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The impact of Race and Ethnicity on Lipoprotein (a) Levels and Cardiovascular Risk

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Abstract

Purpose of review: Lipoprotein(a) is a plasma circulating apoB100 (apoB) containing lipoprotein. It has a unique glycoprotein bound to the apoB100, apolipoprotein (a) [apo(a)]. The majority of the population expresses two apo(a) isoforms, when bound to apoB100 they create two circulating Lp(a) particles. Lp(a) levels are genetically determined and epidemiological studies have established elevated levels of Lp(a) to be a causal risk factor of Cardiovascular Disease. Lp(a) levels differ across racial groups and Blacks of sub-Saharan decent have higher levels when compared to white. In comparison to white populations, studies in minorities are less represented in the published literature. Additionally, there is lack of standardization in the commercial assays used to measured Lp(a) levels, and hence it is difficult to assess risk based on individual Lp(a) levels, but risk seem to occur in the upper percentiles of the population.

Recent findings: A recent study using data form the UK biobank highlights the racial differences in Lp(a) levels and the increase risk in cardiovascular disease amongst all races.

Summary: This review will highlight Lp(a) biology and physiology with a focus on available data from racially diverse cohorts. There is a need to perform studies in diverse populations to understand if they are at higher risk than whites are.

Keywords

Lipoprotein (a); Cardiovascular Disease; Race; Ethnicity

Introduction to Lipoprotein(a) and Cardiovascular Risk

Lipoprotein(a) [Lp(a)]was discovered by Kare Berg in 1963[1]. Lp(a) is an apoB100 containing protein made unique by its linkage with glycoprotein apolipoprotein(a) [apo(a)] [2]. Lp(a) concentrations are determined by the *LPA* gene [3]. Racial differences affect the heritability of apo(a), with African-Americans having a lower heritability when compared to Caucasian populations [4]. Despite lower heritability, absolute Lp(a) levels are highest in people of African ancestry[4]. In multi-ethic studies, Lp(a) has been found to be higher in Blacks Americans of African descent when compared to Hispanics, Chinese Americans, or Whites[5, 6]. In the MESA study associations of Lp(a) with calcific aortic[7] disease, and heart failure[8] were found but these were not limited to Blacks. Circulating Lp(a) particles can

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have a single isoform of apo(a) or most commonly individuals can express two distinct apo(a) isoforms[9]. Apo(a) isoforms differed in size and this is regulated by the kringle -IV type 2 (KIV-2) domain within the particle [10, 11]. This KIV-2 is well studied for genetic variations in the *LPA* gene regulates apo(a) size in both Whites and Blacks[10–12].

Genome Wide association studies (GWAS) and Mendelian Randomization studies have highlighted the associations of elevated Lp(a) levels with coronary and atherogenic vascular disease [13–15]. In addition, Genetic studies have provided convincing evidence that *LPA* is associated causally with coronary heart disease (CHD) and the development of aortic stenosis[14, 16–19]. Large studies, in mostly Europeans, show that approximately one in five individuals has Lp(a) plasma concentrations greater than 50mg/dl (120nmol/L) and is at increased risk for development of cardiovascular disease (CVD) and aortic stenosis [13, 20]. Apo(a) particles have been identified in human atheroma dissections[21, 22] indicating that the molecule is involved in atherogenic mechanisms. Over the last 40 years our knowledge on Lp(a) has advanced significantly [23]. Recent enthusiasm for the development of targeted therapies towards the apo(a) moiety of Lp(a) [24] has provided hope for the population at risk and highlighted the need for additional understanding of how lowering the apo(a) component of Lp(a) will decrease cardiovascular risk and in which at risk population. Lp(a) levels are highest in people of African ancestry. However, ongoing studies fall short of addressing the need to examine if these high levels place individuals at higher risk and phase 2 studies of novel treatments have low enrollments of underrepresented populations.

Lipoprotein(a) measurements and Risk Assessment

Current ongoing efforts are underway to standardize Lp(a) measurements via validated assays[25–27]. There are various ways to measure Lp(a) and it is important to note that the available assays are based on measurement of the apo(a) component of Lp(a)[28]. The commercially available methodologies used are enzyme-linked immunosorbent assay (ELISA), immunonephelometric and, immunoturbidimetric assay. The current use of conversion factors from mg/dl to nmol/dl do not provide exact levels due to the variability in apo(a) sizes that exist in various study populations [28]. Experts recommend that Lp(a) levels be reported in nmol/l [29]. Various recent publications have focused on new assay developments, one using an ELISA assay [30] and the other mass spectrometry, both improve the challenges observed when using non-reference material and apo(a) isoform size [31]. It is important to note, that assay comparison studies have provided conclusive evidence that high levels of Lp(a) are detected by various assays using multiple apo(a) size standards and that despite the limitations, when Lp(a) levels are high, this is the same across assays[25, 30, 32]. A recent manuscript describes the large variation in the Lp(a) particles cholesterol content (approximately 5-58%) [33] which may lead to additional considerations in accessing risk. . The need for standardization, stems for the fields need to access cardiovascular risk and the latter must be done across racially diverse populations. Once the risk is access, target therapies may be able to help with risk improvements.

The COVID-19 world pandemic has highlighted the effects of cardiovascular disease on disease outcomes. The outcomes were worst in those with cardiovascular disease and also from underrepresented populations. Recent studies highlight the role of Lp(a) in regulating

inflammation through its oxidized phospholipid content [34]. In addition, a recent review suggest IL-6 pathways[35]. This area of research may be relevant as we study the role of Lp(a) in populations of different races.

Over the last decade, only a minor proportion of the Lp(a) literature has focused on diverse populations. Additionally, the available data is hard to compare due to the inability to compare levels across different assays or studies not reporting assays used. Lp(a) concentrations are elevated in Blacks compared to their White and East Asian counterparts; however, there exists considerable variation in these data, with mean concentrations ranging between 43 mg/dL and 99 mg/dL (71-132 nmol/L), and median concentrations ranging between 27.11 mg/dL and 46 mg/dL (60-79 nmol/L), with wide IQRs. Hispanic participants tend to have relatively low mean (14.9 mg/dL; n = 2073) and median serum Lp(a) levels (14.7-24 nmol/L); it is necessary to acknowledge that data on this group are limited, and few studies [36–40]examining serum Lp(a) in Hispanics are published. Published literature suggests that East Asian populations tend to have lower mean and median serum Lp(a) concentrations compared to Whites, and especially Black and South Asian counterparts. East Asian median Lp(a) concentrations range between 1.11 mg/dL and 12.9 mg/dL (22-38 nmol/L).

A recent study using samples from the UK Biobank and validated in various cohorts showed that Lp(a) risk may be similar despite varying racial distributions of Lp(a) levels [41]. Additionally, it found a linear risk gradient across Lp(a) levels distribution. In a smaller study, the relationship of *LPA* single nucleotide polymorphisms were examined in the Dallas Heart Study. In this study, the relationship to major cardiovascular events (MACE) was best explained by the elevated plasma Lp(a) levels, even accounting for racial differences in the cohort[42].

Current Lipoprotein (a) Guidelines and Future Directions

In the United States, there are no current guidelines for the screening or risk assessment of elevated Lp(a) levels. The National Lipid Association scientific statement reviewed evidence for testing Lp(a) in clinical practice and the utilization of Lp(a) levels to inform primary and secondary prevention strategies. The group provided recommendations to use Lp(a) levels for reclassification of patients at risk for ASCVD and VAS[43]. The consensus statement from the American association of clinical endocrinologist and American college of endocrinology on the management of dyslipidemia and prevention of cardiovascular disease recommends that individuals of south Asians and African ancestry, especially with a family history of ASCVD or increase Lp(a) measure Lp(a). The 2019 European lipid management guidelines did include measurement of Lp(a) levels once in an adult life and provided suggested cut offs for Lp(a), the latter not taking into account racial distributions of the population studied[44].

Studies that have examined Lp(a) concentrations in underrepresented groups with minority population sample sizes greater than 500 is severely limited compared to available sample sizes for Whites. The inclusion of larger sample sizes will not eliminate disparity; however, it will provide greater precision for understanding the race contribution.

Currently, there are no specific guidelines to lower Lp(a) levels. Lipoprotein apheresis is approved by the FDA, but it is not an Lp(a) specific lowering treatment [45] and there are many limitations to this modality to use as standard of care. The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have shown promise in decreasing Lp(a) and therefore the incidence of CV mortality in clinical trials[28]. As PSCK9 inhibitors also decrease LDL cholesterol, the mortality benefit associated with this intervention is not exclusively linked to its effect on Lp(a). Additional studies have demonstrated a favorable relationship between niacin (nicotinic acid) therapy and cardiovascular risk reduction[46], however high doses of the drug are required before any significant changes in serum Lp(a) levels are observed[39].

There are multiple programs developing treatments targeting the apo(a) component of Lp(a) to lower its plasma concentrations (NCT04606602 and NCT0423552) [47]. These therapies include anti-sense mRNA silencing via oligonucleotides (ASO)[48] and siRNAs[49]. An ASO is a single strand of deoxynucleotides that bind to a complimentary mRNA target, shutting off its translation; in siRNA-mediated gene silencing, multi protein RNA-induced silencing complexes (RISC) are recruited that complementarily bind to and cleave target mRNA. The targets of ASOs are the primary mRNA transcripts of apo(a). Complexing of ASO and apo(a) mRNA blocks translation of the nascent proteins, resulting in decreased serum Lp(a).

Conclusion:

Significant evidence points to lipoprotein (a) levels as highly useful markers of CVD and CHD risk; however, much work still remains in terms of investigating differences in Lp(a) levels stratified by race. Though existing studies primarily identify Black and South Asian patients as populations with elevated Lp(a) (despite lower heritability), available sample sizes and assay variability certainly pose limitations on the generalizability of these findings.

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Article Summary:

- High Lp(a) levels are causal of Atherosclerotic Cardiovascular Disease.
- There is a need to standardize commercial assays so that disease risk can be access.
- There is a need for research studies in diverse racial and ethnic cohorts that can help understand the higher Lp(a) levels expressed in Blacks and Hispanics and access if these high levels are linked to increase in disease risk.