the lack of substantial LDL-C level decreases in certain individuals undergoing statin medication, since their cholesterol may be more closely linked to Lp(a) molecules. However, alternative therapeutic methods such as pelacarsen, an antisense oligonucleotide, have demonstrated the potential to effectively decrease Lp(a) levels in clinical trials by specifically

targeting apo(a) production in the liver (Tsimikas, 2017). Additional treatments, including mipomersen, lomitapide, and niacin, are serious approaches for treating high Lp(a) levels (Jawi *et al.*, 2024; Santos *et al.*, 2015; Scanu & Bamba, 2008). However, each treatment has limitations and possible adverse reactions.

Pelacarsen exhibited significant effectiveness in reducing Lp(a) levels in the first clinical study, with certain patients experiencing a reduction of up to 90 %(Marcovina *et al.*, 2017). Mipomersen, which has received FDA approval for the treatment of homozygous familial hypercholesterolemia (HoFH), has demonstrated efficacy in lowering Lp(a) levels (Crooke & Geary, 2013; Santos *et al.*, 2015). However, it does not affect apo(a) synthesis and has been linked to hepatotoxicity(Crooke & Geary, 2013; Santos *et al.*, 2015). Lomitapide, another medicinal drug, blocks the microsomal triglyceride transfer protein, resulting in a reduction in LDL-C and, to a lesser degree, Lp(a) levels(Cuchel *et al.*, 2013). Nevertheless, these medicines frequently require the use of additional lipid-lowering drugs and meticulous supervision owing to their adverse effects, such as the possibility of liver toxicity with mipomersen and lomitapide.

Additional therapies, such as CETP inhibitors, aspirin, PCSK9 inhibitors, and inclisiran, have been investigated for their ability to reduce Lp(a) levels(Akaiek *et al.*, 2002; Ray *et al.*, 2017; Santos & Watts, 2015). CETP inhibitors substantially decrease Lp(a) and LDL-C concentrations; however, additional investigations are required to validate their therapeutic advantages (Teramoto *et al.*, 2013). PCSK9 inhibitors such as evolocumab and alirocumab have shown encouraging outcomes in lowering Lp(a) levels(Koren *et al.*, 2015; Markham, 2015). Research is underway to gain a better understanding of these effects. In addition, inclisiran, a prolonged-acting small interfering RNA (siRNA) drug, substantially decreased Lp(a) levels(Bandyopadhyay *et al.*, 2017). The most efficient treatment for removing Lp(a) is apheresis, although this is hindered by the requirement for numerous sessions and related expenses(Vogt, 2017). However, additional research is required to fully understand the effects of these therapies on cardiovascular outcomes.

Muvalbumin, an oral inhibitor of Lp(a), has demonstrated encouraging results in reducing Lp(a) levels, providing a simple substitute for injectable treatments(Hooper *et al.*, 2024). During a phase I clinical trial, muvalaplin induced a dose-dependent decrease of up to 65 % in Lp(a) levels over 14 days(Hooper et al., 2024). The effects of higher doses lasted for more than two months. The drug effectively prevented the formation of Lp(a) by binding to the apo(a) KIV domains. It has shown a positive safety profile, with only moderate adverse events recorded and a minimal impact on PLG activity(Hooper *et al.*, 2024). This finding suggests that it does not have a substantial effect on fibrinolysis. While olpasiran injections provide a greater reduction in Lp(a) than muvalaplin, oral administration of muvalaplin is beneficial in terms of patient acceptance and possibly cost-effectiveness(Hooper et al., 2024; Malick *et al.*, 2023). Continuing trials involving research on kidney damage and a phase II clinical trial (KRAKEN) among persons at high risk are anticipated to provide additional clarity regarding the effectiveness of this treatment(Malick *et al.*, 2023).

Current Management: Mitigating Risk Through The Control of Risk Factors:

In the absence of effective and approved Lp(a)-lowering medications, individuals with elevated Lp(a) levels should prioritize aggressive management of other cardiovascular risk factors(Nordestgaard & Langsted, 2024). Although most interventions do not directly influence Lp(a) levels, they can substantially diminish the overall CVD risk, thereby indirectly alleviating the genetic risk associated with high Lp(a) levels(Nordestgaard & Langsted, 2024). In addition to endorsing a healthy lifestyle, a rigorous reduction in LDL-C levels is essential. Elevated Lp(a) levels

exacerbate CVD risk stemming from pre-existing atherosclerosis linked to high LDL and remnant cholesterol levels(Nordestgaard & Langsted, 2024). Standard LDL-lowering protocols should be adhered to, including the administration of high-intensity statins followed by the incorporation of ezetimibe and PCSK9 inhibitors to attain target LDL levels(Nordestgaard & Langsted, 2024).

Conclusions

Overall, Lp(a) level is an unknown factor in cardiovascular diseases. Its intricate structure and function contribute to both its ability to cause diseases and normal functions in the body. Although LDL-C and Lp(a) are similar, Lp(a) is distinct because of its distinct apo(a) component, which largely influences its biological characteristics and association with cardiovascular disease risk. High levels of Lp(a), which are mostly influenced by hereditary factors, are associated with an elevated risk of cardiovascular diseases, although the precise mechanisms are not fully understood. Lp(a) plays a role in important biological processes, such as the formation of atherosclerosis, malfunction of the endothelium, and inflammation. This is achieved by interacting with oxidized phospholipids and different cellular receptors. Although Lp(a) is commonly considered a risk factor for cardiovascular events, recent research has indicated that it may also play a protective role in processes such as wound healing and angiogenesis. This additional function may also have therapeutic implications. The metabolism and elimination of Lp(a) involves complex pathways, primarily in the liver and kidneys, where factors such as receptor interactions and genetic variability play essential roles in determining its levels in the bloodstream. The difficulties in quantifying and managing increased Lp(a) levels, together with their contradictory functions, emphasize the need for ongoing investigations to gain a deeper understanding of their influence on cardiovascular well-being and to develop focused therapeutic approaches. As our understanding of Lp(a) improves, it continues to become a crucial area of emphasis for the advancement of cardiovascular disease prevention and management.

Lp(a) contributes significantly to cardiovascular diseases. The distinctive apo(a) component differentiates it from LDL-C, affecting its biological characteristics and significant genetic association with cardiovascular risk. Increased Lp(a) levels are predominantly genetic and correlate with an elevated risk of atherosclerosis, endothelial dysfunction, and inflammation. However, the precise mechanisms are not fully understood. Although Lp(a) has been implicated in disease promotion, recent studies indicate that it may facilitate wound healing and angiogenesis, thereby confounding its therapeutic potential. The difficulties in quantifying and regulating Lp(a) levels underscore the necessity for additional studies to elucidate its influence on cardiovascular health and formulate targeted therapies.

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