

Lipoprotein(a) and its Clinical Importance

Malihe Moammeri Salahshooh (MSc)

Department of Biochemistry, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Farnaz Zahedi Avval (MD, PhD)

Department of Biochemistry, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Fatemeh Sadabadi (PhD)

Department of Modern Sciences and Technologies, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Corresponding author: Malihe Moammeri Salahshooh

Email: Malihe.salahshur@gmail.com

Tel: +989155584570

Address: Mashhad University of Medical Sciences, Mashhad, Iran

Received: 29 Dec 2018

Revised: 17 Jun 2019

Accepted: 16 Jul 2019



This work is licensed under a [Creative Commons Attribution 4.0 License](https://creativecommons.org/licenses/by-nc/4.0/).

ABSTRACT

Reports have shown that lipoprotein (Lp)(a) can serve as an indicator of atherosclerosis and cardiovascular diseases. Several cardiovascular disease risk factors including age, ethnicity and type 2 diabetes mellitus have been linked to Lp(a) metabolism. Given the structural similarity between Lp(a) and plasminogen, there may be a relationship between Lp(a) level and thrombosis and atherogenesis.

In this review, we summarize the latest data about Lp(a) and related conditions on the PubMed database using the following keywords: "Lp(a) and diseases" and "Lp(a) and racial groups". All available information was extracted and categorized according to the purpose of this study. In conclusion, evidence suggest that increased level of Lp(a) results in coronary artery disease and increases the risk of ischemic stroke. Lack of Lp(a) has no adverse effect on human health. Moreover, Lp(a) can be effective in wound healing as it degrades apolipoprotein(a) products which might have anti-tumor and anti-angiogenic effects.

Keywords: Lipoprotein(a), Atherosclerosis, Apo(a).

INTRODUCTION

Lipoprotein (LP) (a) is a unique lipoprotein and an independent risk factor for vascular diseases. High level of this lipoprotein (300 mg/dl) in humans, especially when accompanied with other lipids or thrombogenic factors, increases the risk of developing cardiovascular diseases (CVDs).

Studies have shown that the level of Lp(a) is highly variable according to individual genetic control. The Lp(a) level varies widely and is controlled by genetic factors. Some reports have shown that Lp(a) is highly associated with arterial wall and atherosclerosis, displaying many thrombogenic properties, but no certain function has yet been identified for Lp(a)(1).

Different studies have highlighted the relationship between Lp(a) and risk of developing CVDs. Direct deposition of Lp(a) in arterial wall increases low-density lipoprotein (LDL) oxidation. Despite the pathogenic effects of Lp(a), it is not yet proven that decreased concentration of Lp(a) can reduce the risk of CVD.

The discovery of the structural similarity between apo (a) and plasminogen shed light on the possible association between plasma Lp concentration and thrombosis/athrogenosis. It is hypothesized that Lp(a) intervenes with the fibrinolytic system by competing with plasminogen at its endothelial cell bindings site. This leads to fibrinolysis inhibition and intra-arterial thrombus formation and consolidation. In this hypothesis, Lp(a) is a factor linking athrogenosis to thrombogenesis (Figure 1) (2).

Lipoprotein (a) Biology and Importance

As shown in figure 2, chemical structure of Lp(a) is similar to that of LDL. In the Lp(a) structure, apo(a) is connected to apoB (100) through disulfide bonds. Lipoprotein (a) is synthesized in the liver and its concentration in plasma ranges from less than 1 mg/dl to over 1000 mg/dl. However, Lp(a) level of 20 to 30 mg/dl doubles the risk of CVDs.

Black people seem to have distinctively higher levels of Lp(a) compared to Caucasians and Asians; but this difference is not associated with increased incidence of CVD. Nevertheless, the risk of this factor in progression of CVD in black people should be taken into account. Sex and age also have little effect on Lp(a) level (2).

Lipoprotein (a) Structure

Lipoprotein (a) particles were first detected by Berg in 1963 (3). This particle has a round macromolecular complex with a thickness of about 25 nm and density of 1.05-1.12 g/ml. Another protein called apo(a) is produced through non-covalent disulfide bonds with 550 kDa apoB100 (4). The protein consists of an inactive domain of protease or serine protease with 94% similarity of amino acid sequence with that of plasminogen. In addition, two other domains exist in heavy chain three-dimensional structure that contains large amounts of glycosyl called "Kringle"(5).

Apolipoprotein(a) serine protease domain shows a substitution of serine for arginine in activation site that is equivalent to plasminogen. Similar to plasminogen III, this entity prevents the tissue plasminogen activators (t-pA) such as urokinase or streptokinase from converting Lp(a) to active protease (6). One domain of Kringle apo(a) is similar to Kringle V plasminogen and only 9% difference in amino acid is observed. The rest of Kringle IV within the structure of plasminogen correlates with 10 different structure in apo(a).

Only Kringle type 2 is permanently present in the structure of apo(a) which has 84% similarity to that of plasminogen; thus KringleV exists as a unique copy, while KringleIV is 10-40times repeated in the structure of apo(a). KringleIV repetition times are genetically determined. Repetition times range from 12 to 51 times, producing 34 different apo(a) isoforms (5,6).

Six different forms for Lp(a) have been identified using electrophoresis and immunoblotting: Lp(a) F, Lp(a) BT, Lp(a) S1, Lp(a) S2, Lp(a) S3 and Lp(a) S4. The letters F (fast), S (slow), B (similar apoB100) are related to apo(a) movement compared to apoB100. Isoforms of apo(a) are indicative of Lp(a) concentration in plasma. Smaller proteins are secreted more effectively compared to proteins with higher molecular weights.

The concentration of Lp(a) is mostly dependent on isoforms with smaller KIV, which also have more thrombogenic activity. Therefore, there is an inverse relationship between molecular weight and apo(a) isoforms and Lp(a) plasma concentration. The presence

of seventh allele called Lp(a) (o) null that leads to lipoproteins deficiency in plasma, has been shown using sensitive techniques. However, its serum levels have not yet been determined (6).

The presence of apoB100 in Lp(a) causes precipitation of lipoprotein with LDL. In the chemical deposition method, LDL is calculated using the Friedewald formula. Therefore, in patients with high Lp(a) concentration, Lp(a) level should be adjusted in the formula to correctly calculate the LDL concentration (7).

Lipoprotein (a) Measurement

Generally, the concentration of Lp(a) is determined by antibody-based methods such as radioimmunoassay, radial immunodiffusion (8), ELISA and nephelometry or turbidometry using monoclonal antibody against apo(a). Notable alterations in apo(a) molecular weight cause volume to molar ratio variability among people. Different studies must be compared to standardize the methodologies used to determine Lp(a). Thus, methodologies need to be improved to determine Lp(a) level (9).

Lipoprotein (a) Synthesis and Metabolism

Despite the structural similarities between LDL and Lp(a), little is known about Lp(a) synthesis and metabolism except for the fact that it is entirely independent of LDL. Studies have shown that the apo(a) synthesis occurs in the liver and its relationship with apoB100 is built in epithelial cells (10). There is no proportionality between apo(a) and apoB100 synthesis pathways, nor between Lp(a) and plasminogen. In patients with high triglyceride levels, Lp(a) is reduced which may be due to the increased clearance of lipoprotein (11, 12). Interestingly, the concentration of Lp(a) is not related to serum lipoprotein lipase activity. In this line, it has been shown that stimulation of lipolysis during heparin therapy does not affect serum Lp(a) concentrations (13).

Several studies have shown that Lp(a) binds to specific LDL receptors in spite of less affinity (14). There are two interpretations for different tendencies: 1) A portion of Lp(a) domains bind to apo(a) close to the LDL receptor domain, 2) apo(a) does not bind to apoB100 in its receptor binding sites(14). Evidence suggest that LDL receptor is not very important in plasma Lp(a) uptake by cells.

Large clinical studies have reported that statins have no effect on Lp(a) concentration. Statins stimulate expression of LDL receptors, resulting in increased Lp(a) plasma uptake; hence it is expected that Lp(a) level decreases. Macrophages play an important role in Lp(a) uptake. By further uptake of lipoproteins, macrophages transform to foam cell that is a major mechanism of atherogenesis (15). Although the LDL receptor plays a role in Lp(a) uptake, its effectiveness in the process is limited (16).

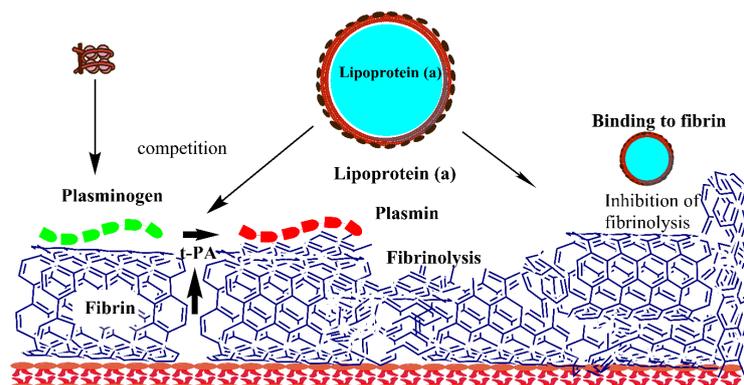
Apolipoprotein (a) Genetics and Related Ethnic Aspects

The gene encoding apo(a) protein in humans has been cloned and sequenced in 1987. The gene is located on human chromosome 6q26-27, in the same cluster of plasminogen. There is 70% similarity between this gene and plasminogen gene.

Since genetic variability of apo(a) and other genes are dependent on Lp(a) synthesis and metabolism, the plasma lipoprotein levels may vary over 1,000 times among different individuals (17). Apolipoprotein (a) gene is responsible for 91% of variability in Lp(a) concentrations. Greater allele frequency variations among different races indicates that the racial factors have a significant impact on the level of Lp(a) (18).

In a study performed on 7 races, Lp(a) polymorphism ranged from 17% to 77% correlation with variations in Lp(a) concentrations (19).

Figure 1- Competitive inhibition of plasminogen and Lp(a)



Lipoprotein (a) and Racial Groups

Lipoprotein (a) concentration varies widely in the general population. Generally, Lp(a) concentration is lower in bigger isoforms and higher in CVD patients. In the African-American population, normal distribution shifts toward higher concentrations of Lp(a) (20). High level of Lp(a) is a risk factor for CVD and stroke (21).

Lipoprotein (a) Pathogenicity

Similar to acute-phase proteins (haptoglobin, alpha-1 antitrypsin and C-reactive protein), Lp(a) increases temporarily in inflammation as a result of tissue damage but will return to baseline values within a month (22). Following a heart attack, the level of Lp(a) increases in the first 24 hours and may return to baseline level within 30 days (23). In addition, Lp(a) increases in chronic inflammatory diseases, such as rheumatoid arthritis (24), systemic lupus erythematosus (25), acquired immunodeficiency syndrome (26), and some other conditions including heart transplantation (27), chronic renal diseases (28) as well as pulmonary arterial hypertension (29).

Lp(a) decreases in some liver diseases or by intake of steroid hormones (28). The relationship between Lp(a) and diabetes mellitus has not been firmly established yet. Some studies demonstrated a link between diabetes mellitus and increased levels of Lp(a) (30).

Contrary to other studies, no difference was found in the concentration of Lp(a) in the San Antonio Heart Study (31).

Direct deposition of Lp on arterial walls, similar to LDL oxidation, may be involved in the process of atherogenesis. In fact, Lp(a) is more tolerant to oxidation than LDL, which may be a result of facilitated uptake by macrophages (15). The effect of Lp(a) on the arteries is still open to debate. The relationship between inflammatory cytokines such as α TNF-, TGF- β , IL-6, MCP-1 and Lp(a) has been reported (32,33). In addition, reduced fibrinolysis, as well as platelet aggregation is the result of adhesion molecules expression, infiltration and migration of endothelial cells and smooth muscle cells and foam cells formation.

Lipoprotein (a) as a Risk Factor for Atherosclerosis

There are numerous research indicating an association between Lp(a) and CVD. Kostner

et al. reported that the risk of CVD increases up to 2.3 times in patients with more than 50 mg/dl of Lp(a) (34). However, Porter and Riches estimated that the risk of CVD doubles with Lp(a) levels above 20mg/dl (32). The relationship between Lp(a), CVD and ischemic events has also been shown by Murai et al. (35). In a Japanese population, a study reported that the risk of CVD in individuals with high Lp(a) concentration decreases with age (36).

In a Brazilian population, the risk of developing coronary artery disease increases by 2.3 when the level of Lp(a) reached above 25mg/dl (37).

Although most studies have not reported a relationship between gender and Lp(a) levels, it seems that increased level of Lp is a more specific risk factor in women than in men (38). In a study conducted on a Atherosclerosis Risk in Communities (ARIC) population, Lp(a) was considered a risk factor for sex-related atherosclerosis because plasma Lp(a) concentration was higher in women than in men (39). In postmenopausal women, increased level of Lp(a) and triglycerides are considered as predictors of coronary artery disease (40). Early prospective studies have shown no relationship between Lp(a) and risk of myocardial infarction (41,42). In a study performed on 68 patients with CVD, small-sized apo(a) was identified as an independent risk factor (43). Apolipoprotein(a) is accompanied with plasminogen or fibronectin, which can be either bound or separated(44). Studies have shown that Lp(a) can bind to glycosaminoglycans (45), fibrin (46), platelets (47), Beta-2 glycoprotein (48) and glycoprotein 330 (gp330)/megalin (49) in human plasma. Lp (a) increases during fibrinolysis in patients with stroke (50).

Lipoprotein (a) and Cancer

The relationship of Lp(a) with certain cancers is well documented. Increase in Lp(a) levels has been reported in breast cancer (51) and lung cancer (52); however, Lp(a) level decreases in liver cancer (53) since the main site of apo(a) synthesis is impaired in this condition. Controlling angiogenesis should be considered as a main therapeutic objective. Early studies showed that removal of primary tumors increases the risk of cancer progression and metastasis. This led to the notion that primary tumors might produce angiostatic factors that inhibit tumor growth and

metastasis (54).

Expressing cDNA fragment containing apo (a), KIV-9, KIV-10 and KV in murine CT26 colon carcinoma line inhibited liver metastasis in BALB/c mice (54). Effect of angiogenic activity on endothelial deformation is as follows (55): KV>KI>KIII>KII>KIV. Angiogenesis is required for wound healing and endothelium regeneration (56). Yano et al. reported that Lp(a) accumulation contributes to wound healing and stimulates migration and proliferation of vascular endothelial cells (57). In summary, Kringles are produced by break down of apo(a) and exhibit anti-tumor and anti-angiogenesis properties, while Lp(a) facilitates wound healing by activating endothelial repair of injured endothelium and removing angiogenesis.

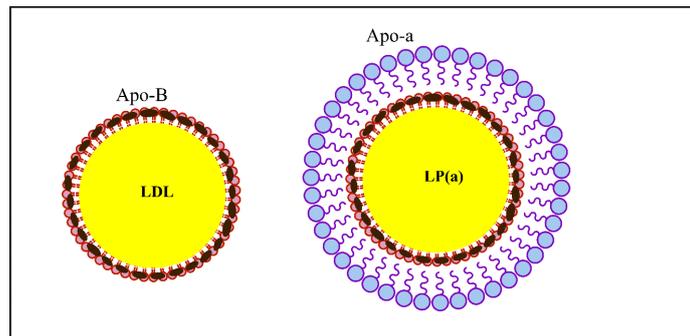
Several studies have shown that Lp(a) reduction is associated with progression of hepatocellular carcinoma (58).

Drugs and Lp(a)

Taking statins have different effects on plasma Lp(a) levels.

Nicotinic acid and its derivatives can reduce Lp(a) levels by up to 30%. The most effective method for lowering Lp(a) is extracorporeal elimination with apheresis (59). Taking statins or fibrates medication, the traditional treatment for hypertriglyceridemia, do not steadily cause Lp(a) reduction. Ezetimibe lowers Lp(a) concentration as much as 29%. Other agents that could lower Lp(a) concentration include mixture of L-lysine and ascorbate, thymimetics, L-carnitine, cholesterylester transfer protein inhibitors, as well as monoclonal antibodies such as anti-proprotein convertase subtilisin/kexin type 9, anti-tocilizumab antibody and proteins responsible for degrading LDL receptor (2). Despite the beneficial effects of curcumin on components of metabolic syndrome such as hypertriglyceridemia, low high-density lipoprotein-cholesterol and central obesity(60, 61), it seems that this drug does not improve risk factors of CVD including cholesteryl ester transfer protein inhibitors (62) or Lp(a) (63) at doses prescribed in the studies.

Figure 2- Structural similarity between Lp(a) and LDL



CONCLUSION

Increased level of Lp(a) is an independent risk factor for CVD events and has been observed in coronary artery disease and ischemic stroke events (64).

Lack of Lp(a) has no adverse effects on humans. However, the pathological effects of Lp(a) in vascular diseases with remaining oxidized LDL particles still requires further investigation.

Apolipoprotein(a) is highly glycosylated and can attach to several different extracellular matrices, thus participating in vascular diseases. However, Lp(a) also plays a role in

tissue repair and may have a protective effect on LDL cholesterol. Lipoprotein(a) can be effective in wound healing, but it is not clear whether this effect is related to the affinity of apo(a) to the extracellular matrix composition. Apolipoprotein(a) degradation products have anti-tumor, anti-angiogenic effects. In this case, the Lp(a)/apo(a) can be beneficial for humans and therefore a relationship between Lp(a) and longer life expectancy can be anticipated. The balance between these roles of Lp(a)/apo(a) can be a subject of future investigations (65).

REFERENCES

1. McCormick SP. *Lipoprotein(a): Biology and Clinical Importance*. ClinBiochem Rev. 2004; 25(1): 69-80.
2. Maranhão RC, Carvalho PO, Strunz CC, Pileggi F. *Lipoprotein (a): structure, pathophysiology and clinical implications*. Arq Bras Cardiol. 2014; 103(1): 76-84. DOI:10.5935/abc.20140101
3. Berg K. *A new serum type system in man--the LP system*. ActaPatholMicrobiol Scand. 1963; 59: 369-82. DOI:10.1111/j.1699-0463.1963.tb01808.x
4. Gaubatz JW, Chari MV, Nava ML, Guyton JR, Morrisett JD. *Isolation and characterization of the two major apolipoproteins in human lipoprotein [a]*. J Lipid Res. 1987; 28(1): 69-79. PMID: 2951469.
5. McLean JW, Tomlinson JE, Kuang WJ, Eaton DL, Chen EY, Fless GM, et al. *cDNA sequence of human apolipoprotein(a) is homologous to plasminogen*. Nature. 1987; 330(6144):132-7. DOI: 10.1038/330132a0.
6. Utermann G. *The mysteries of lipoprotein(a)*. Science. 1989; 246(4932): 904-10. DOI: 10.1126/science.2530631.
7. Scanu AM, Kurschinski D, Conn M, Garcia M. *Important limiting features of the precipitation method in estimating LDL cholesterol: interference by IDL and Lp(a)*. Atherosclerosis. 1988; 8: 574a.
8. Albers JJ, Adolphson JL, Hazzard WR. *Radioimmunoassay of human plasma Lp(a) lipoprotein*. J Lipid Res. 1977; 18(3): 331-8. PMID: 405443.
9. Jenner JL, Ordovas JM, Lamon-Fava S, Schaefer MM, Wilson PW, Castelli WP, et al. *Effects of age, sex, and menopausal status on plasma lipoprotein(a) levels. The Framingham Offspring Study*. Circulation. 1993; 87(4): 1135-41. DOI:10.1161/01.cir.87.4.1135.
10. White AL, Lanford RE. *Cell surface assembly of lipoprotein(a) in primary cultures of baboon hepatocytes*. J Biol Chem. 1994; 269(46): 28716-23. PMID: 7961823.
11. Krempler F, Kostner G, Bolzano K, Sandhofer F. *Lipoprotein (a) is not a metabolic product of other lipoproteins containing apolipoprotein B*. BiochimBiophysActa. 1979; 575(1): 63-70. DOI:10.1016/0005-2760(79)90131-0.
12. Bartens W, Rader DJ, Talley G, Brewer HB Jr. *Decreased plasma levels of lipoprotein(a) in patients with hypertriglyceridemia*. Atherosclerosis. 1994; 108(2): 149-57. DOI:10.1016/0021-9150(94)90109-0.
13. Santos RD, Vinagre C, Maranhão RC. *Lipoprotein lipase does not affect lipoprotein (a) levels in normotriglyceridemic patients*. Int J Cardiol. 1995; 50(1): 79-81. DOI:10.1016/0167-5273(95)02345-w.
14. Armstrong VW, Harrach B, Robenek H, Helmhold M, Walli AK, Slidel D. *Heterogeneity of human lipoprotein Lp[a]: cytochemical and biochemical studies on the interaction of two Lp[a] species with the LDL receptor*. J Lipid Res. 1990; 31(3): 429-41.
15. Argraves KM, Kozarsky KF, Fallon JT, Harpel PC, Strickland DK. *The atherogenic lipoprotein Lp(a) is internalized and degraded in a process mediated by the VLDL receptor*. J Clin Invest. 1997; 100(9): 2170-81. DOI: 10.1172/JCI119753.
16. Wiklund O, Angelin B, Olofsson SO, Eriksson M, Fager G, Berglund L, et al. *Apolipoprotein(a) and ischaemic heart disease in familial hypercholesterolaemia*. Lancet. 1990; 335(8702): 1360-3. DOI:10.1016/0140-6736(90)91242-3.
17. Crawford DC, Peng Z, Cheng JF, Boffelli D, Ahearn M, Nguyen D, et al. *LPA and PLG sequence variation and kringle IV-2 copy number in two populations*. Hum Hered. 2008; 66(4): 199-209. DOI: 10.1159/000143403.
18. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. *Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations*. J Clin Invest. 1992; 90(1): 52-60. DOI: 10.1172/JCI115855.
19. 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(6): 607-14. DOI:10.1007/bf00201550.
20. Islam S, Gutin B, Smith C, Treiber F, Kambh MI. *Association of apolipoprotein(a) phenotypes in children with family history of premature coronary artery disease*. ArteriosclerThromb. 1994; 14(10): 1609-16.
21. Moliterno DJ, Jokinen EV, Miserez AR, Lange RA, Willard JE, Boerwinkle E, et al. *No association between plasma lipoprotein(a) concentrations and the presence or absence of coronary atherosclerosis in African - American*. ArteriosclerThrombVascBiol. 1995; 15(7): 850-5. DOI:10.1161/01.atv.15.7.850.
22. Maeda S, Abe A, Seishima M, Makino K, Noma A, Kawade M. *Transient changes of serum lipoprotein(a) as an acute phase protein*. Atherosclerosis. 1989; 78(2-3): 145-50. DOI:10.1016/0021-9150(89)90218-9.
23. Ornek E, Murat S, Duran M, Turfan M, Kurtul A, Demircelik MB, et al. *The relationship between lipoprotein(a) and coronary artery disease, as well as its variable nature following myocardial infarction*. Clin Invest Med. 2011; 34(1): E14-20. DOI:10.25011/cim.v34i1.14908.
24. Wang J, Hu B, Kong L, Cai H, Zhang C. *Native, oxidized lipoprotein(a) and lipoprotein(a) immune complex in patients with active and inactive rheumatoid arthritis: plasma concentrations and relationship to inflammation*. ClinChimActa. 2008; 390(1-2): 67-71. DOI: 10.1016/j.cca.2007.12.015.
25. Borba EF, Santos RD, Bonfa E, Vinagre CG, Pileggi FJ, Cossermelli W, et al. *Lipoprotein(a) levels in systemic lupus erythematosus*. J Rheumatol. 1994; 21(2): 220-3.
26. Enkhmaa B, Anuurad E, Zhang W, Abbuthalha A, Li XD, Dotterweich W, et al. *HIV disease activity as a modulator of lipoprotein(a) and allele-specific apolipoprotein(a) levels*. ArteriosclerThrombVasc Biol. 2013; 33(2): 387-92. DOI: 10.1161/ATVBAHA.112.300125.
27. Maranhão R, Santos RD, Furlaneto C, Graziosi P, Stolf N, Vinagre C, et al. *Lipoprotein (a), apolipoproteins and the lipid profile late after heart transplantation*. Arq Bras Cardiol. 1994; 63(6):465-8.
28. De Lima JJ, Maranhão RC, Latrilha M da C, Diament J, Romão JE, Krieger EM, et al. *Early elevation of lipoprotein(a) levels in chronic renal insufficiency*. Ren Fail. 1997; 19(1): 145-54.
29. Santos RD, Foronda A, Ramires JA, Maranhão RC. *Levels of lipoprotein (a) in pulmonary arterial hypertension*. Cardiol Young. 2001; 11(1): 25-9. DOI:10.1017/s1047951100012385.

30. Bruckert E, Davidoff P, Grimaldi A, Truffert J, Giral P, Doumith R, et al. *Increased serum levels of lipoprotein(a) in diabetes mellitus and their reduction with glycemic control.* JAMA. 1990; 263(1): 35-6. doi:10.1001/jama.1990.03440010033016.
31. Haffner SM, Morales PA, Stern MP, Gruber MK. *Lp(a) concentrations in NIDDM.* Diabetes. 1992; 41(10): 1267-72. PMID: 1397699
32. Riches K, Porter KE. *Lipoprotein(a): cellular effects and molecular mechanisms.* Cholesterol. 2012; 2012: 923289. <http://dx.doi.org/10.1155/2012/923289>
33. Ramharack R, Barkalow D, Spahr MA. *Dominant negative effect of TGF-beta1 and TNF-alpha on basal and IL-6-induced lipoprotein(a) and apolipoprotein(a) mRNA expression in primary monkey hepatocyte cultures.* ArteriosclerThrombVasc Biol. 1998; 18(6): 984-90. DOI:10.1161/01.atv.18.6.984.
34. Kostner GM, Avogaro P, Cazzolato G, Marth E, Bittolo-Bon G, Qunici GB. *Lipoprotein Lp(a) and the risk for myocardial infarction.* Atherosclerosis. 1981; 38(1-2): 51-61. DOI:10.1016/0021-9150(81)90103-9.
35. Murai A, Miyahara T, Fujimoto N, Matsuda M, Kameyama M. *Lp(a) lipoprotein as a risk factor for coronary heart disease and cerebral infarction.* Atherosclerosis. 1986; 59(2): 199-204. DOI:10.1016/0021-9150(86)90048-1.
36. Rhoads GG, Dahlen G, Berg K, Morton NE, Dannenberg AL. *Lp(a) lipoprotein as a risk factor for myocardial infarction.* JAMA. 1986; 256(18): 2540-4. PMID: 2945939.
37. Maranhão R, Arie S, Vinagre CG, Guimarães JB, Strunz C, Pileggi F. *Lipoprotein (a) plasma levels in normal subjects and patients with coronary disease confirmed by coronary cineangiography.* Arq Bras Cardiol. 1991; 56(2): 121-5. PMID: 1831344.
38. Frohlich J, Dobiášová M, Adler L, Francis M. *Gender differences in plasma levels of lipoprotein(a) in patients with angiographically proven coronary artery disease.* Physiol Res. 2004; 53(5): 481-6. PMID: 15479125.
39. Virani SS, Brautbar A, Davis BC, Nambi V, Hoogeveen RC, Sharrett AR, et al. *Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) Study.* Circulation. 2012; 125(2): 241-9. DOI: 10.1161/CIRCULATIONAHA.111.045120.
40. Sposito AC, Mansur AP, Maranhão RC, Martinez TR, Aldrighi JM, Ramires JA. *Triglyceride and lipoprotein (a) are markers of coronary artery disease severity among postmenopausal women.* Maturitas. 2001; 39(3): 203-8. DOI:10.1016/s0378-5122(01)00223-7.
41. Ridker PM, Hennekens CH, Stampfer MJ. *A prospective study of lipoprotein(a) and the risk of myocardial infarction.* JAMA. 1993; 270: 2195-9. PMID: 8411602.
42. Wild SH, Fortmann SP, Marcovina SM. *A prospective case-control study of lipoprotein(a) level and apo(a) size and risk of coronary heart disease in Stanford Five - City project.* ArteriosclerThrombVascBiol. 1997; 17(2): 239-45. DOI:10.1161/01.atv.17.2.239.
43. Baños-González MA, Peña-Duque MA, Anglés-Cano E, Martínez-Rios MA, Bahena A, Valente-Acosta B, et al. *Apo(a) phenotyping and long-term prognosis for coronary artery disease.* ClinBiochem. 2010; 43(7-8): 640-4. doi: 10.1016/j.clinbiochem.2010.01.013.
44. Salonen EM, Jauhiainen M, Zardi L, Vaheri A, Ehnholm C. *Lipoprotein(a) binds to fibronectin and has serine protease activity capable of cleaving it.* EMBO J. 1989; 8(13): 4035-40.
45. Bihari-Varga M, Graber E, Rotheneder M, Zechner R, Kostner GM. *Interaction of lipoprotein Lp(a) and low density lipoprotein with glycosaminoglycans from human aorta.* Arteriosclerosis. 1988; 8: 851-7. doi: 10.1161/01.ATV.8.6.851.
46. Harpel PC, Gordon BR, Parker TS. *Plasmin catalyzes binding of lipoprotein(a) to immobilized fibrinogen and fibrin.* Proc Natl Acad Sci USA. 1989; 86: 3847-51. DOI:10.1073/pnas.86.10.3847.
47. Malle E, Ibovnik A, Steinmetz A, Kostner GM, Sattler W. *Identification of glycoprotein IIb as the lipoprotein(a) - binding protein on platelets. Lipoprotein(a) binding is independent of an Arginyl-Glycyl-Aspartate tripeptide located in apolipoprotein(a).* ArteriosclerThromb. 1994; 14(3): 345-52.
48. Köchl S, Fresser F, Lobentanz E, Baier G, Utermann G. *Novel interaction of apolipoprotein(a) with β 2 glycoprotein I mediated by the kringle IV domain.* Blood. 1997; 90(4): 1482-9. PMID: 9269765.
49. Niemeier A, Willnow T, Dieplinger H, Jacobsen C, Meyer N, Hilpert J, et al. *Identification of megalin/gp330 as a receptor for lipoprotein(a) in vitro.* ArteriosclerThrombVascBiol. 1999; 19(3): 552-61.
50. Vuckovic BA, Djerić MJ, Ilic TA, Canak VB, Kojic-DamjanovSLj, Zarkov MG, et al. *Fibrinolytic parameters, lipid status and lipoprotein(a) in ischemic stroke patients.* SrpArhCelokLek. 2010; 138 (Suppl 1): 12-7. DOI:10.2298/sarh10s1012v.
51. Kokoglu E, Karaarslan I, Karaarslan HM, Baloglu H. *Elevated serum Lp(a) levels in the early and advanced stages of breast cancer.* Cancer BiochemBiophys. 1994; 14(2): 133-6. PMID: 7889493.
52. Yang HH, Chen XF, Hu W, Lv DQ, Ding WJ, Tang LI, Jiang JJ, Ye MH. *Lipoprotein(a) level and its association with tumor stage in male patients with primary lung cancer.* ClinChem Lab Med. 2009; 47(4): 452-7. doi: 10.1515/CCLM.2009.094.
53. Jiang J, Nisson-Ehle P, Xu N. *Influence of liver cancer on lipid and lipoprotein metabolism.* Lipids Health Dis. 2006; 5: 4. DOI: 10.1186/1476-511X-5-4.
54. Yu HK, Kim JS, Lee HJ, Ahn JH, Lee SK, Hong SW, Yoon Y. *Suppression of colorectal cancer liver metastasis and extension of survival by expression of apo(a) kringles.* Cancer Res. 2004; 64(19): 7092-8. DOI: 10.1158/0008-5472.CAN-04-0364.
55. Lippi G, Franchini M, Salvagno GL, Guidi GC. *Lipoprotein[a] and cancer: Anti-neoplastic effect besides its cardiovascular potency.* Cancer Treatment Rev. 2007; 33(5): 427-36.

56. Hajjar KA, Nachman RL. *The role of lipoprotein(a) in atherogenesis and thrombosis*. Annual Rev Med. 1996; 47: 423-42. DOI: 10.1146/annurev.med.47.1.423.
57. Yano Y, Seishima M, Tokoro Y, Noma A. *Stimulatory effects of lipoprotein(a) and low-density lipoprotein on human umbilical vein endothelial cell migration and proliferation are partially mediated by fibroblast growth factor- 2*. BiochimBiophysActa. 1998; 1393: 26-34.DOI:10.1016/s0005-2760(98)00052-6.
58. Mario Uccello, Giulia Malaguarnera, Elisa M. Pelligra, Antonio Biondi, Francesco Basile, andMassimo Motta. *Lipoprotein(a) as a potential marker of residual liver function in hepatocellular carcinoma*. Indian J Med PaediatrOncol. 2011; 32(2): 71-75.doi: 10.4103/0971-5851.89775.
59. Kostner K. *Lipoprotein (a): Pathophysiology, metabolism, treatment options*. Recent Advances and Research Updates. 2006;7(1):297-303.
60. Visioli F, Davalos A. *Polyphenols and cardiovascular disease: a critical summary of the evidence*. Mini Rev Med Chem. 2011;11(14):1186-90.DOI:10.2174/138955751111091186.
61. Moammeri SM, Parizadeh SMR, Pasdara A, Karimian MS, Safarian H, Javandoost A, et al. *The effect of curcumin (Curcuma longa L.) on circulating levels of adiponectin in patients with metabolic syndrome*. Comparative Clinical Pathology. 2017;26(1):17-23.
62. Javandoost A, Afshari A, Saberi-Karimian M, Sahebkar A, Safarian H, Moammeri SM, et al. *The effects of curcumin and a modified curcumin formulation on serum Cholesteryl Ester Transfer Protein concentrations in patients with metabolic syndrome: A randomized, placebo-controlled clinical trial*. Avicenna journal of phytomedicine. 2018;8(4):330.DOI: 10.22038/ajp.2018.10348.
63. Saberi-Karimian M, Parizadeh SMR, Ghayour-Mobarhan M, Moammeri SM, Dizaji BF, Safarian H, et al. *Evaluation of the effects of curcumin in patients with metabolic syndrome*. Comparative Clinical Pathology. 2018;27(3):555-63.
64. Forbes AC, Quek RGW, Deshpande S, Worthy G, Wolff R, Stirk L, et al. *The relationship between Lp(a) and CVD outcomes: a systematic review*. Lipids in Health and Disease. 2016; 15:95. DOI: 10.1186/s12944-016-0258-8.
65. Hsieh J. *Lipoprotein(a) in Vascular Disease, Cancer and Longevity*. Chang Gung medical journal. 2011; 34(6): 555-64.