Lipoprotein (a): Structure, Pathophysiology and Clinical Implications

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Abstract

The chemical structure of lipoprotein (a) is similar to that of LDL, from which it differs due to the presence of apolipoprotein (a) bound to apo B100 via one disulfide bridge. Lipoprotein (a) is synthesized in the liver and its plasma concentration, which can be determined by use of monoclonal antibody-based methods, ranges from < 1 mg to > 1,000 mg/dL. Lipoprotein (a) levels over 20-30 mg/dL are associated with a two-fold risk of developing coronary artery disease. Usually, black subjects have higher lipoprotein (a) levels that, differently from Caucasians and Orientals, are not related to coronary artery disease. However, the risk of black subjects must be considered. Sex and age have little influence on lipoprotein (a) levels. Lipoprotein (a) homology with plasminogen might lead to interference with the fibrinolytic cascade, accounting for an atherogenic mechanism of that lipoprotein. Nevertheless, direct deposition of lipoprotein (a) on arterial wall is also a possible mechanism, lipoprotein (a) being more prone to oxidation than LDL. Most prospective studies have confirmed lipoprotein (a) as a predisposing factor to atherosclerosis. Statin treatment does not lower lipoprotein (a) levels, differently from niacin and ezetimibe, which tend to reduce lipoprotein (a), although confirmation of ezetimibe effects is pending. The reduction in lipoprotein (a) concentrations has not been demonstrated to reduce the risk for coronary artery disease. Whenever higher lipoprotein (a) concentrations are found, and in the absence of more effective and well-tolerated drugs, a more strict and vigorous control of the other coronary artery disease risk factors should be sought.

Lipoprotein (a) and apolipoprotein (a) structures

The particle of lipoprotein (a), Lp(a), first detected by Berg in 1963[1], is a spherical macromolecular complex with a diameter of approximately 25 nm, and density ranging from 1.05 to 1.12 g/mL. The Lp(a) structure is similar to that of low-density lipoprotein (LDL), regarding size and lipid composition of the particles and the presence of apolipoprotein B100 (apo B100). The major structural difference between both is that, in addition to apo B, Lp(a) has a second protein, apolipoprotein (a) [apo(a)], bound to apo B100 via noncovalent interactions and one single disulfide bridge. The presence of apo(a) determines the differences in density and electrophoretic mobility between LDL and Lp(a), and the molecular weight of that glycoprotein varies widely from 400 to 700 kDa. For the purpose of comparison, the molecular weight of apo B100 is approximately 550 kDa, and those of apo A1 and apo Cs are approximately 7 and 29 kDa, respectively[2].

A fundamental discovery was that apo(a) is markedly similar to plasminogen, one of the proteins of the fibrinolytic system. Apo(a) comprises a domain of inactive protease or serine-protease, whose amino acid sequence coincides with that of plasminogen in 94%. In addition, there are 2 other domains constituted by tridimensional heavy-chain structures, highly glycosylated, known as kringles[3].

The serine-protease domain of apo(a) shows replacement of the serine amino acid by arginine in the activation site equivalent to that of plasminogen. That hinders the conversion of Lp(a) into active protease by tissue plasminogen activator (t-PA), urokinase or streptokinase, such as with plasminogen[3].

Of the kringle domains of apo(a), one is similar to the kringle V (KV) of plasminogen, with only 9% replacement of amino acids. The other, kringle IV (KIV), which is present only once in the plasminogen structure, has 10 different types in apo(a) (KIV types 1 to 10). Only KIV type 2 occurs repeatedly in the apo(a) sequence, coinciding with about 84% of the amino acid sequence of KIV in plasminogen. Thus, KV is a single copy, while KIV repeats 10 to 40 times in the apo(a) structure. The number of KIV repetitions is genetically determined, ranging from 12 to 51 times, resulting in 34 different apo(a) isoforms[3,4].

Using electrophoresis and immunoblotting, the following 6 different alleles for Lp(a) were identified: Lp(a)F; Lp(a)B; Lp(a)S1; Lp(a)S2; Lp(a)S3; and Lp(a)S4. The letters F, S and B relate to apo(a) mobility as compared to that of apo B100, standing for "fast" (fast mobility), "slow" (slow mobility), and mobility similar to that of apo B100, respectively. The isoform is determinant to Lp(a) plasma concentration, because it represents a limiting factor in Lp(a) synthesis. Smaller proteins are secreted more efficiently than those of higher molecular weight. Isoforms with fewer KIV type 2 repetitions, that is, smaller sequences of apo(a), tend to determine higher Lp(a) concentrations and to increase atherothrombogenic activity[4]. Thus, there is a strong inverse correlation between the molecular weight of apo(a) isoforms and the plasma concentration of Lp(a).

The existence of a seventh allele, called 'null' [Lp(a)0], which would lead to absence of the lipoprotein in plasma, has not been confirmed; by using more sensitive methods to detect Lp(a), none totally negative individuals have been observed. In addition, no subject with more than 2 alleles for apo(a) exists[4].

Keywords

Lipoprotein (a) / metabolism; Lipoproteins, LDL / ultrastructure; Risk Factors; Cardiovascular Diseases.

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The presence of apo B100 in Lp(a) makes that lipoprotein co-precipitate with LDL in the assays currently used to separate lipoproteins by using the chemical precipitation method. This interferes with LDL values calculated with the Friedewald formula[5]. Thus, if the Lp(a) concentration in a patient is high, LDL-cholesterol calculation with that formula is not accurate without corrections that consider the Lp(a) concentration.

Methodology to determine Lp(a)

The most common method to quantify Lp(a) consists in determining the apo(a) concentration by using monoclonal anti-apo(a) antibodies. The first commercial kits measured Lp(a) by use of radioimmunoassay or radial immunodiffusion[6]. Currently, enzyme immunoassay (ELISA) and methods based on nephelometry or turbidimetry are more often used[7]. The wide variation in apo(a) molecular weight makes the ratio between mass and molar concentration vary between individuals. When the method to determine Lp(a) involves antibodies that react with the apo(a) kringle region, which has high individual variability, differences in reaction not related to molar concentration might occur, explaining the differences in normal Lp(a) plasma levels in different population samples. In that context, there are difficulties in standardizing the methodology to determine Lp(a) to allow a more accurate comparison between different studies. So far, new methods to determine Lp(a) are being developed.

Lp(a) synthesis and metabolism

Despite the structural similarities between Lp(a) and LDL, Lp(a) synthesis and metabolism, which have not been completely clarified, are totally independent from LDL synthesis and metabolism. *In vitro* studies have shown that apo(a) synthesis takes place in hepatocytes, and its association with apo B100 should occur on cell surface[8]. Thus, the liver has been described as the major site of Lp(a) synthesis. There is no coordination between the synthesis pathways of apo(a) and of apo B100, as there is no coordination between the synthesis of Lp(a) and of plasminogen, its structural analogue.

Similarly to LDL, Lp(a) does not derive from the catabolism of another lipoprotein[9]. In individuals with elevated triglyceridemia, Lp(a) is reduced, probably due to an increase in the plasma lipoprotein clearance[10]. However, when VLDL lipolysis was stimulated by heparin inoculation during catheterization in patients with normal lipid levels, there was a reduction in triglyceride levels, with no change in Lp(a) concentration. This confirms that Lp(a) levels are not related to the lipoprotein lipase activity[11].

The way Lp(a) cellular uptake occurs has not been well established. Several studies have shown that Lp(a) binds to specific LDL receptors, although with less affinity. Two possible explanations for that difference in affinity are: (1) some Lp(a) domains near the domain of LDL-receptor binding would be covered by apo(a); or (2) apo(a) would not bind to apo B100 in the receptor binding site, causing changes in the apo B100 binding region. However, it is worth noting that, when apo(a) is dissociated from Lp(a) by cleavage of disulfide bridges, the binding capacity of the lipoprotein increases, becoming equivalent to that of LDL[12].

There is evidence that the LDL receptor might not be so important in Lp(a) plasma removal. Large clinical studies have reported that statins have no effect on Lp(a) concentrations. Because statins induce superexpression of LDL receptors, greater Lp(a) plasma removal and consequent lower Lp(a) plasma levels would be expected if the receptor was essential for that process. Other receptors, such as asialoglycoprotein receptors, megalin receptors, and macrophage scavenger receptors, can also be involved in Lp(a) uptake[13]. The capacity of macrophages to uptake Lp(a) is important, because the excessive uptake of lipoproteins by macrophages, with their subsequent transformation into foam cells, is the major mechanism of atherogenesis.

Other studies have shown elevated Lp(a) plasma levels in patients with heterozygous familial hypercholesterolemia, known to have deficiency of LDL receptors. Considering that such increase is a direct consequence of a defect in the receptor that interacts with the apo B100 of Lp(a), the genetic defect in apo B100 would be expected to cause that same situation, similarly to that with LDL. However, that condition could not be confirmed, because the Lp(a) plasma levels were not affected by apo B100 mutation. In addition, only a small fraction of Lp(a) binds to hepatoma cells via LDL receptor, and the major part of lipoproteins associates with those cells via another cellular mechanism[14]. Thus, although the LDL receptor acts upon Lp(a) removal, its role in that process is limited.

The experiences carried out so far have not evidenced a physiological function for Lp(a) in lipid transportation or metabolism regulation. Up to now, Lp(a) remains conceptually only a "pathogenic lipoprotein". In individuals with residual Lp(a) concentrations, neither organic deficiencies nor predisposition to any disease have been reported[15].

Apo(a) genetic and ethnic aspects

In men, the gene encoding the apo(a) protein, the *LPA*, was cloned and sequenced for the first time in 1987, showing homology with up to 70% of the human plasminogen gene. The *LPA* gene is located in the same cluster of the plasminogen gene, in the long arm of chromosome 6, in the 6q2.6-2.7 region[3]. The *LPA* gene is characterized by 10 different variants present in the KIV domain and by multiple repetitions, ranging from 2 to 43, in the KIV type 2 domain[3,4].

Because of that impressive genetic variability of apo(a) and the involvement of other genes related to Lp(a) synthesis and metabolism, that lipoprotein plasma levels can vary more than 1,000 times between individuals of the same population[16]. The *LPA* gene might be responsible for 91% of the variation in Lp(a) concentration. Of that variation, 69% are due to the number of KIV type 2 repetitions, and 22% to other factors[17].

The allele frequency varies even more according to ethnicity, indicating that the racial factor has an important influence on Lp(a) levels. Such levels have a non-Gaussian distribution in white and Oriental individuals, being similar in those 2 populations. In the Sub-Saharan population and Afro-Americans, that distribution is Gaussian, and Lp(a) levels are more elevated, reaching means up to 2 to 3 times those of the Caucasian or Oriental population[18].

In a study with several ethnic groups, Lp(a) polymorphism has influenced in 17% to 77% of the variation in Lp(a) concentrations[19]. Regarding the variation in Lp(a) levels, 80% resulted from the number of kringles (KIV/KV ratio)[20]. In more than 7,000 individuals, divided into non-Hispanic whites, non-Hispanic blacks, and Mexican Americans, 19 polymorphisms were analyzed. Of the 19 polymorphisms, 15 were associated with Lp(a) levels in at least one of the subpopulations, 6 in at least 2 subpopulations, and none in all 3 subpopulations[21]. Those data are consistent with data from other studies that have shown little or no effect of other factors, such as gender and age, on Lp(a) concentrations[7]. The genetic factor is the major responsible for that variation.

Lp(a) pathophysiology

Plasma concentrations of Lp(a) have a hereditary character, with large interindividual variation, being not altered by environmental factors, and tending to remain constant throughout life. In the general population, Lp(a) concentrations can range from < 1 mg/dL to > 1,000 mg/dL.

Increases in Lp(a) levels can be transient in the presence of inflammatory processes or tissue damages, such as those occurring with other acute phase proteins (haptoglobin, alpha-1-antitripsin, and C-reactive protein)[22]. This can follow an episode of acute myocardial infarction, in which Lp(a) levels increase considerably in the first 24 hours, returning to baseline values in approximately 30 days[23].

Lp(a) levels are increased in chronic inflammatory disease, such as rheumatoid arthritis[24], systemic lupus erythematosus[25], and acquired immunodeficiency syndrome[26], and under some conditions, such as after heart transplantation[27], chronic renal failure[28], and pulmonary arterial hypertension[29]. On the other hand, liver diseases and abusive use of steroid hormones decrease Lp(a) levels[28].

The relationship between Lp(a) and *diabetes mellitus* has not been well established. Regarding type 1 *diabetes mellitus*, some studies have reported higher Lp(a) levels[30], which have not been confirmed by other studies[31]. Conflicting results have also been reported for type 2 *diabetes mellitus*. In a sub-study carried out from the San Antonio Heart Study, diabetic men and women showed no difference in Lp(a) concentrations when compared with non-diabetic individuals[32]. On the other hand, a prospective study carried out with 26,746 North-American women has shown a higher incidence of type 2 *diabetes mellitus* among those with lower Lp(a) levels[33].

Several mechanisms of Lp(a) participation in atherogenesis have been proposed. One of them consists in the direct deposition of that lipoprotein on arterial wall, similarly to that which happens with LDL and oxidized LDL. The fact that Lp(a) is more likely to undergo oxidation than LDL itself might facilitate uptake by macrophages via scavenger receptors[13]. That is the most universal mechanism of atherogenesis, in which macrophages 'indulge themselves' in the cholesterol from LDL, and eventually from Lp(a), transforming themselves into foam cells, precursors of atherosclerosis. Another pro-atherogenic mechanism of Lp(a) would relate to the inverse correlation between that lipoprotein levels and vascular reactivity, in which case the increase in Lp(a) plasma levels would induce endothelial dysfunction[34].

The influence of Lp(a) levels on carotid intima-media thickness is still controversial. While Kotani and Sakane[35] have found an inverse association in the Japanese population, no relationship between that thickness and Lp(a) levels has been found in Spaniards by Calmarza et al[36].

Other authors have found a positive association of Lp(a) gene polymorphisms and that lipoprotein levels with the incidence of ischemic cerebral vascular accident of large vessels, peripheral arterial disease, and abdominal aorta aneurysm. Association with the number of obstructed coronary arteries was observed, but not with carotid intima-media thickness. In addition, patients with coronary artery disease (CAD) and those polymorphisms are more susceptible to atherosclerotic manifestations outside the coronary tree[37].

Associations between Lp(a) and inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β), interleukine 6 (IL-6), and monocyte chemoattractant protein (MCP-1), have been reported[38,39]. Thus, the participation of Lp(a) in atherogenesis could be multifaceted. In addition to a reduction in fibrinolysis, it would involve platelet aggregation, induction of the expression of adhesion molecules, vascular remodeling via changes in the proliferative and migratory capacity of endothelial cells and resident smooth muscle cells, oxidative modification and formation of foam cells.

It is worth noting that the apo(a) gene has multiple elements of IL-6 response, and *in vitro* studies have demonstrated that the expression of that gene is increased by IL-6, leading to the accumulation of Lp(a) particles[39]. The Lipid Analytic Cologne (LIANCO) Study has found an association between the IL-6 polymorphism 74G/C and elevated Lp(a) levels (≥ 60 mg/dL)[40].

Along with the discovery of homology between apo(a) and plasminogen, a mechanism linking thrombogenesis and atherogenesis with plasma lipoproteins via Lp(a) has caused great excitement in the scientific field. The hypothesis is as follows: Lp(a) would interfere with the fibrinolytic system, suggesting that Lp(a) competes with plasminogen for binding sites of endothelial cells, inhibiting fibrinolysis and promoting intravascular thrombosis[41]. In that scenario, Lp(a) would be a link between atherogenesis and thrombogenesis, explaining the redoubled interest in that possible mechanism.

An interesting question has been raised by Edelberg et al[42], who have reported that Lp(a) interferes *in vitro* with the thrombolytic action of t-PA. However, Santos Filho et al[43] have tested the hypothesis in patients undergoing post-acute myocardial infarction thrombolysis with rt-PA, and have observed no difference in the restenosis frequency of those with high Lp(a) levels.

In patients with cardiovascular disease, the possibility of accumulating Lp(a) in the postprandial period, due to competition between Lp(a) and remnants of chylomicrons generated by absorption of fat from the diet, has been studied. However, that possibility has been ruled out by the evidence that Lp(a) levels have not changed in those patients after a fatty meal[44].

Lp(a) as a risk factor for atherosclerosis

Cross-sectional studies performed so far have widely confirmed the association between Lp(a) levels and the risk for developing CAD, regardless of other risk factors. Kostner

et al[45] have estimated that risk as being 2.3 times higher in patients with Lp(a) levels over 50 mg/dL, while Riches and Porter[38] have calculated that risk as twice greater for Lp(a) levels over 20 mg/dL. The relationship between Lp(a) and CAD and cerebral infarction has been confirmed by Murai et al[46] in the Japanese population and by Rhoads et al[47] in Japanese descendants in Hawaii. The latter study has reported that, in individuals under the age of 60 years with Lp(a) levels over 30 mg/dL, the risk was 2.5 times greater and decreased as age increased, dropping to 1.6 in the age group from 60 to 69 years, and to 1.2 in the age group over 70 years. In the Brazilian population of São Paulo, Maranhão et al[48] have reported a risk of developing CAD 2.3 times greater when Lp(a) levels were over 25 mg/dL.

Several prospective studies have been published, and, contrary to the cross-sectional studies, they have not been so assertive in identifying Lp(a) as an independent risk factor. Their results are conflicting, ranging from strong positive associations to complete lack of association between Lp(a) and cardiovascular diseases. However, most prospective studies have supported the hypothesis that Lp(a) is really an independent risk factor for cardiovascular disease.

In one of the first studies, carried out in Boston, United States of America, with almost 15,000 men (age range, 40 to 84 years), no prevalence of high Lp(a) levels was identified in those who would subsequently develop acute myocardial infarction[49]. In the prospective study conducted in Quebec, Canada, for 5 years, with 2,000 men (age range, 47 to 76 years), Lp(a) has not appeared as an independent risk factor for cardiac events, although high Lp(a) levels have apparently exacerbated the potency as risk factors of both hypercholesterolemia and low HDL-cholesterol concentration[50].

Lp(a) has been identified as an independent risk factor in a population of 6,000 Koreans with CAD, in which patients with high Lp(a) levels had worse disease course[51]. A meta-analysis encompassing 27 prospective studies and involving approximately 5,500 individuals has shown a clear independent association between Lp(a) and CAD, although 9 of those studies included individuals with preexisting disease[52].

In addition to CAD, Lp(a) can be a risk factor for atherosclerosis in other arterial beds, such as in ischemic cerebral disease, in which the risk appears with a Lp(a) cutoff point of 30 mg/dL[53].

In a North-American prospective study with approximately 14,000 participants, Caucasian women and Afrodescendant men and women with high Lp(a) have shown a higher incidence of ischemic cerebral disease over a 13-year follow-up. Caucasian men, however, have not shown an increased risk associated with high Lp(a) levels[54].

Smolders et al[55], reviewing 31 cross-sectional and prospective studies involving approximately 50,000 individuals, have suggested that high Lp(a) levels can be associated with the risk for ischemic cerebral vascular accident. A cohort study involving 2,365 individuals with CAD, 284 with ischemic cerebral vascular accident and 596 with peripheral arterial disease has shown an association of increased Lp(a) levels with future events of arterial diseases, but not with ischemic cerebral disease. It is worth noting that such association was independent of LDL-cholesterol levels[56].

Atherogenesis is a common causal factor of abdominal aortic aneurysm, while thoracic aortic aneurysm results from aortic dissection and is not associated with atherosclerosis. Lp(a) levels seem more elevated in abdominal aneurysm than in thoracic aneurysm, which is in accordance with the concept of the association between lipoprotein and atherogenesis[57].

An important aspect relates to extremely high Lp(a) levels, whether they can represent a more significant risk factor. A Danish prospective study involving more than 9,000 individuals over a 10-year follow-up has shown that extremely high Lp(a) levels (≥ 120 mg/dL) increased 3 to 4 times the risk for CAD[58].

In a meta-analysis of 40 prospective studies with 58,000 participants, a 2-fold increase in the risk for developing CAD and cerebral vascular accident has been found in individuals with smaller apo(a) isoforms, regardless of the Lp(a) concentration and the classical risk factors[59].

Another important aspect is the relationship that Lp(a) might have with sex. Although most studies have shown no difference between sexes in Lp(a) concentrations, more elevated lipoprotein levels seem to be more significant risk factors in the female sex than in the male sex[60]. The last Atherosclerosis Risk in Communities (ARIC) Study, assessing Lp(a) as a risk factor, has found a difference between sexes in that lipoprotein plasma concentration, which was higher in women, both Caucasian and black[61]. Knoflach et al[62], assessing risk factors for atherosclerosis in young women, have shown that Lp(a) levels related to the carotid intima-media thickness, while the classical risk factors had no influence on that parameter. In postmenopausal women, elevated Lp(a) and triglyceride levels were predictive of the presence of CAD[63].

In black individuals, the mean Lp(a) concentrations are markedly high, 2 to 3 times greater than in Caucasian and Oriental individuals[18]. In older studies, with a more limited statistical power, Lp(a) levels have been assumed as non-predictive of cardiovascular disease in black individuals. However, a recent study with almost 3,500 Afro-Americans has reported a higher incidence of cardiovascular diseases and events when comparing between the highest and lowest Lp(a) concentrations[61].

Table 1 lists several cross-sectional and prospective studies assessing Lp(a) levels as a risk factor for atherosclerotic vascular diseases.

Effects of drugs on Lp(a) concentration

Traditional lipid-lowering therapies, such as statins or fibrates, do not consistently result in a reduction in Lp(a) concentrations. The use of atorvastatin at the dose of 20 mg/day for 24 weeks has resulted in both lack of effect on Lp(a) levels[64] and a decrease in that lipoprotein levels in hypercholesterolemic individuals with no disease[65]. In a double-blind study with placebo, using doses of 10 or 40 mg/day for 12 weeks, the Lp(a) concentration has significantly decreased[66]. Of lovastatin, simvastatin and gemfibrozil, the latter has shown greater efficacy in reducing Lp(a)[67].

Table 1 – Studies assessing lipoprotein (a), Lp(a), as a risk factor for atherosclerotic vascular disease: coronary artery disease (CAD), acute myocardial infarction (AMI), and ischemic cerebral vascular accident (ICVA)

Study type / duration	Population	Lp(a) cutoff point (mg/dL)	Independent risk or association	Atherosclerotic manifestation	Reference
Cross-sectional	183 men	> 50	2.3 times higher	AMI	Kostner et al[45]
Cross-sectional	426 Japanese: 268 men and 158 women	> 17	Positive	CAD and ICVA	Murai et al[46]
Cross-sectional	711 Japanese men in Hawaii	> 30	2.5 times: < 60 years 1.6 time: 60-69 years 1.2 time: > 70 years of age	AMI	Rhoads et al[47]
Cross-sectional	162 Brazilians: 112 men and 50 women	≥ 25	2.3 times higher	CAD	Maranhão et al[48]
Prospective (5 years)	15,000 North-American men	30	Negative	AMI	Stampfer et al[49]
Prospective (5 years)	2,000 Canadian men	30	Negative	CAD	Cantin et al[50]
Meta-analysis (10 years)	27 prospective studies, 5,500 individuals of both sexes	20-100	Positive	CAD	Danesh et al[52]
Retrospective (1997-1999)	182 Brazilian postmenopausal women		2 to 3 times higher	Obstructive CAD	Sposito et al[63]
Prospective	346 men and 184 women of European descent		2 times higher	CAD Lp(a) 2 times higher in women	Frohlich et al[60]
Prospective (13.5 years)	14,000 Caucasians and Afrodescendants of both sexes	30	Positive	ICVA, except for Caucasian men	Ohira et al[54]
Meta-analysis (1966-2006)	31 cross-sectional and prospective studies, 50,000 individuals of both sexes	≥ 30	Positive	ICVA	Smolders et al[55]
Meta-analysis (1966-2008)	2,000 individuals of both sexes		Positive	Abdominal aortic aneurysm	Takagi et al[57]
Cross-sectional	205 young women (18 to 22 years of age)	≥ 30	Positive	Carotid intima-media thickness	Knoflach et al[62]
Prospective	730 Caucasian, black and Hispanic individuals of both sexes	≥ 30	Positive	ICVA Higher incidence in men and black individuals	Boden-Albala et al[53]
Meta-analysis	58,000 individuals of both sexes	smaller apo(a) isoforms	2 times higher	CAD and ICVA Individuals with smaller apo(a) isoforms had higher risk	Erqou et al[59]
Prospective	6,000 Koreans of both sexes	≥ 20.1	1.8 time higher	CAD Worse disease course	Kwon et al[51]
Prospective	2,000 Europeans of the United Kingdom of both sexes	≥ 25	Positive	Future events of arterial diseases (coronary and peripheral), but not ICVA	Gurdasani et al[56]
Prospective (20 years)	3,467 Afro-Americans and 9,851 Caucasians of both sexes	≤ 10 and > 10 ≤ 20 and > 20 ≤ 30 and > 30	Positive	Higher number of cardiovascular events in women, higher incidence when comparing between the highest and lowest Lp(a) concentrations	Virani et al[61]
Prospective (10 years)	9,000 Danish individuals of both sexes	≥ 120	3-4 times higher	CAD	Kamstrup et al[58]

Ezetimibe reduces Lp(a) levels in as much as 29%[68]. However, ezetimibe is most often used in association with simvastatin, which has no additive effect to that of ezetimibe in regard to Lp(a).

Another compound widely used in the treatment of dyslipidemia, niacin, effectively reduces Lp(a) levels when administered at high doses. Patients receiving 2 g/day and 4 g/day of niacin have shown a 25% and 38% reduction in Lp(a) levels, respectively. At lower doses (1 g/day), niacin has not shown that effectiveness[69]. Etofibrate, a hybrid drug that combines niacin and clofibrate, at the dose of 1 g/day reduces Lp(a) levels by 26% in type IIb dyslipidemic patients[70]. Patients with type IIa and IIb hyperlipidemia, undergoing treatment with neomycin, have reduced their Lp(a) levels by 24%, while the neomycin-niacin association has resulted in a 45% reduction. That effect is obtained with high doses of both drugs[71].

Extended-release (ER) niacin has reduced Lp(a) levels in diabetic patients with dyslipidemia. Both ER niacin and conventional niacin at high doses are good drugs to treat dyslipidemia, because, in addition to reducing LDL-cholesterol levels, they increase HDL-cholesterol levels and decrease Lp(a) levels[72]. However, high doses of that drug can be associated with some adverse effects, such as migraine, flushing, diarrhea, vomiting, tachycardia, and liver toxicity. The administration of aspirin 30 minutes prior to niacin can relieve some of those effects. Japanese patients with elevated Lp(a) levels (> 300 mg/L) have shown a 20% reduction in Lp(a) levels with low doses of aspirin (81 mg/day)[73]. Women with high Lp(a) levels and an apo(a) polymorphic allele seem to have benefited more from the treatment with aspirin than those who lack that allele[74].

In addition, LDL apheresis has been able to reduce Lp(a) concentration in more than 50% of patients with familial hypercholesterolemia[75].

In hormone replacement, for both men and women[76], as well as in hypothyroidism[77], Lp(a) concentrations seem to decrease. Even considering the beneficial effects of estrogen therapy on Lp(a) and other plasma lipids, it is worth noting the controversies on hormone replacement regarding the increased risk for certain malignant neoplasias and thromboembolic accidents.

Other agents that might reduce Lp(a) levels are as follows: L-carnitine; a combination of L-lysine and ascorbate; thyromimetics; CETP inhibitors; anti-proprotein convertase subtilisin/kexin type 9 (anti-PCSK-9) monoclonal antibodies; protein responsible for degrading LDL receptor; and anti-tocilizumab antibody, that can block IL-6 signaling and is still in an experimental phase[75].

Mipomersen, approved by Food and Drug Administration (FDA) to be used in homozygous familial hypercholesterolemia in January 2013, might be a promise to decrease Lp(a) levels[75]. Mipomersen is an antisense oligonucleotide that acts on messenger RNA, inhibiting apoB 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 not been established[78].

Methotrexate, an immunosuppressive and anti-inflammatory drug used in the treatment of rheumatoid arthritis, has also reduced Lp(a) levels[79].

So far, there is no specific therapy to decrease Lp(a) levels. New therapeutic agents that can more effectively reduce the concentration of that lipoprotein, which has a high pro-atherogenic potential, being thus a risk factor for cardiovascular disease, are still being sought.

Final considerations

Almost half a century after the discovery of Lp(a) by Berg, there is little doubt whether Lp(a) is an independent risk factor for cardiovascular disease. However, the mechanisms linking Lp(a) to atherogenesis are still unclear. In extreme cases, LDL apheresis is recommended[80], but studies proving that the therapeutic decrease of Lp(a) reduces the number of events still lack.

In daily clinical practice and in the absence of well-tolerated drugs that effectively decrease Lp(a) concentrations, levels over 25-30 mg/dL should lead to a more strict control of the other risk factors for CAD.

Author contributions

Conception and design of the research: Maranhão RC; Acquisition of data: Carvalho PO; Writing of the manuscript: Maranhão RC, Carvalho PO, Strunz CC; Critical revision of the manuscript for intellectual content: Maranhão RC, Carvalho PO, Strunz CC, Pileggi F.

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