Lipoprotein(a)

The bad cholesterol

Syed S. Habib, *MBBS, FCPS.*

ABSTRACT

The aim of this review is to highlight the role of lipoprotein(a) [Lp(a)] in atherogenesis and coronary artery disease. After 40 years from discovery, Lp(a) still remains an enigma and we are still far in understanding the pathophysiological role of Lp(a). Based on its peculiar structure, Lp(a) has both atherogenic and thrombogenic potentials as it is internalized by macrophages and has structural similarity with plasminogen. The results of the prospective studies performed over the past decade have also shown that Lp(a) is a predictor of coronary artery disease (CAD), even though some of the studies have failed to show a statistically significant difference in Lp(a) levels on subjects that subsequently developed CAD and those that did not. Within the population, the plasma levels can vary from <0.5 mg/dl to >200 mg/dl. There is currently no safe drug for long term treatment of patients with high levels of Lp(a). However, it has been proposed that there is a possibility of interfering with apolipoprotein(a) (apoA) translation by using adenovirus mediated antisense RNA technology. Despite more than 3 decades of intense scientific research, the physiopathological role of Lp(a) is still poorly understood and the extent to which Lp(a) levels should be assessed in clinical practice remain controversial until now.

Saudi Med J 2004; Vol. 25 (4): 429-433

Lipoprotein(a) [Lp(a)] was first identified by Berg[1] in 1963 as a low density lipoprotein (LDL) variant and was initially thought to be a cause of unexplained transfusion reactions. It remained pernicious when previous study succeeded in separating it into its lipid and protein components. They determined that the molecule comprised of a lipid which was very similar to that found in LDL and was linked to a molecule of apolipoprotein(b) (apoB) and a second apolipoprotein called apolipoprotein(a) (apoA).[2] Lipoprotein(a) is the most complex and polymorphic of the lipoprotein particles. It was later found that apoA was linked to apolipoprotein B-100 (apoB100) of LDL by disulfide linkages.[3] The structural gene for apoA is located on chromosome number 6 with the gene for plasminogen, giving a clue that both may have arisen from a common ancestral gene.[4] The most intriguing feature of apoA is that it shares an extensive structural homology with plasminogen, a key proenzyme of the fibrinolytic cascade. Kringle V and the protease domain of apoA share >85% amino acid identity with the corresponding plasminogen domains, even though the protease domain of apoA does not appear to have a catalytic function.[3] The number of kringle IV type 2 repeats, which is encoded by a varying number of copies in the apoA gene,[5] varies both within and among individuals and approximately 35 apoA size isoform have been detected in human plasma.[6] The aim of this article is to highlight the role of Lp(a) in coronary heart disease and thrombogenesis.

From the Department of Physiology, Shifa College of Medicine and Shifa International Hospital, Islamabad, *Pakistan.*

Address correspondence and reprint request to: Dr. Syed S. Habib, Assistant Professor, Department of Physiology, Shifa College of Medicine and Shifa International Hospital, H-8/4, Islamabad, *Pakistan.* Tel. +92 (51) 4446801 Ext. 3377. Fax. +92 (51) 4435046.

Pathogenecity. Based on its peculiar structure, Lp(a) has both atherogenic and thrombogenic potentials. Lipoprotein(a) is believed to contribute to lipid induced atherogenesis similar to LDL particles.[7] Lipid peroxidation of LDL particles modifies its structure and makes it susceptible to be engulfed by macrophages, leading to foam cell formation and initiation of atherosclerosis.[8] Compared with LDL, it contains lower amount of antioxidants and exhibits a high affinity to extracellular matrix and fibrinogen, which prolongs residence time in the subintima.[9] A number of potential mechanisms have been invoked to explain the role of Lp(a) in atherogenesis. There is an evidence that oxidized Lp(a) can be internalized by macrophages, thus, contributing to foam cell formation.[10,11] Both properties of Lp(a) facilitate its oxidative modification and may enhance its capacity to cause injury.

There are 3 potential mechanisms whereby Lp(a) may exert a prothrombic effect by inhibiting generation of plasmin, a protease causing fibrinolysis (**Figure 1**). Lipoprotein(a) competes with plasminogen for binding to endothelial cells and fibrin. This leads to reduced activation of endothelial cell and fibrin dependent activation of plasminogen by tissue plasminogen activator (t-PA). Furthermore it interferes with plasminogen activation by reducing the activity of t-PA by competitive inhibition and by itself enhances the expression of plasminogen activator inhibitor 1 (PAI 1).[4] It is also possible that the pathogenicity of Lp(a) may also reside in unique functions of this lipoprotein that are independent of its structural similarity to either LDL or plasminogen.[10]

Metabolism. So far, little is known on the metabolic pathways involved in Lp(a) handling. Despite the presence of LDL, apoA imparts to Lp (a)'s unique properties with respect to synthesis and catabolism. In fact, apoB-100 in Lp(a) particles does not appear to mediate the catabolism of this lipoprotein via the LDL receptor, thus, suggesting that the attachment to apoA produces a steric hindrance or a conformation 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.[12] Plasma Lp(a) concentration is primarily controlled at the level of the gene that encodes apoA,[13] and an inverse correlation has been shown between plasma Lp(a) concentration and apoA size that may arise, at least in part, from the relatively inefficient secretion of the larger apoA isoform from hepatocytes.[14] We are still far from understanding the pathways involved in Lp(a) catabolism and the physiological function of this lipoprotein.

Lipoprotein(a) and coronary artery disease (CAD). Although, clinical interest in this particle was limited for many years, it was stimulated again in the late 1970s with the discovery that high concentrations of Lp(a) may be associated with CAD. Moreover, it was found that raised values are associated with severity of CAD and with increased risk of future cardiac events. The relative risk of myocardial infarction has been reported to be 1.75 fold higher when Lp(a) levels are above 30 mg/dl.[15] Numerous follow up studies have now confirmed that Lp(a) is an independent risk factor for CAD.[16] In contrast to the initial studies in which Lp(a) was considered to be a fixed parameter, it has been found that it is changeable and is significantly affected by lipoproteins metabolic pathways. This observation may have important implications regarding the design of therapies aimed at reducing CAD risk due to high Lp(a) concentrations.[17]

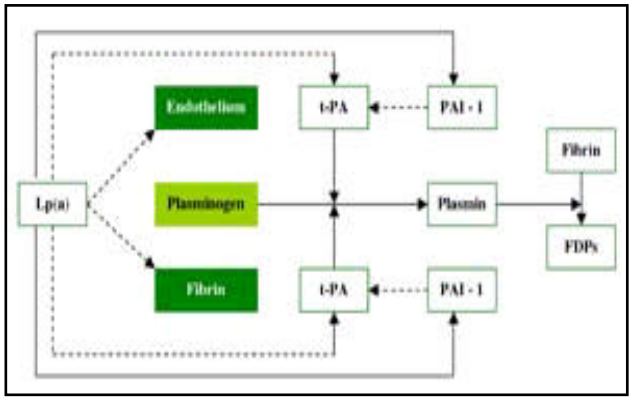

Figure 1 - Representation of the interaction between lipoprotein(a) and fibrinolytic system. Lipoprotein(a) competes with plasminogen for binding to endothelium and fibrin. FDPs - Fibrin degradation products, t-PA - Tissue plasminogen activator, PAI-1 - Plasminogen activator inhibitor

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. 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 that subsequently developed CAD and those that did not.[18] 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 apoA size isoforms.[19,20] Additionally, it has been demonstrated that apoA 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 apoA size.[21] This can have a great effect on the interpretation of clinical studies if the distribution of apoA size isoform 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.[22] In a study of men with CAD and elevated apoB and LDL cholesterol, Lp(a) values at baseline were the best predictor of CAD severity. 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.[23] Kronenberg et al[24] 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 apoA 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) 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.

A meta analysis of 27 prospective studies with information on 5436 CAD cases observed during mean follow up of 10 years provided the most reliable assessment of the association between plasma Lp(a) and CAD.[25] In this regard, it was already been demonstrated that both Lp(a) levels and apoA isoform size distribution vary between racial groups.[20] As such, it is possible that apoA 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 apoA phenotypes in different racial groups are required to address this question. It is also clear that additional structure function studies need to be carried out to address the mechanism by which low molecular weight (LMW) apoA isoform confer increased risk in advanced lesions. Finally, the question arises as to whether Lp(a) concentration and apoA phenotypes should be determined in the general population. The relative risk of myocardial infarction has been reported to be 1.75 fold higher when Lp(a) levels are above 30 mg/dl. Numerous follow up studies have now confirmed that Lp(a) is an independent risk factor for CAD.[26]

Lipoprotein(a) in clinical studies. Population Lp(a) values follow a skewed distribution with median values lower than mean values, thus sometimes necessitating the use of non parametric statistics when evaluating a data.[3] Previous study reported that based on the Physician's Heart Study there was no evidence of association between baseline plasma concentration of Lp(a) and future risk of thromboembolic stroke in healthy individuals.[27,28] While Gillum[29] included Lp(a) in a review paper as one of the risk factors for stroke in black Caucasians. In another study, Lp(a) was suggested as one of the important risk factors for venous thromboembolism during childhood.[30]

Racial differences have also been reported with black caucasians having a less skewed distribution and higher levels than white caucasians.[31] Age related differences are also relevant. Lipoprotein(a) levels are reported to increase during the early years of life, reaching a plateau in adulthood.[32] No significant difference has been observed as far as gender is concerned. However, gender related differences may arise during later years of life when women report to have higher values after the menopause. The significant decrease in its level has been seen with estrogen and progesterone therapy.[33,34] Lipoprotein(a) is also raised in patients of hyperlipidemias.[35] Lipoprotein(a) has also been shown to be an acute phase reactant with levels increasing after myocardial infarction,[36] stroke[37] and coronary artery bypass graft.[38] Studies have also reported that Lp(a) levels are increased in renal diseases.[39] Raised levels of Lp(a) have been observed in smokers but it is proposed that the impact of cigarette smoking on premature CAD incidence far out weighs abnormalities in any of the major lipid or lipoprotein fractions, hypertension or glucose intolerance.[15] Lipoprotein(a) continues to be a focus of intense research and new exciting data have been continuously documented. 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 apoA isoform in clinical practice.

Shall we perform Lp(a) estimation routinely? 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. Within the population the plasma levels can vary from less than 0.5 mg/dl to over 200 mg/dl.[40] The lack of standardized and apoA size independent methods for Lp(a) measurement makes it impossible to compare results from different clinical studies. Different methods have been used for measurement of Lp(a). Early methods included immunodiffusion,

radioimmunoassay but later was replaced by more sensitive and less laborious enzyme linked immuno absorbent assays.[3] The cutoff Lp(a) value to classify subjects as being at increased risk for CAD varies greatly among studies and ranges from 20-40 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. As the National Institutes of Health National Heart, Lung and Blood Institute (NIH-NHLBI) 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).[41,42] However, as Lp(a) values continue to emerge as a potent CAD risk factor, at least in Caucasians, as also confirmed by the present study by Kronenberg et al[24] 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, It has been suggested that clinicians use a conservative Lp(a) value of 20 mg/dl, particularly in patients with concomitantly elevated LDL cholesterol. Given the uncertainty related to Lp(a) cutoff value, it has been suggested that clinicians use a conservative Lp(a) value of 30 mg/dl, particularly in patients with concomitantly elevated LDL cholesterol.[43,44]

At present, it does not seem cost effective to add the estimation of apoA isoform to assess CAD risk assessment. Clinicians should decide on an individual basis whether the determination of apoA isoform is necessary to generate a more complete risk profile. Lipoprotein(a) continues to be a focus of intense research and a 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 apoA isoform in clinical practice.

Treatment of high risk levels of Lp(a). There is currently no safe drug for long term treatment of patients with high levels of Lp(a). However, it has been proposed that there is a possibility of interfering with apoA translation by using adenovirus mediated antisense RNA technology. The administration of antisense apoA has led to an almost complete disappearance of apoA from plasma. As antisense technology becomes routine for human use, it may be used for treatment of high risk levels of Lp(a).[45] Apolipoprotein(a), however, suppresses angiogenesis and may interfere with the infiltration of tumor cells.

Despite more than 3 decades of intense scientific research on the structure and biochemistry of Lp(a), the physiopathological role of Lp(a) is still poorly understood. In spite of its recognition as a risk factor for CAD, the role of Lp(a) in atherogenesis and the extent to which Lp(a) levels should be assessed in clinical practice remain controversial until now. However, intense research is continuing on Lp(a) and new exciting data are continuously being produced. Thus, both the prothrombic and atherogenic mechanisms of Lp(a) may be better elucidated in the near future, providing more defined indications for the determination of Lp(a) values and apoA isoform in clinical practice.

References

1. Berg KK. A new serum type system in man: The Lp system. ***Acta Pathol Microbiol Scand*** 1963; 59: 369-382.
2. Merz B. Medical News and Perspectives. Lp(a) joins other serum cholesterol lipoproteins as risk determinant. ***JAMA*** 1989; 261: 2013-2014.
3. Wieringa G. Lipoiprotein(a): what's in a measure. ***Ann Clin Biochem*** 2000; 37: 571-580.
4. Hajjar KA. Vascular function in Hemostasis: Lipoprotein (a) and fibrinolytic assembly. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn U. Williams Hematology. 6th ed. New York (NY): The McGraw-Hil; 2001: p. 1451-1470.
5. Lackner C, Cohen JC, Hobbs HH. Molecular definition of the extreme size polymorphism in apolipoprotein(a). ***Hum Mol Genet*** 1993; 2: 933–940.
6. Marcovina SM, Zhang ZH, Gaur VP, Albers JJ. Identification of 34 apolipoprotein(a) isoforms: differential expression of apolipoprotein(a) alleles between American Blacks and Whites. ***Biochem Biophys Res Commun*** 1993; 191: 1192–1196.
7. Kronenberg F, Steimetz A, Kostner GM and Dieplinger H. Lipoprotein(a) in health and disease. ***Crit Rev Clin Lab Sci*** 1996; 33: 495-543.
8. Esterbauer H, Wag G, Puhl H. Lipid peroxidation and its role in atherosclerosis. ***Br Med Bull*** 1993; 49: 566-576.
9. Loscalzo J, Weinfeld M, Fless GM, Scannu AM. Lipoprotein(a), fibrin binding and plasminogen activation. ***Arteriosclerosis*** 1990; 10: 240-245.
10. Marcovina SM, Koschinsky ML. Lipoprotein(a) concentration and apolipoprotein(a) size A synergistic role in advanced atherosclerosis? ***Circulation*** 1999; 100: 1151-1153.
11. Haberland ME, Fless GM, Scanu AM, Fogelman AM. Malondialdehyde modification of lipoprotein(a) produces avid uptake by human monocyte-macrophages. ***J Biol Chem*** 1992; 267: 4143–4151.
12. Parhofer KG, Demant T, Ritter MM, Geiss HC, Markus Donner M, Schwandt P. Lipoprotein(a) metabolism estimated by non steady-state kinetics. ***Lipids*** 1999; 34: 325-335.
13. Kraft HG, Kochl S, Menzel HJ, Sandholzer C, Utermann G. The apolipoprotein (a) gene: a transcribed hypervariable locus controlling plasma lipoprotein (a) concentration. ***Hum Genet*** 1992; 90: 220-230.

14. Sandholzer C, Hallman DM, Saha N, Sigurdsson G, Lackner C, Csaszar A et al. Effects of the apolipoprotein(a) size polymorphism on the lipoprotein(a) concentration in 7 ethnic groups. ***Hum Genet*** 1991; 86: 607-614.
15. Kostner GM, Avogaro P, Cazzolato G, Marth E, Bitollo BG, Quinci GD. Lipoprotein(a) and the risk of myocardial infarction. ***Atherosclerosis*** 1981; 38: 51-54.
16. Bostom AG. Elevated plasma lipoprotein (a) and coronary heart disease in men aged 53 years and younger. A prospective study. ***JAMA*** 1996; 276: 544-548.
17. Rainwater DL. Lp(a) concentrations are related to plasdma lipid concentrations. ***Atherosclerosis*** 1996; 127: 13-18.
18. Marcovina SM, Koschinsky ML. Lipoprotein(a) as a risk factor for coronary artery disease. ***Am J Cardiol*** 1998; 82: 57U–66U.
19. Kraft HG, Lingenhel A, Pang RW, Delport R, Trommsdorff M, Vermaak H et al. Frequency distributions of apolipoprotein(a) kringle IV repeat alleles and their effects on lipoprotein(a) levels in Caucasian, Asian, and African populations: the distribution of null alleles is non-random. ***Eur J Hum Genet*** 1996; 4: 74–87.
20. Marcovina SM, Albers JJ, Wijsman E, Zhang ZH, Chapman NH, Kennedy H. Differences in Lp(a) concentrations and apo(a) polymorphs between Black and White Americans. ***J Lipid Res*** 1996; 37: 2569–2585.
21. Marcovina SM, Albers JJ, Gabel B, Koschinsky ML, Gaur VP. Effect of the number of apo(a) kringle 4 domains on the immunochemical measurements of Lp(a). ***Clin Chem*** 1995; 41: 246–255.
22. Armstrong VW, Cremer P, Eberle E, Manke A, Schulze F, Wieland H et al. The association between serum Lp(a) concentrations and angiographically-assessed coronary atherosclerosis: dependence on serum LDL levels. ***Atherosclerosis*** 1986; 62: 249–257.
23. Maher VM, Brown BG, Marcovina SM, Hillger LA, Zhao X-Q, Albers JJ. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). ***JAMA*** 1995; 274: 1771–1774.
24. Kronenberg F, Kronenberg MF, Kiechl S, Trenkwalder E, Santer P, Oberhollenzer F et al. Role of lipoprotein(a) and apolipoprotein(a) phenotype in atherogenesis: prospective results from the Bruneck study. ***Circulation*** 1999; 100: 1154–1160.
25. John D, Collins R, Peto R. Lipoprotein (a) and Coronary Heart Disease, Meta-Analysis of Prospective Studies. ***Circulation*** 2000; 102: 1082-1085.
26. Bostom AG. Elevated plasma lipoprotein (a) and coronary heart disease in men aged 53 years and younger. A prospective study ***JAMA*** 1996; 276: 544-548.
27. Wityk RJ, Kittner SJ, Jenner JL, Hewbel JR, Ebstein A, Wozniak MA. Lipoprotein(a) and the risk of ischaemic stroke in young women. ***Atherosclerosis*** 2000; 150: 389-396.
28. Ridker PM, Stampfer MJ, Hennekens CH. Plasma concentrations of lipoprotein(a) and the risk of future stroke. ***JAMA*** 1995; 273: 1269-1273.
29. Gillum RF. Risk factors for stroke in blacks: a critical review. ***Am J Epidemiol*** 1999; 15: 1266-1274.
30. Nowak GU, Ralf J, Marion H, Koch HG, Munchow N, Assmann G et al. Increased lipoprotein(a) is an important risk factor for venous thromboembolism in childhood. ***Circulation*** 1999; 100: 743-748.
31. Evans RW, Bunker CH, Ukoli FA, Kuller LH. Lipoprotein (a) distribution in a Nigerian population. ***Ethn Health*** 1997; 2: 47-58.
32. Wilcken DL, Wang X, Dudman NP. The relationship between infant and parent Lp(a) concentrations. ***Chem Phys Lipids*** 1994; 67/68: 299-304.
33. Farish E, Rolton HA, Barnes JF, Hart DM. Lipoprotein(a) concentrations in postmenopausal women taking norethisterone ***BMJ*** 1991; 303: 694.
34. Shlipak MG, Simon JA, Vittinghof E, Conner EB, Knop RH. Estrogen and progestin, Lipoprotein(a), and the risk of recurrent coronary heart disease after menopause. ***JAMA*** 2000; 12: 242-248.
35. Bartens W, Rader DJ, Talley G, Brewer HB Jr. Lipoprotein (a) in patients with hyperlipidaemia. ***Eur J Clin Invest*** 1995; 25: 647-653.
36. Slunga L, Johnson O, Dahlen GH, Eriksson S. Lipoprotein (a) and acute phase proteins in acute myocardial infarction. ***Scand J Clin Lab Invest*** 1992; 52: 95-101.
37. Woo J, Lam CWK, Kay R, Woing HY, Teoh R, Nicholls MG. Acute and long term changes in serum lipids after acute stroke. ***Stroke*** 1990; 21: 1407-1411.
38. Cobbaert C, Segeant P, Meyns B, Szesci J, Kesteloot H. Time course of serum Lp(a) in men after coronary artery bypass grafting. ***Acta Cardiol*** 1992; 47: 529-542.
39. Thomas ME, Freestone A, Varghese Z, Persaud JW, Moorhead FJF. Lipoprotein (a) in patients with proteinuria. ***Nephrol Dial Transplant*** 1992; 7: 597-601.
40. Utermann G. The mysteries of lipoprotein(a). ***Science*** 1989; 246: 904-910.
41. Garg A, Grundy SM. Nicotinic acid as therapy for dyslipidemia in non insulin dependant diabetes mellitus. ***JAMA*** 1990; 264: 723-726.
42. Hernandez-Mijares A, Lluch I, Vizcarra E, Martinez-Triguero ML, Ascaso JF, Carmena R et al. Ciprofibrate effects on carbohydrate and lipid metabolism in type 2 diabetes mellitus subjects. ***Nutr Metab Cardiovasc Dis*** 2000; 10: 1-6.
43. Maher VM, Brown BG, Marcovina SM, Hillger LA, Zhao XQ, Albers JJ. Effects of lowering LDL cholesterol on the cardiovascular risk of lipoprotein(a). ***JAMA*** 1995; 274: 1771-1774.
44. Marcovina SM, Albers JJ, Jacobs DR. Lipoprotein(a) concentrations and apolipoprotein(a) phenotype in Caucasians and African Americans: the CARDIA study. ***Arterioscler Thromb*** 1993; 13: 1037-1045.
45. Kostner KM, Kostner GM. Lipoprotein(a): still an enigma? ***Curr Opin Lipidol*** 2002; 13: 391-396.