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Lipoprotein (a): A Novel Cardiovascular Risk Factor

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Lipoprotein (a) (Lp[a]) was first described by Professor Berg 60 years ago,[1] however, the biological function of Lp(a) in humans is still not precisely elucidated. Lp(a) is a low-density lipoprotein (LDL-C)-like particle (Figure 1) produced by the liver in which a single apolipoprotein B100 is covalently linked to a single apolipoprotein (a) in a 1:1 ratio.[2,3]

Plasma levels of Lp(a) depend on the number of identical Kringle IV (KIV) type 2 repeats, which directly influence the apo(a) isoform size and inversely affect the plasma levels of circulating Lp(a).[4] Lp(a) levels are independent of LDL-C levels. Lp(a) catabolism is not well described. Despite similarities between LDL-C and Lp(a), the role of the LDL receptor in the catabolism of Lp(a) remains elusive.[4] Lp(a) is the lipoprotein with the strongest genetic control (> 90%) determined by genetic variability in the lipoprotein (a) gene Lp(a).[4] Adult Lp(a) levels are usually achieved by the age of 5 years in humans.[5] Lp(a) levels range from < 0.1 to > 300 mg/dl (< 0.2-750 nmol/l).[6] The measurement of Lp(a) in molar units is preferred, and converting measurements between the units are inaccurate.[4] Clinical guidelines advocate the use of risk thresholds with "gray" zones (e.g., 30-50 mg/dl or 75-125 nmol/l) to either rule in (≥ 50 mg/dl; 125 nmol/l) or rule out (< 30 mg/dl; 75 nmol/l) cardiovascular (CV) risk.[4] Observational, genetic, and Mendelian randomization studies have shown that a high Lp(a) level has causal association with CV diseases, aortic valve stenosis, and CV-related and all-cause mortality in men and women across all ethnic groups (Chinese, White, South Asian, and Black people).[4] A high Lp(a) level is an independent risk factor even at very low LDL-C levels. In children and young adults, an Lp(a) level of > 30 mg/dl (> 75 nmol/l) is associated with an increased risk of cryptogenic ischemic stroke.[4,7] The causality between Lp(a) and venous thromboembolism risk is not supported by Mendelian randomization studies despite homology with plasminogen.[4] Lp(a) levels remain stable throughout life, notably unaffected by diet, physical activity, or medication. Guidelines recommend measuring Lp(a) levels at least once in a lifetime.[4,8,9] The measurement of Lp(a) should be routinely included as part of an initial lipid profile. Close relatives of the index case should undergo cascade testing for Lp(a). Individuals with very high Lp(a) levels (> 180 mg/dl or > 430 nmol/l) have lifetime CV risk equivalent to untreated heterozygous familial hypercholesterolemia.[8] Despite the overall estimation that > 20% of the patients have Lp(a) levels of ≥ 125 nmol/l (i.e., ~1.4 billion people worldwide),[9] the contribution of high Lp(a) levels to CV risk remains underestimated. Thus, the inclusion of Lp(a) in CV risk-stratification strategies is encouraged.[4,9] Early management of traditional risk factors is recommended for individuals with high Lp(a) levels. Lp(a) apheresis is an effective treatment option for patients with very high CV risk, and PCSK9 inhibitors decrease Lp(a) levels by 25-30%. Emerging therapies that specifically lower Lp(a) levels (pelacarsen and olpasiran) are in phases II/III of clinical testing.

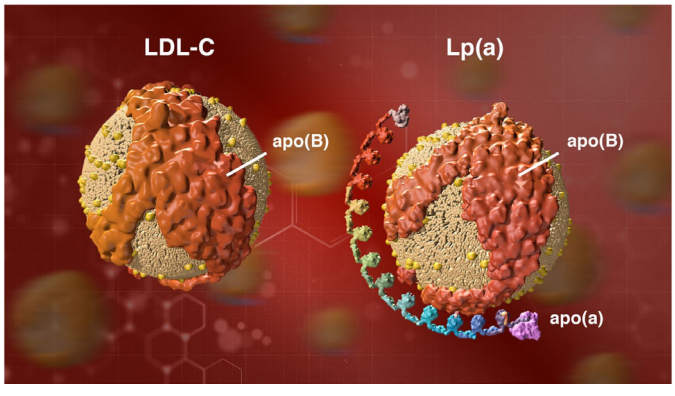

FIG. 1. Lipoprotein(a) - a modified LDL-C particle.
LDL-C, low density lipoprotein cholesterol.

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