Review Article:

Lipoprotein(a): An Independent Risk factor of Cardiovascular Disease

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Abstract

Background: *Cardiovascular disease is currently one of the most common causes of morbidity and mortality in developed and developing countries. Many traditional risk factors such as age, gender, smoking, diabetes mellitus, dyslipidemia and hypertension play an important role in the development of vascular disorders. Lipoprotein (a) or Lp (a), an intriguing lipoprotein particle is also considered to be an important risk factor for the development of cardiovascular disease. Lp(a) is a LDL-like molecule consisting of an apolipoprotein B-100 (apo B-100) particle attached by a disulphide bridge to a unique protein, apolipoprotein(a)/ apo(a) which distinguishes it from LDL. Many epidemiological studies have reported the positive associations of Lp(a) concentration with atherosclerosis, coronary artery disease and stroke.*

Keywords: *Lipoprotein (a), Pathogenicity, Cardiovascular Diseases, Lp (a) Lowering Measures.*

Introduction: Atherosclerosis is a complex silent process characterized by amorphous lipid accumulation in the intima, which may result in coronary heart disease[1]. High serum cholesterol concentrations carried by low density lipoproteins (LDL), high blood pressure, diabetes and cigarette smoking have been established as major risk factors for atherosclerosis. A number of epidemiological and clinical studies have now established that high plasma concentrations of the lipoprotein (a), an LDL-like particle is also a major and independent risk factor for coronary heart disease[2]. For instance, in a recent meta-analysis of statin trial data, those with Lp (a) concentrations above 50 mg/dl were at 35% higher risk of incident CVD events compared to those with Lp(a) <15 mg/dl after adjusting for confounders[3-4].

Lp(a) was discovered in human serum in 1963 by Kare Berg during a study of variation in LDL antigenicity[5]. Lp (a) is LDL like particle that consist of one molecule of apolipoprotein (a) and another molecule of apolipoprotein B-100. Apo (a) covalently bound to apo B-100 by disulphide bond. Lp (a) is a plasma lipoprotein synthesized by the liver and circulated in blood. Lp (a) plasma concentrations mainly controlled by LPA gene located on chromosome 6q26-27[6].The serum level of Lp (a) is mostly genetically determined and not very much influenced by gender, dietary habit, fasting state or physical activity[7].

LPA is structurally similar to plasminogen, the precursor for plasmin that degrades fibrin in blood clots. Due to this similarity, LPA can competitively inhibit plasmin activity and thereby increase risk for thrombosis[8-9]. Additionally Lp(a) transports the more atherogenic pro-inflammatory oxidized phospholipid which attract inflammatory cells to vessel wall and leads to smooth muscle cell proliferation and plaque formation[10]. The atherogenic properties of Lp (a) levels are expressed over 30 mg/dl[11].

There is no peer-reviewed evidence with regard to lifestyle management (exercise and diet) for reduction of serum Lp (a). Management of elevated Lp (a) includes consideration of pharmacologic intervention. Statin therapy has mixed and minimal effects on Lp (a). However, nicotinic acid has had the longest and most robust history for reduction of Lp(a) [9,12].

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Structure of Lp (a):
Lp (a) is a large "sticky" lipoprotein particle which is formed in the liver and found in the plasma. It consists of a LDL-like core lipoprotein molecule with apolipoprotein B-100/apo-B100, to which a glycoprotein of variable molecular weight, apolipoprotein (a)/apo (a), is covalently bound via a cysteine cysteine disulphide bond (Cys 4326 and Cys-4057)[13]. Apo (a) was formerly termed "Lipoprotein(a) antigen". Apo (a) is a large glycoprotein that exhibits size heterogeneity among individuals. Apo (a) is composed of repeating kringle-IV and a protease-like domain. Chemically, Lp (a) consists of approximately 30% protein, 10% carbohydrates, 37% cholesterol +cholesteryl esters, 18% phospholipids and 5% triglycerides[14].

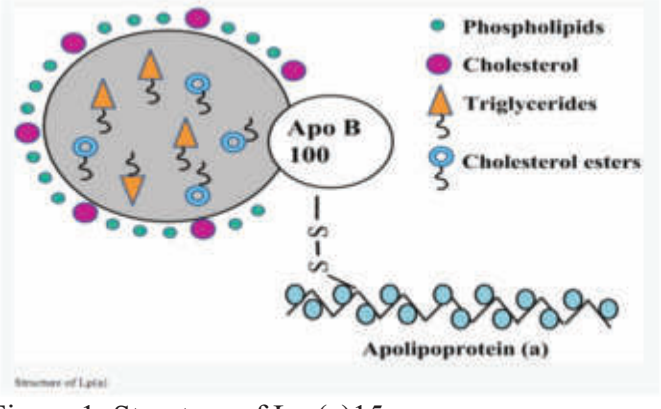

Figure 1: Structure of Lp (a)15

Biosynthesis of Lp(a):
The protein part of Lp(a) consists of two main components: apo B-100 and apo(a). In vitro studies have shown that apo(a) synthesis takes place in hepatocytes and its association with apo B-100 should occur on cell surface[16]. Thus, the liver has been described as the major site of Lp (a) synthesis. The locus for the apo(a) gene is situated at chromosome-6. The rate of apo (a) biosynthesis is significantly influenced by the promoter activity and its activation by transcription factors and nuclear receptors. It is evident that the apo (a) promoter contains more than 70 transcription factors including HNFs, FXR, PPARs, RXR, SREBPs, CCAAT-Enhancer, IL-6. The researcher suggested that the apo(a) promoter is the key for apo(a) transcription and the abundance of apo(a) in blood plasma[17].

Assembly of Lp (a):
The majority of evidences were suggested that Lp(a) assembly occurs extracellularly, either in circulation or at the hepatocytes surface[18]. However, some kinetic studies in human also suggested the intracellular assembly of Lp(a)[19]. Studies over the last decade have indicated that Lp (a) is assembled in a two steps. The first is noncovalent docking of the KIV-5 to KIV-8 domains to the N terminus of apoB-10019. In the second step, the covalent binding of apo (a) to apoB occurs through the formation of a disulphide bond between apo (a) Cys4057 and apo BCys 432620. Additional non-covalent interactions play accessory roles in promoting, mediating and reinforcing the association between the apolipoprotiens[21].

Lp (a) Genetics:
Lp (a) can be reasonably considered a genetically determined variant of LDL. The human apo(a)/LPA gene located in a gene cluster within 400kb of genomic DNA on the telomeric region of chromosome-6 (6q26-27)[22]. LPA alleles are expressed co-dominantly. The apo(a) gene belongs to a puzzling gene family includes several similar sequences encoding plasminogen, prothrombin, t-PA, urokinase-A chain, coagulation factor-XII, macrophage stimulating factor and hepatocytes growth factor[23]. According to amino acid sequencing and cDNA cloning, apo (a) consists of repeated tri-loop structure referred to as kringles and includes 10 unique copies of kringle-IV(K-IV1 to K-IV10), which additionally includes variable numbers of identical K-IV type-2 repeatswhich ranges from3 to >40 and a protease like domain that is catalytically inactive[24].
Each K-IV type-2 copy has a size of ~5.5 kb and consists of 2 exons. Kringle-IV copies of plasminogen in apo(a) are similar but not identical. Variability in kringle-IV type-2 repeat is known as apo(a) isoforms. There are 34 different isoforms of apo(a) have been identified[25-26]. Isoforms sizes ranging from 300-800 kDa have been determined by SDS-PAGE. Individuals expressing a low number of K-IV repeats resulting in so called small apo(a) isoforms (upto 22 K-IV repeats) and individual with high number of K-IV repeats resulting in large apo(a) isoforms. There is inverse correlation between the size of apo(a) isoforms and plasma levels of Lp(a)[27]. In addition to variations in K-IV type 2 repeats (14%), several SNPs (6%), splice site mutation (6%) and nonsense mutation (2%) explain the variability in blood Lp (a) levels. In particular, SNPs rs3798220 and rs10455872 have been strongly associated with both increased Lp(a) and increased risk for CAD.

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Individual who consisting one risk allele of two SNPs had a 1.5 fold elevated risk for CAD and individual consist two alleles had a 2.5 fold increased risk for CAD[28-29].

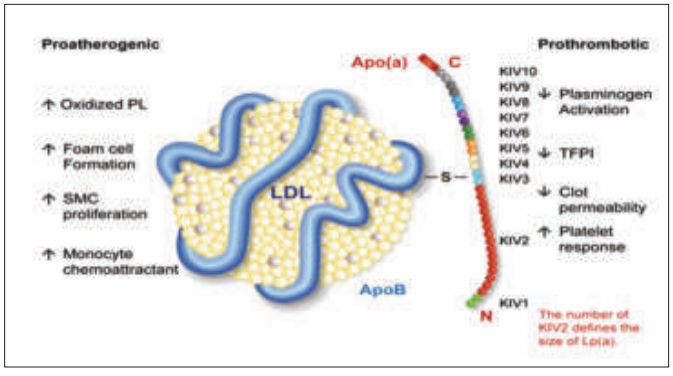

Figure 2: Genetic structure of Lp (a)30

Main Physiochemical Properties and Composition of LDL and Lp (a):31

A. Physiochemical Properties	LDL	Lp(a)
i. Molecular mass (Dalton)	2.9×10^6	$(3.8 - 4) \times 10^6$
ii. Diameter (nm)	25.19 ± 0.1	28.3 ± 0.5
iii. Density (g/L)	1019 - 1063	1006 - 1125
iv. Half-life (days)	2-3	3-4
B. Composition (%)	**LDL**	**LP(a)**
i. Protein	26-31	17-29
ii. Free cholesterol	9	6-9
ii. Esterified cholesterol	40-43	35-46
iv. Triglyceride	4-6	4-8
v. Phospholipids	20-22	17-24

Reference Range of Serum Lp(a):
At present, there are different methods to measure Lp(a). But a standardized international reference material has been developed and is accepted by the WHO Expert Committee on Biological Standardization and the International Federation of Clinical Chemistry and Laboratory Medicine[6].
Lipoprotein(a)/Lp (a) :

Desirable	: <14 mg/dl	(<35 nmol/L)
Borderline risk	: 14- ≤30 mg/dl	(35-75 nmol/L)
High risk	: 31-50 mg/dl	(75-125 nmol/L)
Very high risk	: >50 mg/dl	(>125 nmol/L)

Methods of Lp(a) Measurement:
Several types of Lp(a) assays are currently available, some commercially; prominent among them are[32]-

a) Immunonephelometric assays
b) Immunoturbidometric and fluorescence assays
c) Latex immunoassays
d) Sandwich Enzyme Linked Immunosorbent Assays (ELISAs)
e) Non-competitive ELISAs

Whom to Screen for Lp(a):
As numerous studies confirming Lp(a) is an important, independent predictor of cardiovascular disease and shows a strong correlation between elevated Lp(a) and cardiovascular disease. The European Atherosclerosis Society (EAS 2010) currently recommends that any patient with one of the following risk factors should be screened for Lp(a):[32]
(i) Premature cardiovascular diseases,
(ii) Familial hypercholesterolaemia,
(iii) Family history of premature cardiovascular diseases,
(iv) Family history of premature elevated Lp(a),
(v) Recurrent cardiovascular disease despite statin treatment,
(vi) ≥3% 10-year risk of fatal cardiovascular disease according to the European guidelines and
(vii) ≥10% 10-year risk of fatal and/or non-fatal cardiovascular diseases according to the US guidelines.

Pathogenicity of Lp(a):
Lp(a) is said to be a genetic variant of LDL and shows a high degree of structural homology with plasminogen. Since Lp(a) resembles both LDL and plasminogen, itcould possibly act as a link between atherosclerosis and thrombosis[33]. The accumulation of Lp(a) on the surface of fibrin and cell membranes as well as the inhibition of plasmin generation favors the deposition of fibrin and cholesterol at sites of vascular injury[34]. Recent studies have shown that Lp(a) inhibits the generation of Transforming Growth Factor-b (TGF-b) leading to migration and proliferation of smooth muscle cells into the intima, thus further enhancing the formation of atheroma plaque[35].
Other athero-thrombogenic mechanisms of Lp(a) include:
(a) Modification of protein synthesis: Lp(a)may stimulate the expression of PAI-1 (Plasminogen Activator Inhibitor-1) and inhibit the synthesis of t-PA (tissue Plasminogen Activator) by endothelial cells. Thus, inhibition of tPA by PAI-1 and low t-PA antigen levels may enhance Lp(a)-dependent

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hypofibrinolysis[36].
(b) Binding of Lp(a) to extracellular matrix Components: Binding of Lp(a) to ECM components like proteoglycans or glycosaminoglycans leading to accumulation of Lp(a) in the vascular wall[37].
(c) Oxidation of Lp(a): The Lp(a) and LDL particles are sensitive to oxidative processes. Phagocytosis of oxidized Lp(a) and LDL particles results in the formation of foam cells[38]

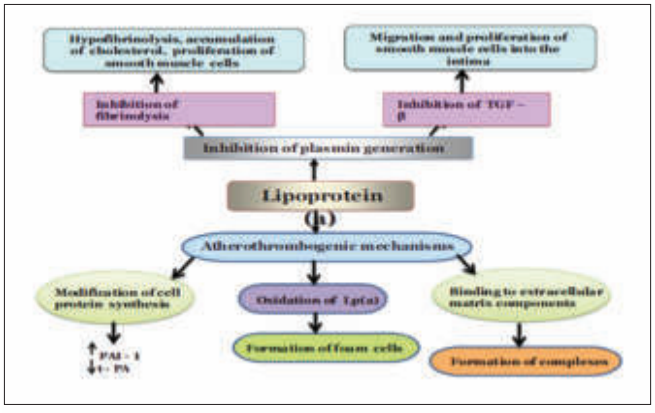

Figure 3: Schematic diagram representing different modes of action of Lp(a) in vessel wall[15]

Lp(a) and Cardiovascular Diseases:
A series of studies have suggested a causal link between circulating Lp(a) and CHD2,[39-40]. Amongthe recognized risk factors of atherosclerosis, Budde etal found that only Lp(a) plasma levels correlated significantly with the vessel score, stenosis score and extent score[41]. Habib et al, demonstrated that Lp(a) levels were associated with more severe and diffuseblockage of the coronary vessels in a Saudi population[42]. In a recent meta-analysis of 36 cohort studies, pooling 126,634 individuals, there was a16% and 10% relative increase in CHD events and stroke, respectively, for each standard deviation increase in Lp(a)[39]. Similarly, in the Copenhagen City Heart Study, participants with Lp(a) levels above the 90th percentile and 95th percentile had a 1.9-fold and 2.6-fold increasedrisk of myocardial infarction (MI) over a 16-year follow-up period, respectively, when compared to individuals with Lp(a) levels <5 mg/dL (22nd percentile)[43].
In addition, in the PROCAM study, participants with Lp(a) ≥20 mg/dl; had an increased riskfor coronary events compared to those with lower levels, especially if they had an increased LDL-C and decreased HDL-C level[44].The importance of Lp(a) in the pathophysiology of ACS may be even more pronounced in younger individuals, particularly in those <45 years old, in whom elevated Lp(a) levels (>120 nmol/L, 80th percentile) are associated with a 3-fold increased risk of MI[45-46]. This likely reflects the importance of other, traditional atherosclerotic risk factors in older individuals in contrast to a more important role of Lp(a) in younger individuals.
Another recent very large 20-year prospective cohortstudy of 3467 blacks and 9851 whites showed a graded risk between Lp(a) concentration and incident CVD events whichwas significant only when the highest and lowest quintileswere compared with respective HRs of 1.35 and 1.27 for the two populations[47]. A high serum Lp(a) level may be a high-risk factor for CCSP (clinical coronary stenosis progression) and restenosis after PCI (percutaneouscoronary intervention). In a study serum Lp(a) concentrations ≥25 mg/dl were found in 14 of 21 patients (67%) with rapid progression of coronary artery disease but in only 19 of 58 patients (33%) in the group without progression[48]. In addition, recent evidence suggests that genetic variation in the LPA locus mediated by Lp(a) concentration may also predict aortic valve stenosis[49]. However, some studies failed to demonstrate a positive correlation between the increasing Lp(a) concentrations and the severity of CHD[50-51].

Lp(a) Catabolism:
Lp(a) is thought to be catabolized primarily by hepatic and renal pathways, but these metabolic routes do not appear to govern plasma Lp(a) level[52]. A variety of cellular receptors have been suggested to play a role in Lp(a) clearance including the LDL receptor, the VLDL receptor, the LDL receptor-related protein, plasminogen receptors, asiaglycoprotein receptor, plasminogen receptor and megalin gp330. Reblin et al reported that neither LDL receptor nor LRP plays a significant role in Lp(a) removal in human[53]. Lp(a) binds to two other related receptors in the LDLR family-VLDL receptor and megalin gp330 which have higher affinity than LDLR or LRP[46-47]. A combination of in vitro and in vivoclearance studies in mouse suggest that the VLDL-receptor could play a role in Lp(a) removal in non-hepatic tissues like kidney, heart, adipose tissue and skeletal muscle[54].
Other in vitrostudies in mouse suggested that megalingp330 also involved in Lp(a) uptake and degradation[55]. Megalin is an endocytotic receptor expressed on the plasma membrane of epithelial cells andmost abundantly expressed in thyroid tissue and

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to a much lower extent in the proximaltubule cells of the kidney and in skeletal muscle. Lp (a) binds to megalin and is taken up and degraded in megalin expressing fibroblasts[56].

Lp(a) Lowering Measures:

Currently, there are few available options for lowering Lp(a). Niacin has been shown to significantly reduces the plasma Lp(a) level by decreasing its synthesis rate. Extended-release niacin reduces Lp(a) level by 25% to 30% in dose dependent manner (1gm/day or 2gm/day)[57].Other agents that might reduce Lp(a) levels are as follows:L-carnitine-a combination of L-lysine and ascorbate, CETP (cholesterol ester transfer protein)-inhibitors (Torcetrapib, Dalcetrapib and Anacetrapib), PCSK-9 (Proprotein convertase subtilisin/kexin type 9) inhibitors (evolocumab or alirocumab) and antitocilizumab antibody-that can block IL-6 signaling and is still in an experimental phase[58].

Mipomersen, approved by FDA to be used in homozygous familial hypercholesterolemia in January 2013, might be a promise to decrease Lp(a) levels. Mipomersen is a second generation antisense oligonucleotide that actson messenger RNA, inhibiting apo-B synthesis by the liver, reducing the concentration of lipoproteins that contain that apolipoprotein. That drug can reduce both LDL-cholesterol and Lp(a) levels; however, the safety of its use has notbeen established[59].Another most promising medication, at the time being, appears to be APO(a)Rx, a specific antisense oligonucleotides drug from ISIS® pharma. It suppresses apo(a) protein synthesis and preventing the generation of Lp(a) particles[60].

Conclusion:

Epidemiologic and genetic studies provide evidence that Lp(a) is an independent, causal risk factor for cardiovascular disease. Elevated Lp(a) levels promote atherosclerosis and thrombosis. So, Lp(a) screening might be a useful biomarker for detecting individuals with a high CVD risk.

Conflict of Interest: The authors declare to have no conflicts of interest.

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