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REVIEW ARTICLE

Lipoprotein (a): Biology and role in atherosclerotic vascular diseases

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Lipoprotein (a) (Lp(a)) is a genetically determined lipoprotein molecule. Its constituent, low density lipoprotein cholesterol participates in the process of atherosclerosis, and its prothrombotic tendency is due to its homology to plasminogen. In normal subjects plasma levels of Lp(a) are controlled by the apolipoprotein(a) (apo(a)) gene locus. The polymorphism of apo(a) is determined by more than 34 alleles, plasma levels of Lp(a) being inversely correlated to its isoforms. Plasma levels in healthy subjects are highly variable, and also depend on the ethnic group studied. Indians, both immigrant and native, display high plasma level of Lp(a). Many studies record them to have higher levels than most of the other ethnic groups. It is now established as a powerful and independent risk factor for macrovascular diseases due to atherosclerosis, including coronary artery disease (CAD), stroke and peripheral artery diseases. High levels of Lp(a) (> 30 mg/dl) appear to increase the risk of premature CAD. The risk is increased several-fold in the presence of high levels of other lipid and non-lipid risk factors. Lp(a) plasma concentrations are abnormal in other diseases, nephrotic syndrome and chronic renal failure and possibly in insulin-dependent diabetes mellitus as well. Unfortunately, this lipoprotein is not readily amenable to therapeutic intervention. Predictive value of this lipoprotein, and its observed high plasma levels makes it an important research, investigative, and prognostic tool, particularly for the Asian Indian population.

FACTOR(S) presumed to be responsible for increased propensity to atherosclerosis in Indians are abdominal obesity, smoking, glucose intolerance, resistance to the insulin-mediated glucose uptake, and a peculiar dyslipidemic profile[1,2]. The dyslipidemia seen in Indians include high triglycerides (TG), low high density lipoprotein cholesterol (HDL-c), and increased lipoprotein(a) (Lp(a)). A new dimension has been provided by the emerging role of Lp(a) and its importance in atherosclerosis-prone Indians. The following discussion shall outline in detail the genetics, biochemistry, metabolism, and clinical relevance of this lipoprotein.

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Lp(a): Biology and genetics

Lp(a) is a cholesteryl-ester-rich lipoprotein of unknown function formed by the covalent disulfide linkage of apolipoprotein (a) (apo(a)) to apolipoprotein B (apo B) of low density lipoprotein cholesterol (LDL-c). Recent studies of Lp(a) using scanning force microscopy showed for the first time a belt-like structure of apo(a) with both ends attached to a spherical LDL-c. The two ends of apo(a) were bound to the LDL-c sphere at two distant sites[3].

Apo(a) is a glycoprotein with approximately 29% (w/w) carbohydrates[4] and resembles plasminogen, the plasma zymogen for plasmin[5]. The apo(a) gene contains between 12 and 51 copies of a DNA sequence encoding a tandemly repeated cysteine-rich motif called kringle IV(K-IV), which is found in one copy in the plasminogen gene[6]. Apo(a) exists in multiple genetically determined isoforms with molecular weights ranging from approximately 350 to 1000 kDa. The number of K-IV repeats is inversely correlated with the plasma Lp(a) concentration[7,8].

The apo(a) and plasminogen cDNAs have been cloned[9–11] and the two genes are closely linked on chromosome 6(q26-27) (refs 12–16). Analysis of the apo(a) cDNA revealed a characteristic structure consisting of numerous K-IV repeats, one K-V, and a protease domain. These are homologous to corresponding structures in plasminogen mimicking its functional properties as well. This could partially explain the thrombogenic properties of Lp(a)[2].

Apo(a) occupies a unique evolutionary niche, mainly restricted to old-world monkeys, apes, humans and hedgehogs[17]. Primate and hedgehog apo(a) genes probably evolved independently from different domains of the plasminogen gene and are conspicuous examples of convergent evolution. Genetic size polymorphism of apo(a) has been demonstrated at the protein[7], mRNA[18] and DNA levels[19,20]. This polymorphism of apo(a) was originally identified by Utermann and his co-workers by SDS-polyacrylamide gel electrophoresis. The isoforms were designated as F, B, or S based on the pattern of mobility that is either faster, equal to or slower than apo B-100. Sophisticated separation techniques such as SDS-agarose gel electrophoresis have allowed identification of more than 34 apo(a) size isoforms[21]. Pulsed-field gel electrophoresis of genomic DNA digested with appropriate restriction enzymes from subjects with different apo(a) protein isoforms confirm that the size variation in the apo(a) protein is a result of a variable number of K-IV repeats at the apo(a) gene locus. There exists a perfect correlation between the size of apo(a) DNA fragments, size of protein isoforms and apo(a) mRNA size. However, some apo(a) alleles are not expressed at the protein level, and the expression of individual alleles in terms of plasma apo(a) concentration varies widely. Information on both the size and the degree of expression of an allele is obtained by performing apo(a) DNA and protein typing. The apo(a) gene locus is thus best described as a transcribed and translated VNTR locus that determines the extensive variation in size and concentration of the apo(a) protein.

Metabolism of Lp(a)

The largely varying plasma concentration of Lp(a) is randomly distributed in the population and correlates inversely with the molecular mass of apo(a). This protein is shown to have an unusual secretory pathway, mostly derived from studies of the intracellular metabolism of apo(a) in transfected human hepatoma cells and in primary baboon hepatocytes[22]. It is known that apo(a) is synthesised in the liver. *In vivo* turnover studies have revealed that variations in the plasma levels of Lp(a) are due to its synthesis rather than the degradation. An immature precursor form of apo(a) is retained in the endoplasmic reticulum for a prolonged time due to complex folding and processing. Since the retention time correlates positively with the apo(a) isoform size, this intracellular mechanism could explain the inverse correlation between the isoform size and the plasma concentrations. Another unusual feature of the biogenesis of Lp(a) is that the mature Lp(a) complex is formed only following separate secretion of apo(a) and LDL-like particles. Upon secretion from hepatocytes, apo(a) is assembled with plasma LDL-c to form Lp(a)[23]. This process requires docking and formation of a single disulfide bond between apo B-100 in LDL-c and K-IV in apo(a)[24–26]. The metabolism of Lp(a) is independent of other lipoproteins[27]. The major source of circulating plasma Lp(a) is the human liver. Serum Lp(a) concentration is determined by the rate of Lp(a) production and correlates directly with hepatic mRNA abundance[28,29]. Studies in primary cultures of baboon hepatocytes showed that the majority of apo(a) is secreted by liver cells into the medium in its free form[30]. Wilkinson *et al.*[31] showed that apo(a) in the human liver is not associated with apo B-100 and occurs extracellularly after secretion. The assembly of apo(a) and LDL-c, which is determinant for plasma Lp(a) levels, takes place extracellularly and requires specific structural motifs in apo(a) and apo B. Frank and Kostner[32] studied structural features of apo(a) necessary for high efficient assembly. According to their observations, K-IV T6 and T7 recombinant constructs were responsible for the high-yield assembly and K-IV T5 had an amplifying effect.

There are conflicting observations regarding the catabolic pathways of Lp(a). Because of its resemblance to LDL-c, it was initially postulated that Lp(a) degradation

was mediated by the LDL receptor (LDL-R). The apo B-100 in the Lp(a) may interact with the LDL-R[33–35]. However, the role of LDL-R in the removal of Lp(a) from the plasma is not defined despite a number of *in vitro* and *in vivo* studies. Lp(a)/apo(a) receptors on macrophages, receptor-related protein, and the asialoglycoprotein receptor have been implicated[36]. Lp(a) binds to LDL-R and is removed more rapidly from the plasma of transgenic mice having over-expressed receptors[37]. However, catabolism of ^{125}I was not significantly reduced in patients with defective LDL-R function[38], suggesting that the LDL-R is not directly responsible for Lp(a) clearance *in vivo*. Further, recent studies suggest that mouse embryo fibroblasts do not take up Lp(a) via the LDL-R[35]. Lp(a) turnover studies have shown that approximately 70% of the apo(a) component of Lp(a) may be released in the circulation, and the rest is degraded via the LDL-R[39].

Huby *et al.*[40] have demonstrated the presence of two distinct structural domains in apo(a) linked by a flexible and accessible region located between K-IV-IV and IV-V. They isolated the Lp(a) particle following removal of the N-terminal domain by proteolytic cleavage; the residual particle (containing the C-terminal domain spanning the region from K-IV-V to the protease domain), is linked to apo B-100 by disulfide linkage, termed 'mini Lp(a)'. The observation that mini-Lp(a) exhibits the same binding affinity to fibrin as the corresponding Lp(a) suggests that the kringles responsible for fibrin binding are restricted to K-IV-V to K-IV-X. This observation is supported by failure of the N-terminal domain to bind to fibrin. N-terminal fragments of apo(a) have been detected in the urine of normal subjects, thereby indicating that part of the catabolism of Lp(a), which is largely indeterminate, could occur via the renal route[40]. This possibility is supported by the observation that the excretion of apo(a) fragments was lesser in patients with reduced renal function[41]. Collagenase digestion of Lp(a) released apo(a) fragments of similar size to those found in urine, producing a particle that could then bind to LDL-R[42].

Lp(a) estimation

Laboratory estimation is performed by radioimmunoassay, immunoelectrophoresis and using monoclonal antibodies. Antibodies are raised against either Lp(a) or apo(a) in the intact Lp(a) molecule since disassociation of apo(a) from apo B-100 decreases its immuno reactivity. If antibodies are raised against K-IV repeats, it would lead to heterogeneity due to variation in their numbers[43]. A recent report suggests that patients suffering from cornary artery disease (CAD) excrete significantly higher amounts of apo(a) into the urine than controls and that urinary apo(a) is a valuable predictor of CAD. Using urinary apo(a) as a marker for CAD has the advantage of easier sampling compared to plasma samples[44].

Apo(a) size polymorphism, Lp(a) concentration and ethnic variation

Apo(a) protein, mRNA and DNA size polymorphism studies demonstrate that the number of K-IV repeats in the gene and the resulting size of the protein are inversely correlated with Lp(a) levels in the plasma in all populations studied so far[7,8,19,20,45]. Mean Lp(a) concentrations and apo(a) isoform frequencies vary significantly between populations. The plasma concentration of Lp(a) has a skewed distribution that varies over a 1000-fold range in white populations, with most individuals having low plasma Lp(a). In whites, studies in sibpairs indicate that over 90% of the individual variation of the apo(a) gene may be responsible for it, however, in other ethnic groups the contributions of this locus may be smaller[45]. A pentanucleotide sequence repeat polymorphism (TTTTA) at position-1373 before the translation initiation codon of the apo(a) gene may be one of the factors associated with variable plasma Lp(a) concentration[46]. This polymorphism could account for about 10–14% of the inter-individual variations of Lp(a) levels in Caucasians[47,48].

Tibetans, Japanese and Koreans have Lp(a) levels similar to the Caucasians. Higher Lp(a) levels are observed in blacks. Close correlation between CAD and Lp(a) levels has been observed in Welsh, Germans, Swedish, Finnish, Icelanders, Austrians, Australians, Chinese, and Japanese[49–51]. Higher levels of Lp(a) compared to other ethnic groups have been recorded in Asian Indians in US[52], UK[53], and Singapore[45]. Further evidence has been provided by another study where mean levels of Lp(a) were nearly double in sons of Asian Indians with CAD compared to similar-aged sons of white parents[54].

Other factors affecting plasma levels of Lp(a)

Lp(a) levels, unlike LDL-c and apo B levels, do not vary with the age of the subject. Lp(a) is fully expressed in the first year of life. Hence, its tracking is more useful than other lipids[51]. Various endogenous and exogenous factors affect Lp(a) levels in humans (Table 1). These include hormones (growth hormone, estrogens), hypothyroidism, and alcohol consumption. Several renal diseases alter Lp(a) levels including renal failure and nephrotic syndrome. Successful renal transplantation leads rapidly to correction of Lp(a) concentrations, especially in patients treated with chronic ambulatory peritoneal dialysis with higher Lp(a) levels[55]. Further,

Table 1. Factors influencing serum lipoprotein(a) concentrations

Physiological factors
Age, ethnic groups, menopause, high saturated fat diet
Chemical compounds and drugs
Estrogen, progesterone, danazol, growth hormone, neomycin, niacin, alcohol, cyclosporin
Diseases
Myocardial infarction, renal failure, nephrotic syndrome, familial hypercholesterolemia

Table 2. Lp(a) and atherosclerosis: Pathophysiological correlation

Contributes to uptake of LDL-c and formation of foam cells
Inhibits plasminogen activation and fibrinolysis leading to procoagulant tendency
Release of cytokines
Release of growth factors, smooth muscle cell proliferation
Increased expression of adhesion molecules
Endothelial dysfunction
Interacts with other risk factors e.g. homocysteine

diseases such as rheumatoid arthritis and familial hypercholesterolemia increase the Lp(a) levels[56]. On the other hand, sex of the subject, other lipoproteins, other coronary risk factors, environmental factors and anthropometric parameters have no significant effect on the Lp(a) level[50]. Lp(a) levels are not readily amenable to manipulation by dietary restriction. However, in one of the studies, substitution of a baseline diet of polyunsaturated fat with medium-chain saturated fat led to reduction in Lp(a) levels by 30% (ref. 57). Other recent studies indicate that Lp(a) level is lowered by saturated fat (e.g. palmitic acid) diet[58]. Moderate drinking of alcohol lowers plasma Lp(a) levels[59]. If the alcohol was withheld from moderate drinkers, this led to increased Lp(a) levels by 64% (ref. 60). This may be an additional mechanism by which moderate alcohol drinking may be beneficial for atherosclerosis.

Except niacin and hormone replacement therapy, no other lipid lowering agent lowers Lp(a) levels[61–65]. Other drugs such as cyclosporin, danazol, and stanazolol can increase the La(a) levels.

Pathogenic effects of Lp(a)

Atherogenesis

Lp(a) provides a carrier system for LDL-c and promotes cholesterol accumulation in cells[66] (Table 2). Oxidized LDL-c and Lp(a) accumulate in excessive amounts in macrophages ('foam cells') forming fatty streak. Intact Lp(a) deposition has been demonstrated in the arterial wall and venous grafts[67,68] and atherosclerotic plaques[69]. A study of the atherectomy specimens showed a correlation of plaque alpha-actin and Lp(a) indicating a role for Lp(a) in plaque growth as well[70]. Further, it stimulates smooth muscle cell proliferation[71], avidly binds to arterial proteoglycans[72], and fibronectins[73]. Plasma homocysteine increases affinity of Lp(a) for fibrin, thus increasing its atherogenic potential[74].

Oxidized Lp(a) is also implicated in the causation of endothelium dysfunction[75]. The endothelium-dependent vasoconstrictive response to L-NMMA was enhanced in subjects with relatively high Lp(a) plasma levels, suggesting an increased basal production and release of nitric oxide[76].

In induction of atherogenesis, recent evidence indicates that Lp(a) involves adhesion molecules. An endothelial cell-activating effect of Lp(a) is potent surface expression of vascular cell adhesion molecule-1 (VCAM-1) and E-selectin. This may be an important event in the initiation of atherogenic disease[77].

Thrombosis

Endothelial cells due to surface-connected fibrinolytic system are important for fibrinolysis. Lp(a), because of its plasminogen-like apo(a), interferes with fibrinolysis due to inhibition of plasminogen binding to its high affinity sites[78]. Lp(a), to some extent, regulates the synthesis of a major fibrinolytic protein, plasminogen activator inhibitor-1 (PAI-1)[79]. These prothrombotic events are now considered essential to the genesis of atherosclerosis.

Lp(a) and the risk for atherosclerotic macrovascular diseases

Association of Lp(a) and CAD was first observed in 1974. The accumulated data have established it as an important inherited risk factor for the macrovascular diseases including CAD, cerebrovascular and peripheral vascular diseases[80,81]. Child–parent association specifically looking for CHD in parents and lipid levels in the offspring in Bogalusa Heart Study indicates that Lp(a) is a marker of CAD in adulthood[82].

Several case-control studies have demonstrated an association of elevated Lp(a) plasma concentrations with premature coronary atherosclerosis and myocardial infarction[83]. Lp(a) is considered to be ten times more atherogenic than LDL-c[84–86]. Relative risk of CAD is increased three-fold if the levels of Lp(a) are more than 30 mg/dl (refs 87, 88). Serum Lp(a) levels have been shown to correlate well with the presence, extent, severity and score of atherosclerotic lesions on coronary angiography[89–91]. The Scandinavian Simvastatin Survival Study provides independent confirmation that a high Lp(a) lipoprotein level is a significant CAD risk factor[92]. In Quebec Cardiovascular Study, however, Lp(a) was not an independent risk factor for CAD but appeared to increase the risk associated with other lipid

risk factors[93]. The pathogenic association of Lp(a) and CAD has been further emphasized in a symposium on this topic held in Oslo in May 1997 (ref. 94). In a meta-analysis, 12 out of the 14 prospective studies showed Lp(a) concentration to be increased in subjects later developing CAD[95].

Recently, some of the studies have suggested that the size of apo(a) is also important. Amemiya and co-workers evaluated 94 Japanese patients with angiographically proven CHD and observed a negative association between Lp(a) levels and apo(a) protein sizes. The authors conclude that apo(a) protein sizes are a significant predictor, and the genotype homozygous for the 8 (TTTTA)-repeats a possible predictor of the degree of atherosclerosis in CAD[46]. In some studies apo(a) size was a better predictor of the disease and its severity[96,97]. Male patients undergoing coronary artery bypass had smaller apo(a) isoforms than the controls though their Lp(a) levels were normal[98]. Theoretically, a combination of small apo(a) size and high Lp(a) concentration should be particularly deleterious.

A few recent studies, however, suggest that Lp(a) levels may not be under such strict genetic control in patients with atherosclerotic vascular disease as has been demonstrated for a healthy population[89,99]. Several studies have explored the association of Lp(a) in centenarians. Almost a quarter of the centenarians had high plasma levels without showing any atherosclerosis[100]. In another study, such subjects had higher Lp(a) levels than the controls[101]. Paradoxically, therefore, some critical level of Lp(a) may be useful for increasing longevity.

Lp(a) has also been noted to be an independent risk factor for peripheral vascular disease[102,103]. Association of elevated Lp(a) level and stroke is controversial. In a study, Lp(a) was observed to be increased in about one-third of patients with acute cerebral ischemia, but did not correlate to stroke characteristics or prognosis[104].

Relationship between Lp(a) and lipid and non-lipid risk factors

Correlation coefficients of Lp(a) ranged from 0.16 to 0.17 for total cholesterol, LDL-c, HDL-c, serum triglycerides, apo A-I, apo A-II, apo B, and truncal fat[105]. Atherogenic risk appears to be increased when there is a cluster of lipid abnormalities. Effects of serum Lp(a) on atherogenesis are increased by high LDL-c and low HDL-c levels. Lp(a) levels more than 30 mg/dl by itself lend a 3-fold risk of CAD[106]. Men with LDL-c values of more than 317 mg/dl and Lp(a) values of more than 30 mg/dl have a 16-fold increased odds ratio of having CAD vs those having an LDL-c level of less than 130 mg/dl and Lp(a) level of less than 10 mg/dl (ref. 87). Hopkins *et al.*[107] studying early familial CAD have reported that the risk associated with elevated Lp(a) was observed in persons having plasma total cholesterol 6.72 mmol/l (260 mg/dl) or higher or with a total/HDL-c ratio of more than 5.8. Indeed when Lp(a) was over 40 mg/dl and plasma total/HDL-c more than 5.8, relative odds for CAD were 25 in multiple logistic regression analysis. Further, if two or more non-lipid risk factors such as hypertension, diabetes, cigarette smoking, high total homocysteine, or low serum bilirubin were also present, relative odds were 122. Risk for the development of CAD can be calculated using 'Lipid Tetrad Index' (product of total cholesterol, triglycerides and Lp(a) values divided by the HDL-c level)[50]. High levels of Lp(a) were found to increase the risk associated with hyperhomocysteinemia by a factor of nine, and a simultaneous elevation in both having an odds ratio of 31 for CAD[107].

Lp(a) and diabetes

In diabetes, conflicting reports are available regarding prognostic significance of Lp(a) levels. A few studies record that it may be elevated in insulin-dependent diabetes mellitus[108]. Particularly, patients with microalbuminuria and proliferative retinopathy show higher Lp(a) levels[109]. Similarly, Lp(a) has been correlated to CAD in diabetics in some studies[110–112], while other trials do not show any such correlation[113]. South Indian non-insulin-dependent diabetes mellitus (NIDDM) patients with high Lp(a) levels, however, show good correlation with CAD[114].

Lp(a) in Indians and CAD risk

In a study of Chinese, Malay, and Indian newborns in Singapore, high levels of cord blood Lp(a) in Indians reflected the adult differences in CAD rates[115]. Anand *et al.*[116] have computed data from three studies, CADI Study, study on Asian churchgoers in Chicago, and SHARE investigation in Canada. In two of the studies, the difference between Lp(a) levels in Asian subjects was higher than North American whites. Particularly, in the sample from the SHARE study, the mean Lp(a) concentration for South Asians was 34.1 mg/dl vs 17.3 mg/dl in white Canadians.

Studies performed in the native Indian population also record increased levels of Lp(a) in patients with atherosclerotic vascular diseases[117]. In another study, Lp(a) levels in 114 consecutive patients undergoing coronary angiography were compared with controls. CAD patients had higher levels of Lp(a). However, those who were alcohol drinkers showed significantly lower Lp(a) levels[118]. In another study done on North Indian patients, apo(a) phenotypic polymorphism and its effect on Lp(a) levels was studied on 130 angiographically proven CAD patients and 130 age and sex matched controls. It

Table 3. Quartile distribution of serum Lp(a) levels (mg/dl) in CAD patients and controls

Group	Mean ± SD	Quartile distribution 1–25	50	75–100	Skew
Patients (n = 130)	42 ± 24	0.79–16.0	31.1	62.9–160	1.21
Controls (n = 130)	27 ± 27	0.69–7.8	17.7	36.6-147	2.13

was observed that low molecular apo(a) isoforms associated with high Lp(a) levels in the general population are significantly over-represented in the CHD patients compared to controls (Table 3)[119]. This observation is in agreement with other studies on Caucasian populations[120,121]. In a recent study on South Indian non-insulin-dependant diabetes mellitus (NIDDM) patients, Lp(a), along with age and HDL-c levels were associated with CAD in NIDDM patients[114]. Since there is increasing prevalence of NIDDM in Indians, this observation has ominous portends in terms of total burden of CAD in Asian Indians.

Perspective

Lipoprotein(a) is now established as a genetically determined predictor of atherosclerotic vascular diseases, and in particular premature CAD. Determination of both Lp(a) and apo(a) isoforms makes cardiovascular risk assessment more comprehensive. Homology to plasminogen enables it to interfere with the fibrinolysis, thus providing additional pathway for atherosclerosis. High levels of this lipoprotein, particularly in Asian Indians, is a matter of clinical concern. Since it is not generally amenable to the lifestyle measures, other lipid and non-lipid risk factors must be modified to decrease the risk in those with high Lp(a) levels. It could be a useful tool for guiding management strategy in the individuals with: (i) family history of premature CAD; (ii) normal total cholesterol and evidence of macrovascular disease; (iii) isolated hypertriglyceridemia; and (iv) those belonging to high-risk ethnic group.

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