Lipoprotein(a): An Emerging Cardiovascular Risk Factor

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein whose levels are genetically determined, with few variations in levels occurring after the age of 5 years. (Alebna P.L., et al. 2023) Lp(a) is primarily produced in the liver and is composed of apolipoprotein(a), which is bound to apolipoprotein B100 via one disulfide bridge. (Farzam K, et al. 2022).

Lp(a) is a risk factor for atherosclerosis, coronary artery disease, stroke, thrombosis, and aortic stenosis, specifically calcific valvular aortic stenosis. (Alebna P.L., et al. 2023) In fact, certain portions of the molecule confer pro-inflammatory, prothrombotic, and proatherogenic properties. Furthermore, Lp(a) can be a risk factor for cardiovascular disease (CVD), even when a patient's LDL-C levels are within guideline limits. (Kronenberg F, et al. 2022) There is also an existing inverse relationship between plasma concentrations of Lp(a) and the apolipoprotein(a) isoform. Isoform variation is dependent on the number of different kringle IV repeats in the LPA gene. In general, individuals with fewer kringle repeats will have smaller Lp(a) particles but higher serum levels. (Farzam K, et al. 2022) The size heterogeneity of apolipoprotein(a), each allele inherited from each parent, reduces the accuracy of antibody-mediated immunoassays to measure true Lp(a) burden in patients. (Heydari M, et al. 2023) Persons of African heritage tend to have higher levels than Caucasians or Asians, with individuals of Hispanic heritage having levels similar to those found in Caucasians. (Alebna P.L., et al. 2023) Interestingly, Lp(a) levels tend to increase in women after menopause, with women generally having higher levels by 5%-10% as compared with men. (Heydari M, et al. 2023).

Certain conditions or diseases can also cause increases or decreases in this lipoprotein as well; conditions such as inflammatory conditions, pregnancy, hypothyroidism, growth hormone therapy, and kidney disease can increase Lp(a) levels while the acute phases of postmenopausal hormone replacement, hyperthyroidism, and liver disease can cause decreases in levels. Thus, screening for other diseases in patients is important when assessing Lp(a) levels. (Alebna P.L., et al. 2023)

Levels of Lp(a) levels above 50 mg/dl (125 nmol/L) are correlated with an increased risk of CVD. It is thought that elevated Lp(a) levels may be correlated with CVD in younger patients with or without additional risk factors. (Farzam K, et al. 2022) Furthermore, Lp(a) levels have been shown to correlate with levels of C-reactive protein, and these two markers are considered joint predictors of major adverse cardiovascular events (MACE). (Alebna P.L., et al. 2023) Mehta et al. (2022) found that elevated Lp(a) levels and CAC scores (≥100) conferred the highest risk of atherosclerotic cardiovascular disease (ASCVD) and suggested using Lp(a) levels in conjunction with CAC scores to provide clinicians with an additional assessment of CVD risk. The American College of Cardiology (ACC), Canadian Cardiovascular Society, and the National Lipid Association determine that a cut-off of 50 mg/dL is acceptable and that levels higher than this impart a greater CVD risk. The European Atherosclerosis Society considers Lp(a) levels <30 mg/dL (or <75 nmol/L) normal, measurements of 30-50 mg/dL (or 50-125 nmol/L) to be intermediate, and levels >50 mg/dL (or >125 nmol/L) abnormal. Thus, there is a lack of international consensus on the level of Lp(a), which may lead to concern among clinicians and an elevated CVD risk in patients.

Screening patients for elevated Lp(a) could help identify those who require more aggressive lipid management therapy and CVD risk management. Most generalized screening aims to identify Lp(a) as an existing risk factor and subsequently seeks to optimize overall cardiac health as the primary treatment. The National Lipid Association recommends testing Lp(a) levels in persons with a significant family history of premature ASCVD among first-degree relatives or if they have a personal history of premature ASCVD and in persons with severe primary hyperlipidemia. If an individual is considered borderline for beginning statin therapy, testing Lp(a) levels may help to determine statin initiation. Interestingly, statins have been shown to increase Lp(a) levels by 10%-20%. At this time, it is unknown if this increase in Lp(a) levels impacts CAD risk, as explicit studies examining this outcome have not been conducted. (Zhu L, et al. 2022) Current ACC guidelines support measuring Lp(a) levels once in an individual's lifetime, even if they are at an increased risk for ASCVD. (Alebna P.L., et al. 2023) The ACC, in partnership with the American Heart Association (AHA), further recommends screening adults for Lp(a) levels who have either a family or a personal history of ASCVD. The European Atherosclerosis Society also has guidelines for Lp(a) screening. The Society recommends screening in patients with a personal history of premature cardiovascular disease, patients who experience recurrent cardiovascular disease events while on statin therapy, and individuals who have ≥ 10%, 10-year risk of CVD. Canadian guidelines (2021) state that Lp(a) levels should be assessed once in a person's lifetime, and a convenient time for this is when the initial lipid screen is being conducted. (Pearson G, et al. 2021)

Despite the lack of international consensus on levels that confer risk and the screening for Lp(a) levels in patients with or without CVD risk, it is clear that this molecule is a risk factor for ASCVD. Testing may be warranted in situations where patients experience early onset MACE, in patients who either themselves or their family members have early, aggressive disease, or when a clinician is unsure of whether statin therapy should be initiated as levels may help guide medication decisions. While no specific medication is indicated for the management of Lp(a) levels, many molecules are being explored for this express purpose. The next news digest in this series will examine potential treatments and their safety profiles, as well as existing procedures that may be used to help lower levels of Lp(a).

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