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Structure and Biologic Roles of Lipoprotein (a) and Its Clinical Implications

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In the past few years, a significant proportion of previously unrecognized risks of atherosclerotic coronary artery disease has been accounted for by lipoprotein(a) [Lp(a)]. It was first identified as an antigenic trait in human plasma by Berg in 1963 (1). For many years this lipoprotein was considered a variant of low-density lipoproteins (LDL) and of little interest for clinicians (2). Later it was found that Lp(a) is a lipoprotein that is similar to LDL in terms of lipid and protein composition, but also contains a highly glycosylated protein designated apolipoprotein (a) [apo(a)], that is linked through a disulfide bridge to apolipoprotein (apo) B100 (3). Now it has become clear that Lp(a) is not simply a variant of LDL, as was once thought, but is immunochemically and physicochemically distinct even though Lp(a) has apo B100 in common with LDL. One of the distinctive structural features of apo(a) is triple looped cysteine-linked amino-acid domains called kringles, which have considerable homology to similar domains within plasminogen (4). Lp(a) may provide a link between the clotting and lipoprotein systems. In case control studies it is shown that Lp(a) is associated with coronary artery disease (5,6). A lot of similar investigations and prospective studies have confirmed this observation (7-12). There are also several reports linking high levels of Lp(a) with cerebrovascular disease (13), peripheral vascular disease (14), and restenosis of coronary bypass grafts (15).

In this review we will focus on structural and possible biological roles of Lp(a) and its clinical implications.

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Apolipoprotein (a) structure

Apo(a) is remarkably polymorphic, with 34 size isoforms (from <300 to >800kDa) identified in human plasma. Apo(a) is homologous to plasminogen and contains a plasminogen-like kringle 5 and protease domain preceded by multiple domains that are homologous to plasminogen kringle 4 (4). The size of apo(a) is determined by the number of kringle 4 domains that are encoded in the apo(a) gene, which can vary from approximately 12 to 51 (4).

Kringles are characteristic triple loop structures that are held together by the formation of three internal disulfide bonds. Ten types of kringle 4-like domains are found in apo(a) based on amino acid differences (16). Each contains N- and O-linked glycosylation sites and, except for kringle 4 type 2, is present in a single copy. The number of kringle 4 type 2 repeats varies with the apo(a) size (4). The conservation of each kringle type in all isoforms suggests that each may impart distinct and important properties to Lp(a).

Factors determining Lp(a) levels

The most important factor in determining Lp(a) levels is apo(a) gene locus (17). It accounts for 90% of variation of plasma Lp(a) levels (17). Apo (a) size is inversely correlated with Lp(a) levels (10,17-19). However exceptions to this correlation do exist suggesting that additional cis-acting sequences at the apo(a) locus may influence plasma apo(a) levels (17). Recently it has been demonstrated that Lp(a) concentration varied by up to 200-fold for apo(a) alleles of the same size (16). In addition 'null' alleles exist and they produce no detectable plasma Lp(a) (20)

In early studies it was established that there is a correlation between plasma Lp(a) levels and Lp(a) production rate (21). Recently new studies have extended these observations and demonstrated that the inverse correlation between apo(a) size and plasma Lp(a) levels, as well as differences in Lp(a) levels associated with similar sized isoforms are a result of variability in Lp(a) production rate (22).

Synthesis and metabolism of Lp(a)

When considering the turnover of Lp(a) it should be taken into account that the dominant effect on its serum concentration in normal man is exerted by the rate of hepatic secretion (21). This is consistent with the fact that after heterologous liver transplantation apo(a) phenotype changes to that of donor (23). In patients with liver disease and in alcohol abuse serum Lp(a) levels are low (24).

In vitro studies suggest that Lp(a) assembly is extracellular (25,26). A recent study in baboon hepatocyte cultures demonstrated that Lp(a) assembly can occur at the hepatocyte cell surface (27). Newly synthesized apo(a) binds to the hepatocyte cell surface via its kringle domains. From this location it can be captured by apoB and released from the cell as a lipoprotein particle. The cell-surface association of apo(a) may also be important to prevent the release of apo(a) into plasma where it may participate in potentially detrimental associations with other cell surfaces (28).

Much less is known about the mechanism of Lp(a) clearance from the circulation. In earlier studies it was found that individuals with familial hyperlipidemia due to LDL receptor defects have two-to-threefold increased Lp(a) levels compared with controls with identical apo(a) phenotype (29). Although Lp(a) can be degraded through the LDL-receptor pathway, accumulating evidence suggests that this is not a major pathway of Lp(a) catabolism in vivo (30). Two recent studies support this view (16,31). Synder et al. showed that the binding and degradation of Lp(a) by the LDL-receptor pathway in human hepatocytes, macrophages, and fibroblasts was only 10-30% that of LDL (31). Because more LDL than Lp(a) is found in vivo, the LDL receptor is unlikely to contribute significantly to Lp(a) catabolism. Perombelon et al examined the apo(a) isoforms and Lp(a) levels in nine families affected with either familial hyperlipidemia or familial defective apoB (16). No difference was observed in Lp(a) levels between the affected and unaffected family members who had inherited identical apo(a) alleles.

Other pathways involved in Lp(a) catabolism are less clear. In-vitro studies demonstrated the uptake and degradation of Lp(a) by non-LDL receptor pathways (31,32). Lipoprotein lipase may facilitate some of this uptake. Recently Keesler et al. (33) characterized a receptor for Lp(a) on human macrophages and Malle et al. (34) established that Lp(a) can bind to glycoprotein IIb on platelets. Whether these pathways play a role in the clearance of Lp(a) from plasma currently is unknown.

Population studies

The frequency distribution of plasma Lp(a) concentration in Caucasian populations is markedly positively skewed (35). The majority of the population thus cluster at the lower end of the concentration range with levels less than 0.1 g/L in more than half. The range encountered is, however, enormous with some individuals having levels exceeding 1g/L while 5% have values below 0.01g/L (35). Black Americans have a higher concentration on average than their white counterparts (36). The same appears to be the case for another population originating from Africa, the Sudanese. The Chinese, on the other hand, may have even lower than Caucasians, the skewed distribution of Lp(a) is a consequence of apo(a) allele frequencies and of the allele-specific effects on Lp(a) concentrations (37). Alleles that lead to high Lp(a) levels are rare in the Caucasian population, whereas those that result in low Lp(a) levels are frequent (37). The extent to which the differences in the distribution of Lp(a) concentrations between ethnic groups are determined by variation at the apo(a) locus or by other factors is yet to be determined.

At birth, Lp(a) concentrations are reported to be low (38). It is reported that Lp(a) concentrations of newborns were not related to any of the indices of fetal maturity, nor to gender or race, which are

known to influence Lp(a) in adults (39). Serum Lp(a) increases during the first year of life, and reaches the adult concentrations in the second year of life (39). Smaller differences or no differences at all in Lp(a) concentrations were noted between males and females in different adult populations (36,40). There was no statistically significant correlation of Lp(a) with age, height, body mass index, total cholesterol, HDL or LDL (35).

Plasma levels of the Turkish population (0.21 g/L) were reported higher than of some populations including Chinese, Malaysian, Hungarian, Korean, Japanese, Swedish, Icelandic, and American (41).

Role of lipoprotein (a) in atherosclerosis and thrombosis

The pathological and laboratory evidence supporting a role for Lp(a) in the atherosclerotic process stems from observations that it accumulates in atherosclerotic plaques (42-44). Lp(a) can traverse the vascular endothelium, although the process is as yet ill defined. Immunofluorescence localization studies, as well as chemical analyses of extracts of the atherosclerotic plaque, have demonstrated that Lp(a), either as intact particles or as a lipid-poor apoB100-apo(a) complex or as free apo(a), can accumulate in the arterial intima either in a readily extractable form or bound to components of the intima matrix (42-44). Lp(a) is not usually found in areas of the intima that are not involved in the atherosclerotic plaque (45). This may mean that, pathophysiologically, in the presence of normoLp (a)proteinemia, Lp(a) either fails to traverse the endothelium or is readily metabolized once it reaches the intima. On the other hand, in hyperLp (a)proteinemia, the plasma gradient would favour the transfer and accumulation of Lp(a) in the arterial intima. The possibility also exists that in subjects with a previously established arterial lesion, the transfer of Lp(a) into the area of injured intima may be less dependent on plasma levels of Lp(a), but more so on local vascular endothelial dysfunction or endothelial injury. In the intima as a function of its residence time, it is likely that Lp(a) undergoes chemical changes due to formation of complexes with components of the intima. It avidly binds to arterial proteoglycans (46) and fibronectin (47,48). These modified Lp(a) particles would become atherogenic by preferentially entering the macrophages that reside in the intima and by promoting their transformation into foam cell, potential precursors of the atherosclerotic plaque (49).

It may also promote thrombosis because it has structural similarities with plasminogen (4). The discovery that apo(a) bears close structural similarities to plasminogen stimulated a number of studies to test the hypothesis that Lp(a) in high plasma levels can interfere with known plasminogen functions in the fibrinolytic system, leading to a decreased generation of plasmin. The results of several in-vitro studies support this hypothesis, suggesting a thrombogenic action of Lp(a) (18,37, 50). Consistent with this view are the results of studies documenting the interference of Lp(a) with the binding of plasminogen to the surface of fibrin or fibrin fragments, and observations which indicate that Lp(a) competes for binding of plasminogen to its membrane receptor in endothelial cells and platelets (51,52). An action of surface-bound lipoprotein(a) on tissue-type plasminogen activator has also been reported (53), as well as impairment of the generation of plasmin by fibrin-bound tissue-type plasminogen activator (54). Lp(a) may also have a direct action on endothelial function. In this context, Etingin et al. have shown that Lp(a) can induce the production of tissue plasminogen activator inhibitor by endothelial cells, an action that can promote attenuation of clot lysis (55).

Clinical Significans of Lp(a)

Lp(a) in coronary artery disease

A lot of studies in various populations have examined the association between Lp(a) and coronary heart disease (CHD), including cross-sectional and case-control studies that investigated the association of Lp(a) levels with the presence of CHD, myocardial infarction or disease severity assessed by angiography (5-7,9,11,56-61). Some of the case control studies evaluated, prospectively, the association between Lp(a) levels and the development of future coronary events (myocardial infarction, nonfatal myocardial infarction, and cardiac death) (9,11,59-61). In most instances,

raised Lp(a) levels were associated with the presence or severity of CHD and with an increased risk of future cardiac events. Furthermore, children whose parents sustained a premature myocardial infarction had higher Lp(a) levels than children with healthy parents (62). However, two recent large prospective studies have cast doubt on the role of Lp(a) in CHD because no association was noted between the occurrence of cardiac events and the patients' Lp(a) levels (60,61).

Although Lp(a) facilitates smooth muscle proliferation, its role in restenosis has yielded conflicting results (63). Two recent studies re-examined this issue. In a study of 85 patients undergoing percutaneous transluminal angioplasty, Cooke et al. observed that Lp(a) levels that correlated with baseline disease severity were unrelated to the rate of restenosis (64). Daida et al. noted a much lower restenosis rate in patients whose Lp(a) levels were reduced markedly with LDL apheresis 2 days before and 5 days after angioplasty (65). This could argue toward Lp(a) being important in the acute phase restenosis, or equally that other mitogenic or prothrombotic factors are removed by this procedure. Further studies are needed to explain this interesting observation.

Because Lp(a) is structurally homologous to plasminogen, its role in modulating the action of thrombolytic agents continues to attract attention. MBewu et al. used the reduction in ST segment elevation that follows myocardial infarction as an index of reperfusion after streptokinase treatment, and failed to demonstrate an influence of Lp(a) levels on this process (66). In addition Brugemann et al. found that infarct vessel patency after treatment with anistreplase was unrelated to the Lp(a) levels (67). However, in this study it was demonstrated that in patients in whom the infarct vessel remained occluded, a significant inverse correlation existed between the Lp(a) level and the reduction in plasminogen during the first 1.5h after treatment. In a study of myocardial infarction patients who had not received thrombolytic agents, Moliterno et al. found that the rate of spontaneous thrombolysis correlated inversely with Lp(a) levels (68). These findings suggest that Lp(a) levels have an impact on spontaneous thrombolysis, but their effect is overwhelmed when large doses of thrombolytic agents are used.

Lp(a) in diabetes mellitus

A number of studies have examined the possible alterations of Lp(a) in individuals with diabetes, and conclusions appear to vary depending on the type of diabetes. IDDM may be associated with elevated Lp(a) concentrations. A study by Salzer et al. of 415 children aged 13-14 years with IDDM, as compared with healthy school children matched for age and gender, showed significantly higher concentrations of Lp(a) in the diabetic children (69). A further examination of 170 children with IDDM stratified by the stage of puberty showed that Lp(a) was higher in the IDDM than in the control group (70). When the data were analyzed according to pubertal stage, only pubertal and post-pubertal patients had higher levels compared with control subjects, suggesting that a rise in Lp(a) may occur during puberty in IDDM. Although increased concentrations of Lp(a) were shown in IDDM patients with microalbuminuria (71), there has been no evidence linking Lp(a) concentrations with cardiovascular disease in individuals with IDDM. A recent study by the Pittsburgh Epidemiology of Diabetes Complications Study group showed no associations between Lp(a) concentrations and either peripheral vascular disease or definite myocardial infarction or angina in a group of 186 individuals with IDDM (mean age 34 years) (72). However, prospective studies of larger cohorts are needed to evaluate the etiologic role of Lp(a) for the development of cardiovascular disease in individuals with IDDM.

In contrast to IDDM, the majority of studies in NIDDM failed to show an increase in Lp(a) associated with NIDDM. It is reported that patients with NIDDM have lower (73,74), higher (75,76) or similar (77-81) Lp(a) levels compared with nondiabetic subjects. Recently we have examined if there is any difference in Lp(a) levels between subjects with NIDDM and control subjects (82, 83); the relationship between Lp(a) levels and diabetic control as assessed by glycosylated hemoglobin levels in subjects with NIDDM (82, 83); and the relationship between Lp(a) and coronary artery disease (CAD) as assessed by

coronary angiography in terms of coronary artery score (CAS) in subjects with NIDDM (82,84). Our study confirmed the findings of studies in which Lp(a) levels of the patients with NIDDM were similar to the Lp(a) levels in control subjects (82,84). We found no significant relationship between Lp(a) levels and glycemic control in agreement with other reports of subjects with NIDDM (85).

Whether Lp(a) excess is a risk factor for CAD in NIDDM is not clear. Haffner and colleagues reported that Lp(a) levels were not higher in subjects with NIDDM who died of CAD than in control survivors (86). In contrast, Velho and co-workers found increased Lp(a) levels in subjects with diabetes and a history of myocardial infarction (79). In our comparison of Lp(a) levels in subjects who had NIDDM with and without CAD, those with CAD had significantly higher Lp(a) levels ($p<0.05$). However we did not find a significant correlation between Lp(a) level and CAS in patients with and without NIDDM. This finding is in contrast with the data of Watts and colleagues (87).

Lp(a) in renal disorders

Markedly elevated Lp(a) concentrations have consistently been described in virtually all kinds of renal disease and their treatment modalities. On average, Lp(a) levels are elevated sixfold in patients with severe nephrotic syndrome (88), and two to threefold in patients receiving hemodialysis or peritoneal dialysis as compared to healthy controls (89,90). Therefore 30-70% of patients (depending on the underlying renal disease and treatment modality) have plasma Lp(a) levels above 30mg/dl (in controls <20%) (91). In a large study of the association between Lp(a) and chronic renal failure the observed differences in Lp(a) levels between patients and controls persisted after adjustment for diabetes and ethnicity (92) In this study the type of treatment for chronic renal failure (diet, hemodialysis, or peritoneal dialysis) did not have an effect on Lp(a) concentrations. Lp(a) levels were not correlated with the level of creatinine in the patients' group. It was suggested that the elevation of Lp(a) must occur early in renal failure, or alternatively, elevated Lp(a) levels may promote progression to chronic renal failure (92). It is interesting to note that kidney transplantation in the patients with end-stage renal failure was accompanied by a significant decrease in Lp(a), which was significantly correlated with an increase in creatinine clearance (93). Irish et al. found that the type of treatment of chronic renal failure influences the plasma level of Lp(a) (94). In this study Lp(a) was elevated in patients treated with continuous ambulatory peritoneal dialysis. In patients treated by hemodialysis or renal transplantation, Lp(a) levels were not significantly different from those in controls (94).

Hormonal influences on Lp(a) levels

Both estrogens and androgens appear to effect Lp(a) levels. Henriksson et al. conducted a randomized trial of two therapies in men with prostate cancer. The men were randomized to either high-dose estrogen treatment or to castration by orchiectomy. Estrogen decreased Lp(a) levels by 50% in contrast to a 20% increase in surgically treated men (95). However the results of the study conducted by Özata et al. on hormone replacement therapy for male hypogonadism suggest that androgens have no significant effect on Lp(a) levels (96). Recently Kim et al. investigated the serial changes in Lp(a) lipoprotein levels after the cessation of female sex hormone production by bilateral salpingo-oophorectomy (BSO) and after the replacement of estrogen in the same premenopausal women (97). In the BSO group, the concentration was increased by 24.5% after two months ($p<0.05$) (97). Estrogen replacement therapy reduced the levels by 30.6% at the end of the following two months (97). In another prospective study of the same group, long term effects of hormone replacement therapy on lipid concentrations in postmenopausal women, using estrogen alone and in combination with various progestogens, and the influence of duration of therapy were investigated (98). Estrogen replacement therapy for 12 months lowered the Lp(a) level by 37.1% (98). The addition of progestogen attenuated the Lp(a) lowering effect of estrogen (98). Duration of therapy had minor effects on Lp(a) levels (98).

Although there are few studies reporting that thyroid hormones do not influence Lp(a) levels

(99, 100), there are several reports conducted both in hypothyroid (clinical and subclinical) (101,102) and hyperthyroid patients (103-105) suggesting that thyroid hormones modulate Lp(a) levels .

Treatment of high serum Lp(a) levels

Dietary modification for decreasing high serum Lp(a) levels has generally been disappointing. In studies using low-fat, low calorie diets, no effects on Lp(a) levels were observed and no effect on Lp (a) was seen in 36 individuals fed a lacto-ovo vegetarian diet (106,107). Caloric restriction in short-term studies has not convincingly affected Lp(a) levels (106). However some dietary studies have reported changes in Lp(a) levels. In a study by Mensink et al. on the effect of dietary fatty acids on Lp(a) levels, diets rich in trans-mono-unsaturated fatty acids raised Lp(a) levels (108). In a parallel study, Nestel et al. also showed that plasma Lp(a) levels increased significantly during a diet enriched in a trans-fatty acid, elaidic acid (109). These fatty acids also raise LDL, occurring after commercial hydrogenation of polyunsaturated oils and the average intake in the United States has been estimated to be approximately %3-5 of the total energy (110). The possible impact on Lp (a) levels in the general population remains to be established.

It has been clear that despite the close structural relationship between LDL and Lp(a), few of the hypolipidemic agents that lower LDL levels were able to modulate Lp(a) levels. Neither bile acid resins nor 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG CoA RIs) lowered Lp(a) levels (2,111,112). In contrast, in some studies the use of HMG CoA RIs resulted in a modest increase in Lp(a) levels (112,113).

Nicotinic acid decreases white adipose tissue lipolysis and the delivery of fatty acids to the liver, resulting in a decrease in hepatic VLDL production (106). In addition, nicotinic acid can also reduce Lp(a) levels as a monotherapy or in combination with neomycin (114,115). Seed et al. reported a 36% decrease in Lp(a) levels in hypercholesterolemic individuals with initial Lp(a) levels above 30mg/dl who were given nicotinic acid daily for two months, although only 14 of the initial 26 individuals completed the study because of side effects (116). Lp(a) turnover studies were performed in three individuals and the fractional catabolic rate of Lp(a) was unchanged. This clearly suggested that the reduction of Lp(a) was achieved through a decrease in the synthetic rate (116).

The mechanism by which fibric acid derivatives exert their hypolipidemic effect is not completely understood, but includes the suppression of free fatty acid release from adipose tissue, inhibition of hepatic triglyceride biosynthesis, and increased postheparin lipase activity (106). A lowering of Lp(a) levels as well as a lack of a significant effect on plasma Lp(a) levels have been reported with bezafibrate (117). In a recent double-blind placebo-controlled study, bezafibrate, at a daily dose of 400mg reduced Lp(a) levels by 13% (118) In another double blind, crossover trial with a daily dose of fenofibrate 200 mg treatment similar data was obtained (119).

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