Lipoprotein (a): Molecular and Epidemiologic Basis about its Role in Cardiovascular Diseases

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IPOPROTEIN (a): Molecular and Epidemiologic basis about its role in cardiovascular diseases

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n 1963, Kare Berg at the University of Oslo discovered Lp(a) as a new human plasmatic antigen set. The interest in Lp(a) increased in 1974 when Berg's team reported an association between high plasma levels of Lp(a) and coronary heart diseases. A number of case-control studies have confirmed their observation and suggested that Lp(a) may be an independent risk factor for premature cardiovascular disease. Several prospective and case-control studies have shown that Lp(a) is an independent risk factor for coronary artery disease, stroke, peripheral vascular disease, accelerated post-transplant atherosclerosis and post-angioplasty restenosis. Lp(a) is now identified as a genetic trait autosomally transmitted, coded by one of the most polymorphic genes known in humans. Variations in this gene are a major determinant of Lp(a) plasma levels, which differ considerably between individuals and also across populations.

The liver is the main organ responsible for its synthesis and catabolism. However, the key receptor that mediates this process has not been found yet, nor any of the enzymes involved. Even though some pharmacologic approaches using niacin, fibric acid derivatives, alcohol-extracted soy protein, growth hormone, and IGF-1 have been tested in order to diminish Lp(a) concentration in high risk patients, none is a therapeutic option to successfully decrease Lp(a) levels.

Key words: Cardiovascular disease, Lipoprotein(a), Lp(a), Apolipoprotein(a), Atherogenesis, Thrombogenesis.

lipoprotein (a) [Lp(a)] was detected in 1963 by Kare Berg by an absorption reaction between rabbit antisera and human sera aimed to identify immunological differences. In this experiment, Berg distinguished different categories of human sera: one of these gave a definite precipitation reaction with absorbed antiserum by double agar gel immunodiffusion technique and a small number of these presented a weak precipitation reaction. Early genetic studies showed a distinctive aggregation bands pattern that clustered in a familial autosomal dominant fashion, evidencing a single locus genetic control of this property. Thus, Lp(a)+ and Lp(a)− were introduced for human sera capable to react with absorbed anti-Lp(a) serum and those lacking this capacity, respectively. Later studies found that these antigenic properties were due to a new circulating plasmatic lipoprotein.

Lp(a) particles share antigens (apolipoprotein B or apo B) with low-density lipoprotein (LDL), but the presence of the apolipoprotein(a) antigen constitutes the unique immunological difference in the molecule. The antigenic properties of Lp(a) lipoprotein still comprise the basis for all its determination procedures1,2,3,4,5.

Structure
Only the European hedgehog, old world primates6 and humans7,8 possess Lp(a) circulating particles, composed by a common low density lipoprotein (LDL) nuclei linked to apolipoprotein(a) by a disulfide bond between a cysteine residue in the Kringle-IV Type 9
The Lp(a) molecule is composed by a lipid-soluble core (cholesteryl ester, and triglycerides) surrounded by polar molecules (phospholipids, unesterified cholesterol) clearly a common a Low density lipoprotein (LDL) linked to an apolipoprotein, Apo(a), by a disulfide bond.

Microscopic analysis show Apo(a) is composed of heavily glycosylated tridimensional structures called Kringles, because of their similitude with a looped Danish pastry. Each kringle contains a mean of 80 amino acids stabilized by three internal disulfide bonds, which finally surround the LDL molecule. A number of plasmatic proteases involved in coagulation and fibrinolysis like urokinase, coagulation factor XII, prothrombin and, most important of all, plasminogen, contain Kringles-like structures (Figure 2).

As mentioned above, Apo(a) has high structural similitude with plasminogen, a key proenzyme of the fibrinolytic pathway. Thus, the kringle IV domains observed in the structure of plasminogen are further classified into 10 distinct subclasses which compose most of the Apo(a) molecule, plus a Kringle V domain linked to an additional one that resembles the catalytic region of plasminogen.

This Apo(a) protease domain, despite of its 89% structural homology with plasminogen’s catalytic domain, lacks the fibrinolytic properties seen in plasminogen because of a substitution of valin and arginin for serin and isoleucin.

The kringle type 2 domain gene can be expressed a variable number of times, resulting in a variable copy number of this structure (3 to 40 copies) within the Lp(a) molecule, which determines the basis for the isoform size heterogeneity of Apo(a); whereas, the remaining 9 subtypes of kringle IV are expressed just in a single copy into the Apo(a) molecule. Due to the variable degree of expression of the Kringle IV type 2 gene, apolipoprotein (a), under genetic control, is able to range between 300 and 800 kD. Thus, it is also a main determinant of the high degree of Apo(a) size heterogeneity(626,871),(946,900) and Lp(a) lipoprotein density among individuals and ethnic groups.

Each type of Kringle IV has an important role in Lp(a) molecule maintenance because Kringle IV types 5 and 8 have lysine residues that help establish disulfide bonds among apo B-100 and Apo(a), and kringle IV type 9 provides a cysteine residue which is essential for disulfide bond formation. Nevertheless, Apo(a) is able to bind other molecules instead of LDL. An example of this is a high affinity lysine binding residue located in Kringle IV type 10, which gives the ability to bond molecules such as fibrin competing with its union to plasminogen, interferring with the fibrinolytic pathways and making it a prothrombotic particle. Moreover, 23% of the mass of the Lp(a) complex, due to N and O-Glycosides linked to Apo(a), provides electronegative properties to the Lp(a) molecule.

Marcovina and cols, in The Lugalawa Study demonstrated the existence of variable size isoforms of Lp(a), even more than 34 apo(a) size isoforms, and the new tendency is to show the smaller size of apo(a) particles as those with the highest proatherothrombotic activity.

There is a wide variety in Lp(a) serum concentrations among individuals. Thus, Apo(a) size isoforms and Lp(a) serum levels change between different ethnic groups. Many studies have shown that the Apo(a) size has an important role in Lp(a) pathogenicity, known to be a function of the number of Kringle IV type 2 repeats. However, there are many other additional factors implicated on Lp(a) pathogenicity.

**Metabolism**

Efforts to explain Lp(a) synthesis and metabolism have been hindered by the lack of an ideal in vitro model. Nevertheless, evidence highlights that the liver is the principal place for Apo(a) synthesis and association with ApoB-100 before its secretion to the extracellular environment. Lp(a) assembly consists of a two-step mechanism: the first one consists of non-covalent interactions, allowing Apo(a) and ApoB-100 to adopt a correct 3D arrangement that facilitates the second step, the disulfide bond formation. Many studies have identified the sequences of amino acids involved in Lp(a) formation.
Lp(a) plasma levels differ among individuals over 1000-fold and are highly heritable as a result of Apo(a) gen expression, which has more than 100 alleles\(^27,28\). Lp(a) plasma concentration depends on its formation rate more than its catabolism.\(^29\) An inverse correlation between Apo(a) size and plasma concentrations exists. Apo(a) size and secretion efficiency is determined by the kringle IV copy number because smaller particles are more efficiently secreted from the hepatic cells than particles with higher molecular weight\(^30\). This inverse correlation has been attributed to an increase in the retention time at the endoplasmic reticulum (ER) of high-sized Apo(a). White et al., using primary baboon hepatocyte cultures, demonstrated that the rate of Lp(a) production is determined by the capacity of the allelic variants to escape from ER\(^30\). Proteasomes play an important role in the rate of secretion of Apo(a) from hepatocytes by mediating pre-secretory degradation of this protein. This process can be avoided by the chaperon calnexin, probably by retaining Apo(a) in the endoplasmic reticulum\(^31\).

The routes for in vivo Lp(a) catabolism are not totally clarified. The liver is the principal site for Lp(a) catabolism, but all the inherent mechanisms are not yet known\(^32,33\). However, the LDL receptor (LDLR) does not seem to have a crucial role in Lp(a) metabolism. This affirmation is based on the fact that statins administration (which causes LDL receptor up-regulation) does not affect Lp(a) plasma concentrations significantly\(^27\). Likewise, other studies have shown that the LDLR, apoE, and the asialoglycoprotein receptor (ASGPR) do not have a primary role on Lp(a) catabolism in mice\(^32-34\). Nonetheless, other receptors that can probably take part in Lp(a) catabolism have been identified. For instance, it has been observed that glycoprotein megalin 330 is able to digest and degrade Lp(a) in vitro\(^35\). Finally, macrophages are able to internalize Lp(a) via the VLDL receptor, a fact that could represent the molecular basis of the atherogenicity of this particle\(^36\).

Reports indicate “free” circulating Apo(a) fractions, composed of interchangeable repetitions of kringle-4 type 2 structures\(^37\). The origin of these fragments is still unknown and enzymatic mechanisms responsible for Apo(a) fragmentation have not been elucidated, but involvement of elastase or collagenases has been proposed\(^38\). A recent work provides evidence regarding neutrophil participation in the Apo(a) splicing process\(^39\), which could explain the presence of Apo(a) fragments in urine, plasma and atherosclerotic plaques.\(^40\) Healthy individuals excrete few quantities (\\(\approx1\%\) of its plasmatic concentration) of small-sized Apo(a) fragments by urine\(^41,42\). This kind of evidence supports the belief in circulating or proteolytic cleavage of urinary Apo(a) fragments origin. Moreover, it is well known that patients with kidney diseases exhibit higher Lp(a) plasma levels than healthy people, probably due to a compensatory increase in albumin and Lp(a) synthesis in order to balance hypoalbuminemia caused by renal damage or as a result of a declination in Apo(a) and Lp(a) catabolic kidney capacity\(^41\).

### Lp(a): Atherogenic Vs Thrombogenic Properties

A number of clinical studies have shown that high plasmatic Lp(a) levels (up to 30 mg/dL) are an important independent risk factor for atherosclerosis-related events like coronary artery disease (including premature and accelerated cardiovascular disease), ischemic stroke and post-angioplasty restenosis with similar pathogenicity in both men and women\(^6,42,43,44,45,46,47,48,49\).

Apo(a) shares 80% of its primary sequence with plasminogen (a serine protease zymogen), but one arginine—serine residue substitution in the protease region suppresses the catalytic activity of this domain\(^50,51\). This explains why Lp(a), once bonded to fibrin, is unable to cleave itself in plasmin. The activation of plasminogen is possible by the formation of a multienzymatic complex with t-PA (tissue plasminogen activator) and fibrin. The Apo(a) from Lp(a), competitively takes the place of plasminogen in the lysine binding sites within fibrin fibers. In essence, Lp(a) acts as a perpetual zymogen without catalytic activity over fibrin in peripheral injured vessels\(^50\).

Other mechanisms by which Lp(a) may increase vascular effects have been described. For example, Lp(a) has been associated to a decrease in t-PA activity as a consequence of plasminogen activator inhibitor (PAI-1) elevation in endothelial cells, smooth muscle cells (SMCs), and macrophages\(^14,52,53\). Other reports have shown that Lp(a) stimulates SMC growth by the inactivation of transforming growth factor-\(\beta\) (TGF-\(\beta\)). Activated TGF-\(\beta\) prevents the migration and proliferation of SMCs. Thus, TGF-\(\beta\) inhibition stimulates SMC growth and blood vessel stenosis, accelerating the atherosclerosis process\(^53\). Furthermore, some studies\(^54,55\) have shown that Lp(a) particles:

1. Accumulated in the sub-endothelium become an important chemoattractant compound for human monocytes during the atherosclerotic process\(^56\).
2. Oxidized Lp(a) inhibits NO-dependent vasodilatation, deteriorating blood pressure control\(^37\), and can be internalized by macrophages via scavenger receptors. Those particles of oxidized-Lp(a) are phagocytosed faster than other lipoproteins, like LDL to form foam cells, stimulating intercellular adhesion molecules expression and, thus, promoting monocyte chemotaxis\(^57,58,59\).
3. Apo(a) can stimulate human umbilical vein endothelial cells to produce C-C chemokine I-309 in vitro, a chemical compound with potent chemoattractant and proinflammatory properties on monocytes in vivo\(^60\).
4. Lp(a) could also modulate platelet interaction by two different ways. Apo(a) from Lp(a) inhibits the interaction between collagen fibers of the injured vessel wall and platelets, decreasing collagen-induced platelet aggregation. Using recombinant Apo(a), platelet aggregation was also enhanced by the activation of Thrombin Receptor–Activating Peptide, probably contributing to thromboembolic complications and atherosclerosis.

Epidemiology
Some conflicting results have been shown in coronary artery disease epidemiological studies linked to Lp(a) levels, ranging from a causative relationship between high plasma Lp(a) levels and acute coronary events incidence, to no clear link between Lp(a) concentrations and cardiovascular disease. This would make us think that the epidemiological evidence for a clear association between elevated Lp(a) plasma levels and cardiovascular pathogenicity has not been totally reached. Meanwhile, many significant studies consider Lp(a) as a reliable predictor for coronary heart disease and, in agreement with this assumption, several studies indicate that low Lp(a) concentrations generally correlate with less incidence of Coronary Artery Disease in Eskimos, French, Native Americans, Caucasians, Hispanic whites, and Chinese populations; whereby, Lp(a) molecule has been lately recognized as an “emerging” risk factor for cardiovascular disease.

Serum Lp(a) levels show marked variation between ethnic groups. This affirmation has been demonstrated by many studies. These ethnic differences also mean different Lp(a) levels and isoforms sizes; for example, in a study conducted in USA by Obisesan et al., children and adolescents showed unequal Lp(a) levels according to ethnic differences among African American, non-hispanic whites and Mexican American children. On the other hand, serum Lp(a) concentration would be variable due to genetics factors (nearly 90% of Lp(a) serum concentrations are determined by genetic influences), age, sex, dietary habits, smoking, waist-hip ratio, glucose tolerance, alcohol consumption and many other factors such as Apo(a) isoform. The association between Lp(a) levels and smaller or bigger isoforms is inverse, showing that high serum levels of Lp(a) generally correlate with smaller Lp(a) isoforms, which are related to an increased cardiovascular pathogenicity, compared to bigger isoforms.

Although several studies show that Lp(a) concentrations are not statistically different between men and women, some reports have demonstrated that elevated Lp(a) levels independently predict an increased risk of stroke and death from vascular disease in men but not in women. Another recent review by Enas et al. shows Lp(a) as an independent risk factor for premature CAD in both sexes. These contradictory results need to be explained by studies based on standardized assays.

In a study conducted by Tavridou and cols. in South Asians, Pakistani, Indian, Bangladeshi and European populations, Lp(a) levels distribution in South Asians was similar to the observed in Caucasian and Chinese populations, in contrast with previous researches which showed South Asians to have higher Lp(a) levels than Europeans. Moreover, twenty-seven different Apo(a) size alleles had been detected in some South Asian groups, fact that may explain the variability in Lipoprotein(a) levels seen in these groups.

Few studies about Lp(a) levels have been conducted in Latin America. Nevertheless, in a research based on Cuban population (mostly African-Caribbean origin) elevated serum concentrations of Lp(a) both in patients with hypercholesterolemia and in those with hypertriglyceridemia were detected. Also, a study conducted by an Uruguayan working group and published in a Mexican Journal, shows considerable higher concentrations of Lp(a) in patients with aortic valvulopathy and going through chronic hemodialysis (n=116) compared to controls (n=90), (p<0.01). Several reports have documented a striking relationship between Lp(a) levels and angiographic documented disease only among younger patients, suggesting that the predictor role of Lp(a) for CAD decreases with age progression. In this sense, Tsimikas et al. studied the relationships between oxidized phospholipids, Lp(a), and CAD discovering that there was a strong association between serum Lp(a) levels plus the oxidized phospholipid:apo B-100 ratio and CAD, but this was observed only in patients under 60 years of age. The reasons for this association are not entirely understood but these findings affirm the existence of clear differences according to age, in terms of Lp(a) pathogenic influences.

The Strong Heart Study demonstrated that American Indian populations had lower Lp(a) concentrations compared to white or black populations. These inter-ethnic differences in Lp(a) levels could be for the most part explained by the well known genetic influences upon Apo(a) expression in hepatic cells, including all biochemical, anthropometric and lifestyle risk factors which would modify in a small sense, serum Lp(a) concentrations. Despite these environmental factors and the general consensus that Lp(a) levels are relatively unaffected by changes in diet and by most of the medications currently used to treat hypercholesterolemia (statins), few studies have shown that a long term diet is able to modify Lp(a) plasma levels. The dietary content of n-3 polyunsaturated fatty acids (PUFAs) is able to interfere with the Apo(a) gene. These results were obtained from studies based on fishermen populations who had a rich intake of PUFAs. More studies are needed.
to confirm these results linked to dietary modifications because of the well-known variability in Lp(a) levels\textsuperscript{13}. It has also been suggested that Lp(a) concentrations can be modified by hormonal influences. Lp(a) levels seem to fluctuate in pregnant women and return to basal values post partum\textsuperscript{13}. Therefore, premenopausal women have lower Lp(a) levels than postmenopausal women\textsuperscript{61}. Lp(a) levels increase in women after the physiological decrease of estrogens by natural or surgical menopause and could contribute to the postmenopausal increase of coronary artery disease incidence. Estrogen replacement therapy has shown to be able to decrease plasma Lp(a) levels and this action could contribute to the reduction in coronary artery disease in women who receive this therapy\textsuperscript{61}. In a recent study conducted by our research group in a city based population from Venezuela\textsuperscript{69}, we found that the elevation of serum Lp(a) levels as a result of estrogen deprivation during menopause is a transitory effect, observing a significant difference on Lp(a) concentration between women with Hormonal Replacement Therapy (HRT) (8.5 mg/dl) vs. women not receiving this therapy (21.5 mg/dl, p<0.001). Nevertheless, differences in Lp(a) levels among these groups (with and without HRT) were not observed after 60 years of age.

There have been discrepancies among results of different studies due to the absence of accurate immunoassays through which Lp(a) measurements would be able to display homogeneous results. Therefore, many studies have aimed efforts to establish an internationally accepted standardized assay for Lp(a) measurement\textsuperscript{49}. Trying to satisfy these deficiencies, the IFCC Working Group for Lipoprotein(a) Assay Standardization has contributed to a practical solution to harmonize test results of immunoassays for Lp(a)\textsuperscript{49}. In this manner, in 1999 the Framingham Heart Study established a reference of normal ranges of Lp(a)-C for men and women in a study based on Caucasian population, indicating that Lp(a) levels of 0.259 mmol/L (10 mg/dl) could be used as a guide to predict higher risk of coronary heart disease in men\textsuperscript{49}.

Moreover, other diseases besides atherosclerosis have been associated with elevated concentrations of Lp(a). The relation between Alzheimer’s Disease (AD) and Lp(a) serum levels has been suggested by recent studies. Serum levels of low molecular weight Apo(a) isoforms are increased in patients with vascular dementia and cerebrovascular disease (CVD). These conditions increase the risk of atherosclerosis and silent CVD, which produce a decline in cognitive functions at advanced age. Atherosclerotic events are associated with AD with an important interaction between apo(a) and apolipoprotein E polymorphism. Clinical data suggest possible links between AD and Lp(a) plasma levels, in which inflammatory events are precursors of Alzheimer’s Disease\textsuperscript{70,71}. In this direction, Mooser et al., demonstrated that Lp(a) is an additional risk factor for late-onset Alzheimer's Disease in carriers of the apoE ε4 allele.

Furthermore, other studies have described increases in Lp(a) level after a myocardial infarction, in postoperative patients and in other acute-phase responses\textsuperscript{72}, clearly suggesting that Lp(a) might be an acute-phase reactant molecule. Likewise, high Lp(a) levels in renal disease and poorly controlled diabetes mellitus have been observed.\textsuperscript{6} Since Lp(a) pathogenicity has been correlated with other plasma lipoproteins such as HDL-C, LDL-C and plasma triglycerides, high Lp(a) levels associated with low HDL-C and elevated LDL-C may have a synergistic role in increasing CAD risk\textsuperscript{13}.

**Table 1. Modifiers of Lipoprotein(a) Serum Levels**

<table>
<thead>
<tr>
<th>Ascending agents</th>
<th>Decreasing agents</th>
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<tbody>
<tr>
<td>hGHSoy Protein</td>
<td>hGH</td>
</tr>
<tr>
<td>Alcohol-Extracted Soy Protein</td>
<td>Niacin / Acipimox</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Gemfibrozil</td>
</tr>
<tr>
<td>Androgenic-Anabolic Steroids</td>
<td>L-carnitine</td>
</tr>
<tr>
<td>Hormone Replacement Therapy</td>
<td>Etopibrate hGH</td>
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The modulator effects of diet upon Lp(a) concentrations have been proven by some studies which demonstrated a beneficial effect of fish and fish oil on lowering Lp(a) levels. In one prospective study, Marcovina et al. studied two populations, racially homogeneous, in Bantu, Tanzania, analyzing their dietary habits linked to Lp(a) concentrations and found that those groups whose diet was based on fish had high frequency of large-size isoforms of apo(a). These individuals had Lp(a) levels 48% lower, compared with vegetarian subjects of the same population, expressing small-size isoform of apo(a). Nevertheless, in this research it was not clear which were the quantities consumed and the specific intakes in the vegetarian groups. These investigators concluded that a long-term diet rich in polysaturated fatty acids decreased Lp(a) plasmatic levels. They suggested that a diet based on fish is capable of diminishing serum levels of Lp(a)\textsuperscript{15}.
Nilausen and Meinertz studied the effects of dietary proteins on Lp(a) concentrations, finding that soy protein may have an Lp(a)-raising effect and that casein could be able to decrease Lp(a) levels in studied subjects. Moreover, the paucity of studied subjects and the absence of women among the patients studied make the results less representative. Nevertheless, years later, Meinertz et al. in another similar research found that alcohol-extracted soy protein lowers Lipoprotein(a) levels, in contrast with intact soy protein, proving the hypothesis that intact soy protein contains Lp(a)-raising alcohol-removable components.

Several studies have shown an increasing effect of GH on serum Lp(a) concentration, including a raise on Apo(a) gene expression in transgenic mice. Therefore, the use of hGH therapy in GH deficient patients has been involved in elevation of serum Lp(a) concentrations and should be employed with caution in subjects with concomitant cardiovascular disease. Paradoxically, (IGF-1) has been strongly related to decreasing this serum lipoprotein concentrations. Even though the molecular basis of these findings has not been successfully achieved yet, we could assume that there must be unknown physiological effects of hGH upon lipid metabolism which are not mediated by IGF-1.

Consistently, all studies have shown niacin to be unique in the ability of effectively decreasing Lp(a) concentrations in a dose dependent effect. In one prospective study, Carlson et al. found that patients who received niacin at doses of 2gr/d and 4gr/d exhibited a decrease in Lp(a) levels by 25% and 38%, respectively. However, many authors do not agree with using niacin as an Lp(a) diminishing treatment, because side effects such as flushing, pruritus, and hyperuricemia are common, and the pharmacological treatment must be maintained throughout life. Aspirin administration 30 minutes before niacin could diminish these side effects in some patients. In addition, an extended-release niacin (nicin ER), that has been approved by the Food and Drugs Administration (FDA) as a wide-spectrum agent used in mixed dyslipidemias to reach adequate levels of serum lipids, can represent a new hope in Lp(a) management. In fact, Pan et al. assessed the effects of the extended release niacin on LDL and HDL size abnormalities and Lp(a) levels in diabetic patients. They studied 36 diabetic subjects between the ages of 34 and 70, concluding that niacin could be a useful drug for diabetic patients who also had dyslipidemia, including a lowering effect on Lp(a) levels (from 37 + 10 mg/dL to 23 +10 mg/dL (P < 0.001)), and, thus, preventing the establishment of a proatherosclerotic lipid profile.

Aspirin was another drug extensively studied regarding Lp(a) levels. In 1999, Kagawa et al. analyzed the effects of aspirin on Apo(a) mRNA expression and the transcriptional activity of the Apo(a) gene promoter in cultures of human hepatocytes, finding that Apo(a) levels are decreased by aspirin through the reduction of Apo(a) RNA expression by 73%. These findings suggest that aspirin could be able to decrease Apo(a) production by hepatic cells. The suppressive effect would play an anti-atherogenic role in cardiovascular disorders. Thus, the effect of aspirin on the transcriptional activity of the Apo(a) gene promoter could be mediated by an unknown transcriptional factor, but further studies are required to clarify the mechanism of this transcriptional regulation. Years later (2002), the same authors studied the effects of aspirin treatment on serum concentrations of Lp(a) in 70 Japanese patients with CAD. They found that aspirin decreased Lp(a) levels in 80% of the studied patients who had high serum Lp(a) concentration (>300mg/L) but there where no significant changes in groups with serum Lp(a) concentrations below 300mg/L. Nevertheless, these paradox results need studies using larger populations and standardized assays to reinforce these findings.

In terms of statin-related studies, Goudevenos et al. studied a group of 90 dyslipidemic, non-smoking patients who were treated with 20 mg/day of atorvastatin during 24 weeks. They analyzed lipid profile and serum levels of Lp (a) and fibrinogen and concluded that Atorvastatin was highly effective in normalizing serum lipid profile but Lp (a) levels did not experience significant changes after atorvastatin treatment. Equally, Kaur et al. demonstrated that simvastatin treatment improved most lipid profile parameters but did not exert significant changes on Lp(a) levels; whereas niacin was the most effective lowering Lp(a) levels but it has several side effects.

In a study conducted by Ramirez et al. lovastatin was compared with Gemfibrozil regarding their effects on Lp(a) in patients with hypercholesterolemia. Gemfibrozil reduced more significantly triglycerides, total cholesterol, LDL, VLDL and Lp(a) levels and increased HDLc when compared with lovastatin. In addition, gemfibrozil reduced Lp(a) levels during the first month of treatment (P= 0.004) and stabilized them during the rest of the treatment. The mechanism of reduction continues to be unknown.

On the other hand, Hormone Replacement Therapy (HRT) has demonstrated a reductive effect on Lp(a) concentration according to results found in a recent study carried out by our research group, in which it was also observed that the increase of Lp(a) levels during menopause was a transitory effect due to estrogen deprivation. Likewise, Shlipak et al. suggest the benefit of estrogen and progestin in women with elevated levels of Lp(a) must be evaluated within the context of the primary results of the HERS study which conclude that these have no benefit nor utility on the preven-
tion of cardiovascular disease. On the contrary, they suggest an increase of cardiovascular risk in the group treated with hormone replacement therapy. Other possible therapeutic options like plant sterols, diacylglycerol, and anabolic steroids have shown a positive effect on Lp(a) levels; however, due to the limited sample size, further studies are required to confirm the utility of these compounds.

Lp(a) and acipimox, L-carnitine and exercise

Acipimox, a nicotinic acid-derivative drug, used in various studies with hyperlipidemic patients with elevated serum Lp(a) (up to 30 mg/dL). The variations in Lp(a) serum levels with the administration of acipimox were low, but patients can tolerate this drug better than nicotinic acid, which enhances the incidence of side effects, commonly cutaneous flushing.

Sirtori et al. studied the effect of L-carnitine in patients with Lp(a) serum concentrations in the range of 40-80 mg/dL. Based on a double blinded study, they determined that 2 gr/day of L-carnitine are able to reduce hyper-Lp(a) in 77.8% of treated patients (-7.7% vs. baseline group and -11.7% vs. placebo), suggesting that L-carnitine shows potential as a well-tolerated agent to decrease Lp(a) levels without major side effects. On the other hand, Derosa et al. included in their study a group of 94 hypercholesterolemic patients with a recent diagnosis of type 2 Diabetes Mellitus. In the treatment group (men=24, women=22) L-carnitine significantly lowered Lp(a) plasma level compared with baseline (P < 0.05) and the placebo group (men=23, women=25) (P < 0.01).

Numerous studies have shown that regular exercise can have beneficial effects in serum lipid profile, decreasing coronary atherosclerosis risk and cardiovascular mortality. Contradictory results have been found in other studies between sedentary patients and athletes, because patients with regular training can have higher serum levels of Lp(a). The answer to this question is seen in the variability of physical condition, ethnicity, age, sex, weight, type of exercise and body fat percentage. These regulate oxygen and caloric contribution, duration and intensity of exercise and resistance.

Ruiz et al. studied three groups of high performance athletes, in volleyball, swimming and soccer and a control group of healthy sedentary patients with similar anthropometrics and sociologic characteristics, to compare the difference between serum Lp(a) levels in relation to each type of sport. They investigated their alimentary habits, health condition and plasma Lp(a) concentration, and determined that soccer players had the highest levels of plasmatic Lp(a) while swimmers had lower Lp(a) serum levels. Although, there are no satisfactory explanations for this phenomenon, it has been suggested that the elevated intensity, hits and falls of soccer, produce an enhancement of pro-inflammatory cytokines and endotoxins (a lipopolisacaride, LPS, from gram negative bacterial cellular wall). The aerobic condition and moderated intensity of swimming do not produce an elevation of cytokines or endotoxins to mediate an inflammatory response. Also, recent studies suggest that after intense exercise (about 9 to 12 months), in some persons serum levels of Lp(a) (10–15%) might modestly increase, while in others persons plasmatic Lp(a) levels stay within normal range.

On the other hand, fibrates and niacin, drugs used in dyslipidemic patients, could be of additional benefit by reducing plasma lipoproteins as demonstrated by some investigators. Likewise, Sposito et al. studied 25 type llb dyslipidemic patients with Lp(a) above 40 mg/dL, triglyceride levels between 200 a 400 mg/dL and total cholesterol over 240 mg/dL, observing the effects of Etofibrate, a synthetic compound drug of niacin and clofibrate, on Lp(a) concentrations and comparing its effects with those of controlled-release niacin. The patients were randomly assigned to a double-blind 16-week treatment period with either etofibrate (500mg twice daily; N=14; 12 males; Age: 56 ± 5 years) or niacin (500 mg twice daily; N=11; 8 males; Age: 57 ± 7 years). In their results both drugs improved lipid profile; nevertheless, the reduction of Lp(a) and LDL cholesterol concentrations was not statically significant in the group treated with niacin. In contrast, etofibrate significantly reduced Lp(a) concentration by 26% and LDL cholesterol by 23%.

In terms of Lp(a) assembly, Sharp et al. studied a synthetic peptide that is able to inhibit Lp(a) assembly. In their results it is observed that a sequence inside ApoB-100 (the apoB4372–4392 sequence) mediates the initial noncovalent binding between LDL and Apo(a), demonstrating that a synthetic peptide based on this sequence (apoB4372–4392 peptide) works as a novel inhibitor of Lp(a) formation that acts by noncovalently binding Apo(a) and inhibiting the first step of Lp(a) assembly. These results are reinforced in 2004 also by Sharp et al. were they describe that the α-helical nature of apoB4372–4392 peptide is critical for its inhibitory activity, effect that can be increased by the substitution of lysines for arginines in the sequence, change that is able to increase the inhibitory capacity of the peptide.


46. Florian Kronenberg, Martina F. Kronenberg, Stefan Kiech, Evi Treinkwald, Peter Santer, Friedrich Oberhollenzer, Georg Egger, Gerd Utermann, and Johann Willeit. Role of Lipoprotein(a) and Apolipoprotein(a) Phenotype in Atherogenesis: Prospective Results From the Bruneck Study. Circulation 1999; 10: 1154-1160.


52. Mark A. Hancock, Michael B. Boyfa, Santica M. Marcovina, Michael E. Neesham, and Marlys L. Koschinsky Inhibition of Plasminogen Activation by Lipoprotein(a): CRITICAL DOMAINS IN APOLIPOPROTEIN(a) AND MECHANISM OF INHIBITION ON FIBRIN AND DEGRADED FIBRIN SURFACES. J. Biol. Chem. 2003 278(26): 23260-23269.


