

EDITORIAL

Lipoprotein (a): Is its systematic determination indicated?



Lipoproteína (a): ¿está indicada su determinación sistemática?

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The addition of highly potent hypolipidemic tools has allowed for significant reductions in cardiovascular risk (CVR). While apolipoprotein B (ApoB)-bearing proteins are primarily responsible for arteriosclerotic lesions, we can find residual CVR involving other contributing factors. Among these factors is lipoprotein (a) [Lp(a)]. Initial epidemiological studies, genome-wide association studies, and data from Mendelian randomization demonstrate a causal relationship between Lp(a) and ischemic heart disease,¹ ischemic cerebrovascular disease, and aortic valve stenosis.^{2–4} Doubling the level of Lp(a) is associated with a nearly 20% increase in the risk of myocardial infarction, and elevated levels of Lp(a) are also associated with an accelerated progression of aortic stenosis.⁴ Once a relationship was postulated between elevated levels of Lp(a) and an increased risk of venous thrombosis, which has not yet been confirmed.⁵ However, an inverse relationship between the prevalence of lipoprotein(a) hyperlipoproteinemia and the incidence of type 2 diabetes does seem to be the case.⁵

The Lp(a) molecule results from the fusion, through covalent bonds, of an ApoB particle with another apolipoprotein called apolipoprotein(a) [Apo(a)]. Both are synthesized in the liver, but it is yet to be elucidated whether their assembly occurs inside the hepatocyte or on its surface.⁵ By the structure of its gene (LPA), it is known that this is the result of the ancestral splitting of the plasminogen gene (PLG),

with which it shares significant homology, which could help explain some of the pathophysiological characteristics of Lp(a).⁴

The PLG encodes 5 kringle (triple loop protein structures, 80–90 amino acids long, resembling the shape of a Scandinavian pastry and numbered from I to V), and a fibrinolytic protease region. LPA lacks kringle I to III, specific to PLG, but encodes 10 subtypes of kringle IV (KIV-1 to KIV-10) and a kringle V-like domain, as well as an inactive protease activity region. Apo(a) molecules and, consequently, Lp(a) molecules, exhibit considerable interindividual variability in their size and density, because the gene may have a highly variable number of copies of the kringle IV-2 subtype. Heterogeneity is also increased due to variable degrees of interindividual glycosylation.^{2–4}

The larger the Apo(a) molecule, due to a greater number of kringle IV-2 copies, the lower its plasma levels. This heterogeneity explains between 20% and 70% of the variability in Lp(a) concentrations.⁴ Additionally, single nucleotide polymorphisms also frequently influence concentration, unrelated to molecular size (more than 500 of these genetic variants of Lp(a) have been identified, some of which have significant effects on its concentration).^{4,5}

Plasma levels of Lp(a) arise from the co-dominant expression of 2 LPA alleles, resulting in 2 detectable circulating Lp(a) isoforms of potentially different sizes, and the levels we measure correspond to the sum contributed by each allele.⁴ The smallest isoform tends to be present at higher levels. A threshold value of 50 mg/dL or 105 nmol/L (>80th

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percentile) has been established as clinically relevant, but even levels > 30 mg/dL can increase CVR.^{2,6} The relationship between Lp(a) concentration and CVR is continuous, without a threshold: higher concentrations imply greater risk. Compared to individuals with mean Lp(a) concentrations of 16 nM, individuals with levels of 70, 115, 175, 230, and 350 nmol/L have 1.22, 1.40, 1.65, 1.95, and 2.72 times higher risk of developing arteriosclerotic vascular disease (ASVD), respectively.⁵ With Lp(a) concentrations >180 mg/dL (430 nmol/L), the CVR is that of familial hypercholesterolemia (FH).⁷

The population distribution of Lp(a) is not normal, so the value ranges discussed are always in terms of median and not arithmetic mean. Elevated concentrations are the most common form of hyperlipidemia. It is estimated that high Lp(a) affects between 10% and 30% of the world's population (approximately 1.42×10^9 people worldwide) and 20% of Europeans,^{2,6} and having Lp(a) levels >100 nmol/L (48 mg/dL) accounts for 5.7% of all cardiovascular events reported.⁶

Since more than 90% of Lp(a) concentration is conditioned by the LPA gene,^{5,8} its values are reasonably constant throughout life, and therefore, a single determination might be enough. However, there is an individual variability of up to 20%,⁴ and there are also non-genetic factors that can modify the concentration (inflammatory processes, chronic kidney disease, especially nephrotic syndrome, liver diseases, among others).^{4,6,9} Therefore, sometimes it is recommended to obtain a mean of 2 Lp(a) determinations at different times, in stable phases of the patient's life, to refine CVR stratification.^{4,6} In any case, Lp(a) should be measured while the patient remains in a stable vital phase and without intercurrent illness.

Determining Lp(a) levels is achieved through immunoassays that use specific antibodies for Apo(a). However, there are 2 problems affecting the accuracy of the results and their clinical interpretation. The first one has to do with Apo(a) size variability.⁴ Due to an inverse association between the number of kringle IV-2 repeats and Lp(a) particle concentrations, polyclonal immunoassays that recognize epitopes in Apo(a) may tend to underestimate high Lp(a) concentrations and overestimate low concentrations depending on whether the isoforms are small or large, respectively.³ More recent methods commercially available reduce this error factor if the assay calibrators are well validated.⁴

The second problem is that there are 2 different approaches to immunoassay calibration, resulting in 2 different units for reporting Lp(a) results. The first highly sensitive analysis for measuring Lp(a) established results in mg/dL, while the current standard is calibrated in nmol/L.⁴ Given the heterogeneity among the molecular sizes of different Lp(a) isoforms, determining their plasma levels expressed in mass units (mg/dL) may not be accurately representative of the number of particles we are actually measuring. This may be especially important when considering that each Lp(a) particle is 6 times more atherogenic than each ApoB.¹⁰ Hence, recommendations for Lp(a) measurement indicate expressing its concentration in terms of molarity.¹¹ The existence of two different units to express Lp(a) levels is confusing for physicians and patients alike, and there is no good conversion factor from mg/dL to nmol/L, or vice versa.⁴ In any case, whatever determination method is used,

if properly calibrated, it allows us to identify patients with higher CVR due to elevated Lp(a) levels.³

Measuring Lp(a) allows us to identify individuals with very high inherited plasma levels. It also enables better stratification of patients' CVR and improved management of cardiovascular disease by helping optimize the medical treatment of other CVR factors.⁶ In certain situations where Lp(a) is elevated, the LDL value should be corrected using the formula:

$$\begin{aligned} &\text{Lp(a)corrected by LDL cholesterol (LDL-C) (mg/dL)} \\ &= \text{LDL-C (mg/dL)} - [\text{Lp(a) (mg/dL)} \times 0.30] \end{aligned}$$

$$\begin{aligned} &\text{Lp(a)corrected by LDL cholesterol (LDL-C) (mmol/L)} \\ &= \text{LDL-C (mg/dL)} - [\text{Lp(a) (mg/dL)} \times 0.0078] \end{aligned}$$

This Lp(a) correction of the LDL value is not routinely recommended except for some situations: patients of sub-Saharan origin, patients with nephrotic syndrome or on peritoneal dialysis, or when the drop in LDL-C is insufficient after receiving lipid-lowering treatment.¹² Also, when FH is suspected, if correcting the LDL value can avoid the need for genetic diagnostic testing.¹³

Since inheritance is autosomal, dependent on a single gene, detecting a case of hyperlipoproteinemia(a) allows us to cascade screening and initiate treatments at earlier ages if necessary.¹⁴ Regarding the spending associated with measuring Lp(a), considering that it would only need to be measured once in a lifetime, and the improvement it would represent in adjusting the treatment of CVR factors in people with elevated levels, it is expected to be efficient.¹⁴

The European Atherosclerosis Society (EAS) and individual cardiology societies from other countries (e.g., France, Germany, UK, Canada, Australia) have developed clinical practice guidelines that include recommendations for the population in which Lp(a) should be determined.^{5,6,15-18} Although all recommend the routine measurement of Lp(a) in individuals with certain characteristics (elevated CVR, FH, first-degree relatives of individuals with very high Lp(a), family history of premature cardiovascular disease, calcified aortic stenosis, or when the LDL drop is not as expected after the established treatment), not all recommend measuring Lp(a) universally. This universal determination only appears in the guidelines of the EAS, the Spanish Society of Atherosclerosis, the German guidelines (which replicate those of the EAS), and the Canadian ones.^{5,6,15,17}

Since CVR is associated with elevated Lp(a), the efficiency of measuring it, and the currently available methodologies, the recommendations from the EAS are perfectly assumable and acceptable for our setting, and we would summarize them as follows⁵:

- Lp(a) should be measured, at least, once in adults to identify those with high CVR.
- Detection is also recommended in young people with a history of ischemic stroke or premature ASVD, or high Lp(a) and without other identifiable risk factors.

• Cascade testing is recommended to detect high Lp(a) in FH environments, family history of high Lp(a), and personal or family history of ASVD.

Conflicts of interest

None declared.

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