2023-A Accuracy-Based Lipids (ABL)

Educational Discussion - - Lipoprotein (a) Testing

Lipoprotein (a), or Lp(a), is a low-density lipoprotein particle that promotes plaque formation, clotting, and inflammation. Lp(a) contains apolipoprotein (a) (apo(a)), apoB, carbohydrates, and a lipid core consisting of cholesterol, cholesterol esters, triglycerides, and phospholipids. Patients with a high molar concentration of Lp(a) particles, rather than large Lp(a) particle size, have an increased risk of atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis (1). Lp(a) has emerged as a leading biomarker for ASCVD risk and is becoming increasingly important as new therapies targeting Lp(a) progress through clinical trials (2). Therefore, it is critical that laboratories consider how to increase availability of Lp(a) testing.

The molecular complexity and heterogeneity of Lp(a) particles have encumbered the development of meaningful Lp(a) assays. Differences in the protein and lipid compartments of Lp(a) cause significant variation in particle mass and size within and between individuals. The *LPA* gene encoding apo(a) is a major contributor to heterogeneity due to a variable number of kringle IV type 2 (KIV-2) domains among different alleles, thereby encoding apo(a) isoforms with a broad mass range (3). Different *LPA* allele combinations further lead to heterogeneity in apo(a) mass within an individual. Assays that use antibodies against the KIV-2 domain overestimate or underestimate the amount of Lp(a) present if the apo(a) isoform contains a high or low number of KIV-2 repeats, respectively (4). Lipid cargo is another source of variability in Lp(a) mass. In addition, the term *Lp(a) mass* has been used ambiguously to refer to different combinations of Lp(a) components (3). Therefore, apo(a) isoforms and Lp(a) heterogeneity continue to be major challenges.

There are several important steps toward standardization of Lp(a) testing. First, Lp(a) values should be assigned by a method validated to be independent of apo(a) isoforms and calibrated in a manner traceable to reference material. The World Health Organization and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) developed a reference material (SRM-2B), which was previously value assigned through an ELISA-based KIV2-independent method (5). However, these materials are no longer available. The IFCC Working Group for Apolipoproteins by Mass Spectrometry is actively addressing this issue (6). Second, results should be reported in nmol/L. However, if Lp(a) is measured in mg/dL, the result should not be converted to nmol/L. Due particle mass variability, there is no reliable conversion factor (3). Finally, survey samples should cover a clinically meaningful range of 90-200 nmol/L, which is associated with intermediate ASCVD risk and clinical decision limits (7).

In this Survey, Lp(a) results were compared to the all-method peer group mean with an evaluation criterion of ± 3 standard deviation (SD). All laboratories participating in this Survey employed turbidimetric and nephelometric methods, which is notable since Lp(a) particle size can impact light scattering. Results were reported in either in mg/dL (n=25) or nmol/L (n=16). Although the all-method SD was between 2 and 3 for most samples, the coefficient of variation of results spanned 25-31% for mg/dL and 6-14% for nmol/L. The Lp(a) concentration in the three samples tested in this

Survey spanned 8-22 mg/dL and 14-47 nmol/L. These samples are from individuals with lower ASCVD risk and represent a limitation of the Survey.

The Survey's data and increasing clinical utility of Lp(a) testing indicates an urgent need to move to accuracy-based proficiency testing programs and to standardize Lp(a) assays.

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