Factors Affecting the Lipoprotein(a) Levels

Subjects: Cardiac & Cardiovascular Systems

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Lipoprotein(a) is a variant of LDL-C, distinguished by the covalent binding of ApoB100 to a unique glycoprotein called apolipoprotein(a) via a disulfide thioester bond.

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1. Lipoprotein(a): Structure, Synthesis, and Metabolism

Lipoprotein(a) is a variant of LDL-C, distinguished by the covalent binding of ApoB100 to a unique glycoprotein called apolipoprotein(a) via a disulfide thioester bond. This structural difference results in variations in molecular weight, density, and electrophoretic mobility compared to LDL-C due to the presence of apo(a) [1]. Apo(a) is highly polymorphic and comprises variable numbers of cysteine-rich domains known as kringles. Kringles are triple-loop structures stabilized by internal disulfide bonds and are also found in coagulation factors such as plasminogen, prothrombin, urokinase, and tissue-type plasminogen activators [2]. While plasminogen contains five kringle domains (KI, KII, KIII, KIV, and KV) and one protease domain, apo(a) consists of a single kringle V domain (KV), ten different types of kringle IV domains (KIV1 to KIV10), and a catalytically inactive protease domain at the carboxyl terminus [3]. The size heterogeneity of apo(a) is determined by the variable number of KIV2 domain copies, which can range from 1 to over 40, while the remaining KIV domains are typically present as single copies [4][5].

Lp(a) synthesis primarily occurs in the liver, although small amounts of apo(a)-mRNA have been detected in various tissues including the brain, lungs, testes, pituitary, and adrenal glands [6]. The assembly of Lp(a) involves two consecutive steps [7]. In the first step, lysine residues at the N-terminus of ApoB100 are noncovalently bound to lysine-binding sites located at the KIV7 and KIV8 domains of apo(a). Subsequently, in the second step, a covalent disulfide bridge is established between cysteine residues in the KIV9 of apo(a) and ApoB100 [8]. The exact location of this assembly process remains uncertain. Recent evidence suggests that the first step occurs intracellularly, while the second step takes place extracellularly [9][10].

The clearance of Lp(a) molecules primarily occurs in the liver, with a small fraction also removed by the kidneys [11]. Additionally, the spleen and muscles may play a minor role in this process [12]. Lp(a) clearance involves various cell surface receptors, including the LDL receptor (LDL-R), scavenger receptors, various plasminogen receptors, Toll-like receptors (TLRs), and carbohydrate receptors or lectins. However, the exact role and degree of involvement of each receptor remain uncertain [8][13]. ApoB100, apo(a), and oxidized phospholipids (OxPLs) on the surface of Lp(a) act as ligands for these receptors [14]. Intracellularly, LDL and apo(a) particles undergo lysosomal degradation, while approximately 30% of apo(a) molecules are recycled to contribute to the formation of new Lp(a) molecules [15]. The relatively similar rate of fractional catabolism among different sizes of apo(a) isoforms ensures that the catabolism rate of Lp(a) remains relatively constant, thus not significantly affecting its plasma concentration [16].

2. Factors Affecting the Lp(a) Levels: Genetics and beyond

2.1. Genetics

Serum Lp(a) concentration displays wide variation among individuals, with up to 90% of Lp(a) levels being inherited and genetically determined by the *LPA* gene [6]. This gene, structurally homologous to plasminogen (PLG), encodes the apo(a) component of Lp(a) [2]. The genetically predetermined number of KIV2 copies on the *LPA* locus, which determines the size of different apo(a) isoforms, explains approximately 30 to 70% of the variability in the Lp(a) concentration [17]. There exists an inverse relationship between the number of KIV2 copies and plasma Lp(a) levels, where fewer KIV2 copies result in smaller apo(a) isoforms and higher rates of Lp(a) secretion. On the contrary, a higher number of KIV2 copies accounts for

larger apo(a) isoforms and lower Lp(a) levels [5][18][19]. This phenomenon is attributed to the susceptibility of larger apo(a) molecules to proteasomal degradation within hepatocytes [20]. Every individual carries two copies of the *LPA* gene located on chromosome 6, with one copy on each allele. Serum Lp(a) levels reflect the combined effects of apo(a) isoforms produced by each allele [21]. Consequently, the allele encoding the smaller apo(a) isoform predominantly determines the main isoform in an individual [22].

In addition to the variability in apo(a) isoform size, genetic variants play a crucial role in determining Lp(a) concentration [23]. Several independent single nucleotide polymorphisms (SNPs) located around the *LPA* gene are among the most important determinants of Lp(a) levels [24]. Some of these genetic variants lead to decreased Lp(a) levels. For example, common splice variants such as 4925G>A and 4733G>A in the KIV region, carried by approximately 38% and 22% of the population respectively, contribute to lower Lp(a) levels [25][26]. Additionally, missense variants like rs41267813 also lead to reduced Lp(a) concentrations [27]. On the contrary, genetic variants, such as rs1800769 and rs1853021, are associated with higher Lp(a) levels [28]. Interestingly, rs10455872 and rs3798220 variants have been further suggested to correlate with the increased risk of coronary heart disease (CHD) [29]. Moreover, certain genetic variants, such as rs41272114, rs41259144, and rs139145675, lead to nonfunctional (null) alleles, which are associated with a protective effect against the risk of ASCVD [5][30].

While the *LPA* gene region plays a significant role in determining Lp(a) levels, other genes outside of this region may also contribute to Lp(a) concentration regulation [23]. Although initial studies did not identify candidate genes outside the *LPA* locus affecting Lp(a) levels, more recent research suggests otherwise [31]. A genome-wide association study conducted on approximately 300,000 individuals from the UK Biobank identified additional loci that influence Lp(a) concentration. Specifically, genes such as *APOE*, *CETP*, and *APOH* were found to be determinants of Lp(a) levels, indicating a broader genetic influence on Lp(a) regulation [32]. Furthermore, genetic disorders affecting lipoprotein metabolism might have varying effects on Lp(a) levels. Conditions such as abetalipoproteinemia, lecithin-cholesterol acyltransferase (LCAT) deficiency, and lipoprotein lipase deficiency are associated with decreased Lp(a) levels. In contrast, familial hypercholesterolemia (FH) and familial defective ApoB100 (FDB) are characterized by increased Lp(a) levels alongside elevated levels of other lipoproteins [33][34].

2.2. Beyond Genetics

2.2.1. Age, Gender, and Ethnicity

Serum Lp(a) concentration exhibits relative stability over an individual's lifespan due to its strong genetic influence. By the age of 2, the genes responsible for Lp(a) synthesis typically reach full expression, and, by around the age of 5, the final adult concentration is generally attained, although levels may continue to rise until adulthood [17][35]. Furthermore, serum Lp(a) levels provide significant variation among different ethnic groups [23]. In a large observational study involving 4732 adults from the Atherosclerosis Risk in Communities (ARIC) study, the absolute change in Lp(a) concentration over a 15-year period was generally modest for most individuals. Participants were categorized based on their baseline Lp(a) concentrations into three groups: normal (<30 mg/dL), borderline-high (30–49 mg/dL), or high (≥50 mg/dL). Traditionally, two cutoff values for Lp(a) levels, namely, 30 mg/dL and 50 mg/dL, have been utilized to identify individuals at higher risk of ASCVD, with 50 mg/dL representing approximately the 80th percentile in the populations studied. Notably, individuals with high baseline concentrations experienced greater changes over time. This study suggested that adults with borderline high Lp(a) concentrations, particularly those who are Afro-Americans, female, or have comorbidities such as diabetes, arterial hypertension, or albuminuria, may benefit from repeated measurements of Lp(a) over time [36].

Data from the UK Biobank indicate a sequential increase in median Lp(a) levels among individuals of Chinese, White, South Asian, and Afro-American descent [37][38]. Similarly, the ARIC study demonstrated wider variation in Lp(a) levels among Afro-American individuals compared to White individuals [39]. Notably, except for Afro-Americans and individuals from India, most ethnicities show a skewed distribution of serum Lp(a) levels towards lower values [40]. In the Dallas Heart Study, the inverse correlation between KIV2 copies and Lp(a) levels was observed across Afro-Americans, White, and Hispanic individuals, with Afro-Americans generally exhibiting higher Lp(a) concentrations for a given number of KIV2 repeats [41]. While earlier studies provided conflicting evidence, recent research suggests a gender difference in Lp(a) levels, with women typically having 5 to 10% higher levels than men [38][42][43][44][45]. Furthermore, while Lp(a) levels tend to remain stable throughout men's lifetime, women may experience an increase in levels after menopause [46]. These gender-related differences appear consistent across various racial groups [47].

2.2.2. Liver and Kidney Disorders

Liver disease can lead to a reduction in plasma Lp(a) levels, as the liver is the primary site of Lp(a) synthesis [47]. Interestingly, in liver transplant recipients, there is a shift in apo(a) isoforms to those of the donor, resulting in changes in Lp(a) concentration [48]. Conversely, chronic kidney disease and nephrotic syndrome have been associated with increased Lp(a) levels. This increase is attributed to either reduced catabolism or increased hepatic production in response to protein loss in urine or during dialysis [49]. Notably, kidney transplantation has been shown to restore Lp(a) levels to their original values within a few weeks [50].

2.2.3. Hormones

Various hormonal changes may also influence Lp(a) levels [51]. Conditions such as hypothyroidism, growth hormone deficiency in adults, and the depletion of endogenous sex hormones (e.g., menopause, ovariectomy, castration, orchidectomy) have been associated with increased Lp(a) concentration [52][53][54][55]. Conversely, hormonal replacement therapy with thyroxine or in cases of hyperthyroidism, as well as hormonal replacement treatment in postmenopausal women, have been shown to reduce Lp(a) levels in a case-dependent manner [56][57][58]. However, the impact of this reduction on cardiovascular disease (CVD) risk remains a topic of debate [59].

2.2.4. The Role of Inflammation

Serum Lp(a) levels are influenced by inflammatory states in various ways. The presence of interleukin-6 (IL-6) response elements in the *LPA* gene suggests that Lp(a) may act as an acute phase reactant in inflammatory conditions, including autoimmune diseases and myocardial infarction (MI) [60][61][62][63][64]. The IL-6 receptor blockade following tocilizumab injection has been shown to effectively reduce Lp(a) levels [65]. Additionally, Lp(a) levels appear to have increased during the Coronavirus disease 2019 (COVID-19) infection, potentially contributing to the increased thromboembolic risk associated with the disease [66]. Interestingly, in life-threatening conditions such as sepsis or severe burns, there is a significant reduction in serum Lp(a) levels, suggesting a possible role of Lp(a) as a negative acute phase reactant [67]. It is important to recognize that serum Lp(a) levels are influenced by coexisting inflammatory or medical conditions and should be interpreted in the context of these factors

3. Lp(a) Measurement and Reporting: Current Knowledge and Concerns

The measurement of Lp(a) concentration presents challenges due to its structural complexity, lipid composition variations, and the diverse sizes of apo(a) isoforms [68]. Many commercial immunoassays utilize polyclonal antibodies that may cross-react with different numbers of KIV2 copies, leading to the potential overestimation or underestimation of Lp(a) levels based on the apo(a) isoform size [69]. A study comparing six commercially available immunoassays revealed significant discrepancies among them, highlighting the need for improved standardization [70]. A newly developed latex-enhanced immunoturbidimetric assay shows promise in mitigating the impact of apo(a) isoform size differences compared to traditional enzyme-linked immunosorbent assays (ELISAs) [71]. Additionally, a liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay has emerged as a potentially superior method unaffected by apo(a) isoform size polymorphism, making it a candidate for standardizing Lp(a) measurements [72]. This advancement holds promise for more accurate and consistent assessments of Lp(a) levels in clinical practice.

Despite challenges in measuring Lp(a) levels, reporting them accurately is equally important. Currently, there are two main methods for reporting Lp(a) levels. The first method involves reporting total Lp(a) mass concentrations, which include the mass of apo(a), ApoB100, lipid, and carbohydrate components. These values are typically expressed in mg/dL. However, there is a lack of traceability from the various calibrators to the reference materials, which can affect the consistency and comparability of results [73]. In contrast, the second method reports Lp(a) particle numbers in molar concentration units, expressed as nmol/L of apo(a). This method utilizes assay calibrators that are traceable to the World Health Organization/International Federation of Clinical Chemistry and Laboratory Medicine (WHO/IFCCLM) secondary reference material. This approach offers comparability to the “gold standard” monoclonal, antibody-based ELISA method [71][74].

Current recommendations advocate for using assays least affected by varying apo(a) isoform sizes and calibrated with WHO/IFCCLM reference material. Additionally, assays reporting Lp(a) particle numbers in molar concentration units (nmol/L) are preferred over those reporting mass units (mg/dL). However, if assays reporting particle numbers are unavailable, using the units in which the assay is calibrated is recommended for reporting. This ensures greater accuracy and standardization of Lp(a) measurements across different laboratories and methods [75][76].

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