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Lipoprotein(a): a Case for Universal Screening in Youth

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Abstract

Purpose of Review Lipoprotein(a) has emerged as a strong independent risk factor for cardiovascular disease. Targeted screening recommendations for Lp(a) measurement exist for adults and youth known to be at high-risk. However, Lp(a) measurements are not included in universal screening guidelines in the US; hence, most families in the US with high Lp(a) levels who are at risk of future atherosclerotic heart disease, stroke, or aortic stenosis are not recognized. Lp(a) measurement included as part of routine universal lipid screening in youth would identify those children at risk of ASCVD and enable family cascade screening with identification and early intervention for affected family members.

Recent Findings Lp(a) levels can be reliably measured in children as young as two years of age. Lp(a) levels are genetically determined. The Lp(a) gene is inherited in a co-dominant fashion. Serum Lp(a) attains adult levels by two years of age and is stable for the lifetime of the individual. Novel therapies that aim to specifically target Lp(a) are in the pipeline, including nucleic acid-based molecules such as antisense oligonucleotides and siRNAs.

Summary Inclusion of a single Lp(a) measurement performed as part of routine universal lipid screening in youth (ages 9–11; or at ages 17–21) is feasible and cost effective. Lp(a) screening would identify youth at-risk of ASCVD and enable family cascade screening with identification and early intervention for affected family members.

Keywords Lipoprotein(a) · Lp(a) · Hyperlipidemia · Youth · Lipid screening · Atherosclerosis · Cardiovascular disease

Introduction

High lipoprotein(a) (Lp(a)) has recently emerged in the literature as a strong genetic risk factor for atherosclerotic cardiovascular disease (ASCVD) including coronary artery disease, stroke, and aortic stenosis.

In this review, we will discuss the structure and function of Lp(a) and its genetic components and variability, modalities of measurement, and demonstrated association with cardiovascular disease. We will also review the current guidelines for universal lipid screening in children and provide an overview of past and current therapies targeting Lp(a).

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Structure and Function of Lipoprotein(a)

Human lipoprotein(a) (Lp(a)) is a complex lipoprotein composed of a low-density lipoprotein (LDL)-like particle containing a 1:1 molar ratio of apolipoprotein B-100 (apoB) and apo(a). Apo(a) is a polymorphic glycoprotein which characterizes Lp(a) [1–4]. Assembly of the Lp(a) molecule is theorized to happen in the liver at the hepatocyte cell membrane surface [1]. The two components of Lp(a), apoB-100 and apo(a), are linked by a disulfide bond between apoB-100 and one of the kringle domains in apo(a) [1].

Apo(a) is encoded by two alleles of the Lp(a) gene [1]. A unique feature of apo(a) is the presence of triple-loop structures called kringles [1]. Kringle domains are stabilized by three internal disulfide bonds and are present in other coagulation factors (plasminogen, prothrombin, urokinase, and tissue-type PLG activators) [1, 4, 5]. A significant discovery was that apo(a) is distinctly similar to plasminogen,

one of the fundamental proteins of the fibrinolytic cascade [1, 6]. The Lp(a) gene shares homology with PLG, the gene encoding plasminogen [1, 6]. Over the course of evolution, *PLG* kringle domains I, II, and III (KI, KII, KIII) were lost, while the KIV domain expanded and diverged to form 10 subtypes (KIV-1 to KIV-10) in apo(a) [1, 4, 6]. Apo(a) isoforms are traditionally designated by the total number of KIV domains [7]. The KIV-2 domain is encoded by a copy number variation that generates over 40 distinct isoforms of apo(a) [8]. KV and the serine-protease domain of PLG remained in apo(a) [1, 4–6]. Of note, however, the serine-protease domain in apo(a) shows replacement of the serine amino acid, preventing the conversion of Lp(a) into active protease by plasminogen activators and serine proteases [1, 4–6].

The physiological role of Lp(a) is not yet fully understood. Multiple functions of Lp(a) in humans have been proposed in the literature [9]. Historically, Lp(a) may have played a role in wound healing, facilitating wound healing and bleeding reduction through fibrinolysis inhibition [9, 10]. Lp(a) binds to fibrin via its kringle domains and may impede bleeding after being transported to sites of injury [10]. Lp(a) may also provide cholesterol for cell proliferation during tissue repair [10]. Furthermore, Lp(a) demonstrates a range of effects on vascular endothelial cells, smooth muscle cells, and monocytes and macrophages [9]. Previous studies show Lp(a)-mediated modification of vascular endothelial cells *in vitro* [11]. Apo(a) promotes proliferation and migration of endothelial cells and is involved in induction of endothelial contraction [12]. Lp(a) influences the function of smooth muscle cells. Studies using migration assays demonstrate a chemorepulsion by apo(a) of smooth muscle cells via Cd51/CD61 and RhoA/Rho-kinase [13]. Lp(a) also downregulates the activity of TGFB in smooth muscle cells [14]. Finally, Lp(a) promotes the differentiation of pro-inflammatory M1-type macrophages, implicating the lipoprotein in inflammation-association pathology [15].

Lp(a) has been thought to compete with plasminogen for binding to fibrin, thus impeding the physiologic activity of PLG in the fibrinolytic cascade and contributing to thrombosis and related Lp(a) pathology [4, 7].

Genetics and Variability

Although originally described as a dichotomous trait (Lp+/ Lp-), the literature soon moved toward a quantitative description of Lp(a) [16, 17]. Compared to other plasma lipoproteins, Lp(a) shows significant variation between individuals [18]. Substantial racial/ethnic differences exist in Lp(a) levels. For example, Black individuals exhibit a higher median plasma concentration of Lp(a) at every age than other racial groups [19, 20]. Well-designed prospective longitudinal data that is specific for each population is necessary to determine risk assessment. Lp(a) concentrations in humans range from <0.1 mg/dL to 200 mg/dL or higher, more than a three-fold magnitude of difference [18]. There is not yet a clear explanation why the Lp(a) gene exhibits such wide variation; however, some of the underlying genetic variation has been studied.

Measuring Lipoprotein(a)

Currently, lipoprotein(a) is reported either in mass units (mg/dL) or in molar units (nmol/L) depending on the assay used [21]. There have been several efforts to standardize Lp(a) measurement to reduce confusion in clinical practice [21, 22]. Lp(a) measurement has been described as potentially isoform-dependent, which creates issues relating to assays using mass measurement [21]. KIV-2 repeats generate the characteristic apo(a) polymorphism with a molecular weight ranging from 250 to 800 kDa [23]. Depending on the isoform, up to 70% of the apo(a) protein can consist of highly homologous KIV-2 repeats [21, 23]. This phenomenon creates issues related to antibodies and calibrators used in assays to quantify Lp(a) in individuals [21]. Antibodies against the repetitive KIV-2 repeat in apo(a) may underestimate the concentration of Lp(a) in individuals with small apo(a) isoforms and overestimate the concentration of Lp(a) in individuals with larger apo(a) isoforms [21]. In contrast, using an antibody against a unique kringle domain (i.e., KV) may allow measurement of Lp(a) in molar units, as each apo(a) molecule would only be recognized once [21]. However, there are still homologous repeats present in the KV domain, so this does not entirely solve the issue [21]. An alternative approach to measuring Lp(a) that avoids apo(a) sensitivity uses an antibody directed against the apoB component of Lp(a), since each Lp(a) molecule has only one apoB [21]. However, this approach is not used often, which may be due to neglect of "free" apo(a), or apo(a) unbound to LDL particles [21]. Some commercial assays reduce isoform-dependent bias by using a 5-point calibrator consisting of a range of Lp(a) isoforms [24].

It has been recommended that the use of mg/dL (mass) be discontinued in the reporting of Lp(a) [25] and that assays and references for Lp(a) be in nmol/L. Lp(a) isoforms create bias in mass-based measurements and complicate direct conversion between mg/dL and nmol/L units [25]. Standardized reporting of Lp(a) measurements in nmol/L would help synchronize Lp(a) assays, reduce confusion in clinical practice, aid comparative analyses in future clinical trials, and contribute to establishing evidence-based guidelines [25].

Lipoprotein(a) and Cardiovascular Disease

Lp(a) promotes inflammation and atherosclerosis by multiple mechanisms [26]. The Lp(a) molecule is susceptible to oxidative modifications, similar to other lipoproteins, and thereby leads to formation of proinflammatory and proatherogenic oxidized phospholipids, oxysterols, and oxidized lipid-protein adducts or "oxidation-specific epitopes" (OSEs), produced in response to reactive oxygen species (ROS) [26]. As previously mentioned, Lp(a) also promotes the differentiation of pro-inflammatory M1-type macrophages [26]. Other mechanisms by which Lp(a) promotes inflammation and atherosclerosis include the binding to and carrying of proinflammatory molecules such as the monocyte chemoattractant protein-1 (MCP-1/CCL2) [26].

High concentrations of Lp(a) have been considered to be a direct cause of cardiovascular disease [27–30]. Lp(a) has the ability to enter into and accumulate in the intima of arteries and aortic valve leaflets [10, 31]. Compared to LDL, in vivo kinetic studies show that Lp(a) in humans enters the intima at a similar rate [10]. However, Lp(a) is considered to be more atherogenic than LDL due to its greater capacity to bind to fibrin and glycosaminoglycans [10]. Lp(a) accumulation is a primary mechanism by which Lp(a) causes cardiovascular disease. Other mechanisms include the induction of Lp(a) by circulating macrophages to produce foam cells [32]. Lp(a) is also a known risk factor for aortic valve stenosis, and genetic variation in Lp(a) is associated with aortic valve calcification [10, 33]. In pediatric populations, the most extensive data comes from stroke studies, which demonstrate strong associations between Lp(a) and incidence of arterial ischemic stroke [34]. Findings from studies linking Lp(a) to cardiovascular disease in adults and children led the European Atherosclerosis Society (EAS) to publish a 2010 statement recommending screening for elevated Lp(a) in certain risk groups, including individuals at risk for cardiovascular disease [35].

Screening in Youth

Guidelines from the National Heart, Lung, and Blood Institute (NHLBI) and American Academy of Pediatrics (AAP) published in 2011 recommend universal cholesterol screening between the ages of 9 and 11 and, if normal, again between 17 and 21 years of age [36, 37]. Rationale for expanded screening was based on research showing early atherosclerosis in young patients with elevated cholesterol, efficacy of early treatment of cardiovascular risk factors in youth, concurrence of lipid disorders in children and childhood obesity, and the fact that approximately 30–60% of children with dyslipidemias are missed using traditional selective screening methods, due to underreported or unavailable family history of ASCVD [36, 37]. The expanded guidelines do not include Lp(a) in universal screening for youth.

Currently, the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) recommends measuring Lp(a) at least once in an individual's lifetime [38]. The National Lipid Association (NLA) recommends that an Lp(a) level be obtained for youth (<20 years) at high risk. This includes clinically suspected or genetically confirmed familial hypercholesterolemia (FH), presence of a first degree relative with premature ASCVD, unexplained ischemic stroke, or a parent or sibling with elevated Lp(a) [25, 39••, 40].

Justification to include Lp(a) in universal lipid screening guidelines for youth is currently being made in the literature. Lp(a) levels in youth are fully expressed by the first or second year of life and remain stable thereafter [41]. This is a unique feature of Lp(a), since other lipoproteins typically reach adult levels only after adolescence [41]. Furthermore, the 2011 NHLBI guidelines for universal lipid screening in youth were developed to detect youth and families with undisclosed FH and high LDL-C. It was recognized at that time that targeted screening alone based on family history of ASCVD would fail to identify families where the history is uncertain or not readily available. Unless measured, the burden of high Lp(a) levels would similarly remain unrecognized as a causative independent risk factor of ASCVD in families. Although high Lp(a) is present in as many as 30% of patents with FH, Lp(a) testing of youth with FH or family history of ASCVD alone would miss many families carrying high Lp(a) [42]. It is anticipated that including Lp(a) as part of universal cholesterol screening for youth will detect many families with a lifelong burden of unrecognized high Lp(a) and with appropriate medical intervention and help to reduce the risk of cardiovascular disease [43, 44].

Lipoprotein(a) in Clinical Trials

Over the past decade, Lp(a) has emerged as a topic of interest in clinical trials due to its association with cardiovascular disease [45]. To date, a variety of approaches have been investigated for their potential to lower Lp(a). Statins are widely used as lipid-lowering drugs to target LDL-C and prevent or delay ASCVD [45]. However, research has shown that statins do not have a similar effect on Lp(a) levels [45]. An analysis of six randomized controlled trials involving a total of 5256 patients showed that statins increased plasma Lp(a) levels from 11.6% to 24.2% compared to placebo [46]. Larger

meta-analyses showed no significant effects of statin therapies on Lp(a) plasma levels [47, 48]. Non-statin lipid-lowering medications such as ezetimibe have shown variable effects on Lp(a) in plasma; however, none significant enough to clinically impact ASCVD progression [49, 50]. Bempedoic acid is another recently approved lipid-lowering therapy that demonstrates variable to no effect on Lp(a) levels in plasma [51].

Other current therapeutic approaches to Lp(a) include PCSK9 inhibitors. PCSK9-inhibiting monoclonal antibodies alirocumab and evolocumab have undergone phase III clinical trials and have demonstrated significant reductions in Lp(a) plasma levels. Alirocumab treatment resulted in a median Lp(a) plasma reduction of 23% after 2.8 years of follow-up in 18,924 patients in the ODYSSEY (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab) clinical trial [52]. Alirocumab was shown to reduce MACE (major adverse cardiovascular events: coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or hospitalization for unstable angina) events with a hazard ratio (HR) of 0.85 [53]. Evolocumab was investigated in the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial comprising 27,564 patients [54]. A total of 25,096 patients demonstrated Lp(a) reduction of 27% after 2.2 years of median duration of follow-up [54]. The primary efficacy endpoint of the FOURIER trial was cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization [54]. The secondary efficacy endpoint was cardiovascular death, myocardial infarction, or stroke [54]. Evolocumab significantly reduced the risk of the primary efficacy endpoint with a HR of 0.85 as well as the secondary efficacy endpoint with a HR of 0.80 [54]. More recently, the small interfering RNA (siRNA) inclisiran has been shown to inhibit PCSK9 in adults with heterozygous FH and result in profound reductions in LDL cholesterol levels across multiple genotypes of FH [55]. Outcome data for Lp(a) is not available yet. The issue with therapies targeting PCSK9 is that they do not specifically target Lp(a), thereby making it difficult to ascribe reductions in MACE to Lp(a) reduction alone.

Lipoprotein apheresis is used in patients with homozygous FH to remove LDL and other apo B–containing lipoproteins [56]. Lp(a) is also an apoB lipoprotein, and studies showed that Lp(a) levels were significantly reduced following apheresis therapy [57]. A study of lipoprotein apheresis for Lp(a)-associated cardiovascular events in 170 patients with Lp(a)-hyperlipoproteinemia (HLP) concluded that Lp(a) lowering had a significant, long-term effect on prevention of cardiovascular events in patients with HLP-associated progressive cardiovascular disease [58]. However, lipoprotein apheresis carries a high per-session cost which, in combination with the frequency of guideline-recommended treatment, results in significant annual costs for patients and presents a barrier to optimal treatment of either FH or HLP [59].

Novel therapies that aim to specifically target Lp(a) include nucleic acid-based molecules such as antisense oligonucleotides and siRNAs [60]. Pelacarsen is an N-acetylgalactosamine conjugated antisense oligonucleotide targeting apo(a) mRNA [61, 62••, 63]. Pelacarsen has shown promising results in early-phase and phase I/II clinical trials [61, 62••, 63]. A randomized, double-blind, placebo-controlled trial showed safety and good tolerance of pelacarsen in 64 participants while reducing Lp(a) levels in plasma [62••]. A second randomized controlled trial showed a dose-dependent lowering of Lp(a) levels in plasma [63]. More than 90% of patients treated at higher levels of pelacarsen achieved Lp(a) concentrations below 50 mg/dL, the level above which is associated with increased risk of heart disease [63]. Currently, pelacarsen is being investigated for MACE reduction in the Lp(a) HORIZON (Assessing the Impact of Lipoprotein(a) Lowering with Pelacarsen on Major Cardiovascular Events in Patients With CVD) clinical trial with an anticipated completion date of 2025 (NCT04023552). Olpasiran, similar to inclisiran, targets PCSK9 and is an siRNA specifically targeting Lp(a) mRNA [64••]. Olpasiran significantly reduced Lp(a) up to 90% in a phase I trial in 65 adults [64••]. Olpasiran is currently undergoing a phase II trial in patients with ASCVD, anticipated to be completed in 2023 (NCT04270760). Another siRNA in early-phase clinical trials is SLN360, which showed a 98% reduction of Lp(a) in plasma in 32 participants [65]. SLN360 is undergoing further clinical trial testing to ascertain safety and efficacy (NCT04606602).

Conclusions Although targeted guidelines for Lp(a) screening have evolved over recent years for individuals at high-risk of premature cardiovascular disease, existing guidelines for universal lipid screening in youth do not include measurement of Lp(a). This omission creates the risk of failure to identify families and children with high Lp(a), which if left untreated, places the individuals at increased risk of premature ASCVD, stroke, and calcific aortic stenosis. Including Lp(a) in universal cholesterol screening for youth, and family cascade screening for high Lp(a) and other inherited lipid disorders, is anticipated to improve risk assessment and recommendations for intervention and positively impact clinical decision making.

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Declarations

Conflict of Interest The authors declare no competing interests.

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