Lipoprotein(a) Concentration and Apolipoprotein(a) Size: A Synergistic Role in Advanced Atherosclerosis?

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Despite more than 3 decades of intense scientific research that has fostered our understanding of the structure and biochemistry of lipoprotein(a) [Lp(a)], the physiopathological role of Lp(a) is still poorly understood. Consequently, despite its recognition as a risk factor for coronary artery disease (CAD), the role of Lp(a) in atherogenesis and the extent to which Lp(a) levels should be assessed in clinical practice remain controversial. Lp(a), which is the most complex and polymorphic of the lipoprotein particles, is formed by an LDL moiety and a unique protein, apo(a), linked to apolipoprotein (apo) B-100 of LDL.1 The most intriguing feature of apo(a) is that it shares an extensive structural homology with plasminogen, a key proenzyme of the fibrinolytic cascade. Kringle V and the protease domains of apo(a) share >85% amino-acid identity with the corresponding plasminogen domains, even though the protease domain of apo(a) does not appear to have a catalytic function. Apo(a) contains 10 different types of a sequence with varied degrees of homology with plasminogen kringle IV. The number of kringle IV type 2 repeats, which is encoded by a varying number of copies in the apo(a) gene,2 varies both within and among individuals, and at least 35 apo(a) size isoforms have been detected in human plasma.3 Despite the presence of LDL, apo(a) imparts to Lp(a) unique properties with respect to synthesis and catabolism. In fact, apo B-100 in Lp(a) particles do not appear to mediate the catabolism of this lipoprotein via the LDL receptor, thus suggesting that the attachment to apo(a) produces a steric hindrance and/or a conformational change of apo B-100. Whereas the rate of removal from the circulation determines the level of LDL, evidence has been provided that the rate of synthesis is the primary determinant of Lp(a) levels. Plasma Lp(a) concentration is primarily controlled at the level of the gene that encodes apo(a), and an inverse correlation has been shown between plasma Lp(a) concentration and apo(a) size that may arise, at least in part, from the relatively inefficient secretion of the larger apo(a) isoforms from the hepatocytes. Additionally, in contrast to LDL, the level of Lp(a) in human plasma is largely unaffected by diet, physical activity, and conventional hypolipidemic therapy.

Since its discovery, Lp(a) has been recognized as a risk factor for CAD, and in the majority of case-control studies, Lp(a) concentrations have been found to be higher in patients with existing CAD than in matched control subjects (reviewed in Reference 4). The results of the prospective studies performed over the past decade have also shown that Lp(a) is a predictor of CAD, even though some of the studies of this design have failed to show a statistically significant difference in Lp(a) levels between subjects who subsequently developed CAD and those who did not (reviewed in Reference 4). The major reasons for the discrepant results of the prospective studies have been attributed to variations in study design, collection and storage of samples, methods used for statistical analysis, and population differences that reflect the known ethnic variability in the distribution of Lp(a) levels and apo(a) size isoforms.5,6 Additionally, it has been demonstrated that apo(a) size heterogeneity greatly affects the accuracy of Lp(a) analytical methods if the assay is based on antibodies that recognize the variably repeated kringle IV type 2. It has been shown that Lp(a) values can be substantially underestimated or overestimated based on apo(a) size.7 This can have a great effect on the interpretation of clinical studies if the distribution of apo(a) size isoforms is different between patients and control subjects.

More recently, the results of several studies have cast some doubt on the independent role of Lp(a) as a risk factor for CAD, suggesting that Lp(a) synergistically contributes to CAD by potentiating the effect of other lipid risk factors. Evidence has been provided that Lp(a) and LDL can act additively in the development of angiographically detectable CAD.8 In a study of men with CAD and elevated apo B and LDL cholesterol, Lp(a) values at baseline were the best predictor of CAD severity.9 However, in the group of patients in whom LDL was substantially reduced, high Lp(a) levels were no longer predictive, which suggests that Lp(a) may not be a primary causative agent in atherogenesis.9 In the Quebec Cardiovascular Study,10 a prospective study of French-Canadian men, Lp(a) was not an independent risk factor for ischemic heart disease, but in this population, Lp(a) was shown to increase the risk associated with high apo B and cholesterol levels and to counteract the beneficial effect of high HDL cholesterol.10 Although the physiological role of Lp(a) is totally unknown and its pathogenic mechanism is only partially elucidated, it is well documented that Lp(a) accumulates at the site of atherosclerotic lesions. In a recent study of the in vivo role of Lp(a) in human coronary artery plaques, Lp(a) was found to be ubiquitous in coronary atheroma specimens.11
association between the amount and location of plaque Lp(a), macrophages, and α-actin (a marker for smooth muscle cells) found in that study supports an in vivo role of Lp(a) in both the pathogenesis of atherosclerosis and the development of acute coronary syndromes. A number of potential mechanisms have been invoked to explain the role of Lp(a) in atherogenesis. Based on its peculiar structure, Lp(a) has both atherogenic and thrombogenic potentials. There is evidence that oxidized Lp(a) can be internalized by macrophages, thus contributing to foam cell formation. Apo(a) may interfere with the activation of plasminogen, hence attenuating the function of plasmin. In this regard, apo(a) has been shown to inhibit the lysis of fibrin clots both in vitro and in vivo and to promote smooth muscle cell proliferation. It is also possible that the pathogenicity of Lp(a) may reside in unique functions of this lipoprotein that are independent of its structural similarity to either LDL or plasminogen.

The large heterogeneity of apo(a) isoform size and its potential role in Lp(a) pathogenicity have not been fully explored. Lp(a) levels and apo(a) isoforms were determined in a large cohort of black and white participants in a multicenter epidemiological study of cardiovascular risk factors in young adults (Coronary Artery Risk Development In young Adults [CARDIA]), and the results indicated that the distribution of Lp(a) levels and apo(a) isoforms was significantly different between black and white Americans. Confirming other reports, blacks had median Lp(a) values that were almost 4 times that of whites. However, blacks had a lower frequency of small apo(a) isoforms (<20 kringles IV repeats), and within the small size range, Lp(a) values were high but not significantly different from whites. The striking difference in Lp(a) values between blacks and whites was found to be associated with the range of intermediate apo(a) sizes. On the basis of the results of this study, and considering that blacks, despite the very high levels of Lp(a), have a similar if not lower incidence of CAD than whites, we hypothesized that Lp(a) concentration is not the only factor that contributes to the pathological role of Lp(a), but the association between small apo(a) polymorphs with high Lp(a) concentrations should be taken into consideration as predictors of CAD risk. Since that time, only a few prospective studies have evaluated apo(a) isoform size and its association with CAD. In the Stanford 5-city prospective case-control study, Lp(a) levels were an independent risk factor for the development of CAD in men, and a higher frequency of lower-molecular-weight (LMW) apo(a) isoform sizes was observed in those who experienced incident myocardial infarction or coronary death. A prospective study by Klausen et al demonstrated that LMW apo(a) isoforms were significantly associated with CAD in men <60 years of age.

In this issue of Circulation, Kronenberg and colleagues report the interesting and novel findings of the Bruneck prospective study, in which the authors evaluated the role of apo(a) phenotype and Lp(a) concentration in the 5-year progression of carotid atherosclerosis assessed by ultrasound. The major novelty resides in the study design, which allowed the authors to differentiate participants with respect to the presence of early (incident nonstenotic) versus advanced (stenotic) atherosclerosis, the latter of which most likely arises owing to thrombotic events that ultimately may result in plaque rupture. These investigators found that in subjects with high LDL levels (≥3.3 mmol/L), plasma Lp(a) concentrations were predictive of risk of development of early atherogenesis in a dose-dependent manner. However, the risk was not correlated with apo(a) isoform size and was not present when LDL levels were <3.3 mmol/L. These results are in keeping with other studies that suggested that Lp(a) may risk may be dependent on additional lipid risk factors and indicate that Lp(a) may not be an independent risk factor for the development of early lesions. Additionally, the lack of dependence of early atherogenesis on apo(a) isoform size may indicate that the role of Lp(a) in this process depends on either the degree of accumulation of Lp(a) in the developing atheroma or events in the developing lesion that are specifically mediated by the carboxyl-terminal part of apo(a). These events may include uptake of native Lp(a) by macrophages, which is mediated by apo(a) kringles IV types 6 and 7. Kronenberg and colleagues, in the stimulating Discussion section, provide a clear and concise evaluation of the possible mechanisms by which Lp(a) may be involved in the early stages of atherosclerosis.

In contrast to the effects on early atherosclerosis, the LMW apo(a) phenotype (<22 kringles) was a powerful predictor of risk for advanced atherogenesis in the Bruneck study group, particularly when associated with high plasma Lp(a) concentrations. Similarly, risk for incident fatal and nonfatal cardiovascular disease was increased in subjects with a combination of high Lp(a) concentrations and LMW apo(a) sizes. Because advanced atherosclerosis is associated with thrombotic events, this finding suggests that smaller apo(a) isoforms may be more antifibrinolytic than larger apo(a) phenotypes, although this remains to be tested directly. It should also be considered that in addition to its potential role in the fibrinolytic process, Lp(a) may have other isoform-dependent effects on thrombosis beyond direct inhibition of plasminogen activation.

The study by Kronenberg et al raises a number of issues for future study and consideration. First, it will be interesting to determine whether the findings of Kronenberg and coworkers in a white population will be the same in different racial groups or subgroups. In this regard, it has already been demonstrated that both Lp(a) levels and apo(a) isoform size distribution vary between racial groups. As such, it is possible that apo(a) isoform size may not be predictive of advanced atherosclerosis in all populations. Clearly, additional large prospective studies to evaluate the risk associated with both Lp(a) concentrations and apo(a) phenotypes in different racial groups are required to address this question. It is also clear that additional structure-function studies need to be done to address the mechanism by which LMW apo(a) isoforms confer increased risk in advanced lesions. Finally, the question arises as to whether Lp(a) concentration and apo(a) phenotypes should be determined in the general population.

Several important factors strongly support the suggestion that determination of Lp(a) levels should not be performed when the general population is screened for risk of CAD. The lack of standardized and apo(a) size-independent methods for Lp(a)
measurements makes it impossible to compare results from different clinical studies. The cutoff Lp(a) value to classify subjects as being at increased risk for CAD varies greatly among studies and ranges from 20 to 40 mg/dL. These differences may be both method- and population-dependent and constitute a serious obstacle to clinicians in the interpretation of patient values and in the correct assessment of risk. Because the National Institutes of Health–National Heart, Lung, and Blood Institute (NIH-NHLBI) has recently awarded a contract for the standardization of Lp(a) measurements, substantial improvement in this area is expected in the coming years. Additional factors that do not support a generalized measurement of Lp(a) are the relative resistance of Lp(a) concentration to diet and drug treatment and the lack of evidence to support the clinical benefit of lowering Lp(a). However, because Lp(a) values continue to emerge as a potent CAD risk factor, at least in whites, as also confirmed by the present study by Kronenberg and coworkers, determination of Lp(a) levels may provide an important contribution to the clinical assessment of individuals at high risk for CAD or of patients with existing CAD. Additionally, considering the evidence indicating that high Lp(a) levels may increase the risk imparted by high LDL cholesterol, the knowledge of Lp(a) concentration may aid in the choice of the most appropriate treatment of high-risk individuals. Given the uncertainty related to the Lp(a) cutoff value, we suggest clinicians use a conservative Lp(a) value of 20 mg/dL, particularly in patients with concomitantly elevated LDL cholesterol.

More controversial at this point in time is the determination of Lp(a) values in the black population. The few clinical studies performed in blacks have been inconclusive as to the role of Lp(a) as a risk factor in this ethnic group. It would be interesting to evaluate in blacks whether there is an association between high Lp(a) values, LMW apo(a) isoforms, and risk of CAD, as in the whites evaluated in the Bruneck study, as well as the described synergistic effect of Lp(a) and LDL. Given the high number of apo(a) isoforms and the low frequency of small polymorphs, which is even more pronounced in blacks, a large number of subjects would need to be studied to achieve unambiguous conclusions.

Despite the very intriguing results of the study by Kronenberg and coworkers\textsuperscript{18} indicating that small apo(a) isoforms are a strong indicator of advanced stenotic atherosclerosis, it does not seem cost-effective at this point in time to add the determination of apo(a) isoforms to CAD risk assessment.Clinicians should decide on an individual basis whether the determination of apo(a) isoforms is necessary to generate a more complete risk profile. Lp(a) continues to be a focus of intense research, and new, exciting data are continuously being produced. Therefore, both the prothrombic and atherogenic mechanisms of Lp(a) may be better elucidated in the near future, thus providing more defined indications for the determination of Lp(a) values and apo(a) isoforms in clinical practice.

References


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