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Lipoprotein (a) and Cardiovascular Risk

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1. Introduction

First epidemiological studies of Lp(a) and CHD were reported at the end of the last century (1-3) but the investigation of this lipoprotein as a potential cardiovascular risk factor has been hampered by the lack of consistent approaches to its measurement for decades. Lp(a) laboratory standardization emerged in 2000 (4) and was accepted by the World Health Organization in 2004 (5). Another challenge associated to its measurement is the fact that population differences can also contribute to variation in Lp(a) serum concentration (6). Since Lp(a) characterization, evidences favoring its association with cardiovascular risk have been reported. At the same time, studies against this association have also been published leading to some confusion regarding to the possible role of Lp(a) in cardiovascular disease. The last years have clarified somewhat this issue and evidences of Lp(a) as an independent cardiovascular risk factor have been proposed (7-13). Several key points such as its homology with plasminogen, differences among the apo(a) isoforms, genetic considerations as well as special circumstances such as the relationship of Lp(a) and atrial fibrillation, dialysis, alcohol consumption and blood coagulation have been investigated. In this chapter, Lp(a) metabolism, epidemiological and genetic considerations, association with coronary heart disease and stroke, special situations as well as controversies and current treatment options are related.

2. Lipoprotein (a) metabolism

Lipoprotein (a), Lp (a), is a low density lipoprotein (LDL)-like particle synthesized in the liver by hepatocytes and then secreted into plasma. It was first described by Berg in 1963 (14). It consists of an apolipoprotein B100 (apoB100) molecule that is linked covalently by a disulfide bond to a large glycoprotein known as apolipoprotein (a), [apo(a)] (15). Lp(a) metabolic route is shown in figure 1. Its molecular weight ranges from 200 kDa to more than 800 kDa (16). The apo(a) gene (*LPA*) is a major determinant of the plasma concentration of Lp(a), including variations in the kringle region-coding repeats, with accounts for the size polymorphism of apo(a) leading to different apo(a) sizes (17). This fact is very important because small size isoforms seem to be associated to worse cardiovascular profile. Apo(a) chain contains 5 cysteine-rich domains known as kringles, and especially Kringle IV (KIV) is very similar to plasminogen (18,19). This particle is not only located in the plasma but also has been shown to enter the arterial intima of humans and has an increased affinity by the

extracellular matrix (20). This issue confers a greater opportunity to Lp(a) oxidation (21) and interaction of Lp(a) with macrophages (22,23). Recently, it has been suggested that Lp(a) could be a preferential carrier of oxidized phospholipids in human plasma (24). These oxidized Lp(a) have a greater atherosclerotic effect as compared to native Lp(a) and this action may be increased by hyperglucemia (25). Different Lp(a) subtypes have been proposed regarding to apo(a) isoforms and these apo(a) isoforms predict the risk for CHD independently of the ethnic group (26). These isoforms are classified in order to their different size (16). Table 1 shows classification of these isoforms and its relation with KIV repeats.

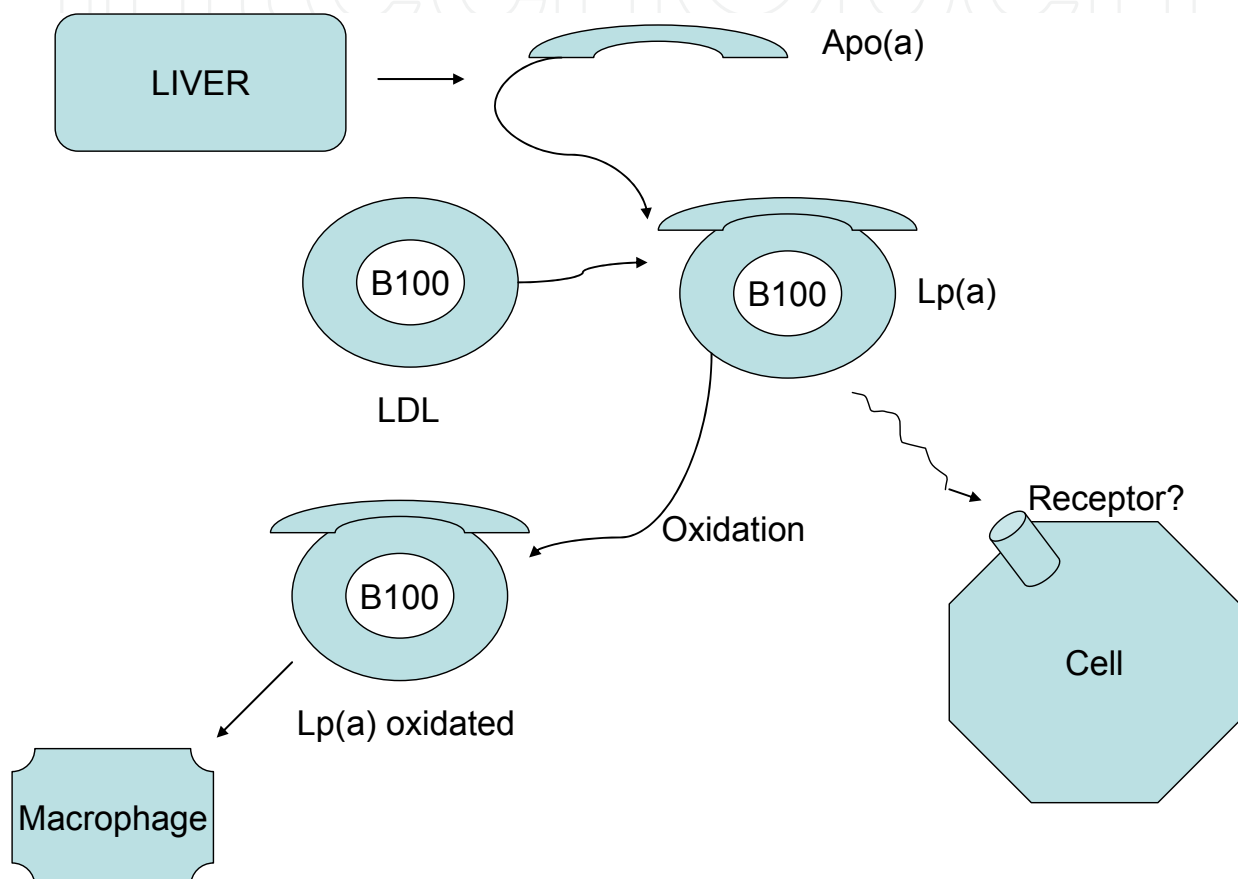


Fig. 1. Metabolic route of Lp(a).

3. Epidemiological aspects

Plasma levels of Lp(a) show great diversity regarding to different ethnical groups but a plasmatic concentration greater than 30 mg/dl is currently considered an independent cardiovascular risk factor (27). In this sense, African-Americans have higher Lp(a) concentrations than Caucasians. These levels may also be very different even in individuals carrying apo(a) of the same size polymorphism. It has been suggested the possibility of the presence of additional factors affecting this ethnical differences or the existence of high risk-Lp(a) or low risk-Lp(a) (28,29). By the other hand, not all ethnic groups show the same relation with Lp(a). In American-Indians, Lp(a) level has been reported to be low and non independently associated with cardiovascular disease (30).

<i>Repeats (No.)</i>	<i>Molecular weight (kDa)</i>
5-12	<400
13-20	400-500
20-25	500-650
>25	>700

Table 1. Relation between KIV₂ repeats and apo(a) isoforms size

Respecting to apo(a) isoforms, it has been suggested a most important pathogenic role of Lp(a) particles with smaller apo(a) isoforms (18,31). This is probably due to several factors. First, an increased capacity to bind oxidized phospholipids, second, the ability to localize in blood vessel walls, and eventually related to its thrombogenic effect by increasing inhibition of plasmin activity. Apo(a) size heterogeneity is related to a copy number variation in the protein domain kringle IV type 2 (KIV₂) (32) (Table 1). This copy number variation (5-50 identically repeated copies) confers heterogeneity in the molecular mass of apo(a) ranging between 200 and 800 kDa. Ethnic differences in the frequency distribution of apo(a) KIV repeated alleles have been reported (33,34). In all ethnic groups, Caucasians, Asians and African-Americans, higher levels of circulating Lp(a) concentrations tend to be associated with smaller apo(a) isoforms (35,36). This finding could explain partially the association of higher Lp(a) levels and cardiovascular disease. People with smaller apo(a) isoforms have an approximately 2-fold higher risk of coronary artery disease and ischemic stroke than those with larger apo(a) isoforms. Furthermore, isoforms with less KIV repetitions (isoforms F, B, S1 and S2) have the greater analogy with plasminogen being associated with higher coronary risk (37,38).

4. Genetic considerations

Apo(a) gen (6q2.6-q2.7) (39,40) have different kringle domains that show a high degree of homology to the kringle domains IV and V of plasminogen (41).

Genetic variants associated with Lp(a) level have been associated with coronary disease (42). More specifically, the apo(a) gen is the major determinant of variation in some populations like African-Americans modulating the plasmatic concentration of Lp(a) (43). It has been reported that apo(a) gene accounts for greater than 90% of the variation of plasmatic Lp(a) concentrations (28). Apo(a) gen polymorphisms as well certain gene cluster associated to *LPA* have been shown to modulate Lp(a) concentrations leading to an increase in the risk for coronary artery disease (44). The genetic basis for apo(a) isoform variation is a segment existing in multiple repeats (KIV₂ polymorphism) located in the *LPA* gene (41). Variations in nucleotide polymorphisms in *LPA* may be an important contributor to the observed Lp(a) between-population variance and increase Lp(a) level in some populations (45-47). Once again, ethnic differences have been reported in people of European continental ancestry where apo(a) isoform polymorphism contributes between 40% and 70% of the variation of Lp(a) concentration showing fewer number of KIV₂ repeats (41,46), (Table 1).

5. Evidences favoring association with cardiovascular disease

- **Coronary heart disease:** Circulating Lp(a) concentration is associated with risk of coronary heart disease (CHD) independently from other conventional risk factors including total cholesterol concentration. Lp(a) excess has been independently associated to myocardial infarction and unstable angina (48), restenosis after coronary angioplasty (49), and coronary bypass grafting (50) respectively. Prospective epidemiological studies have reported positive association of baseline Lp(a) concentration with CHD risk. Based on this epidemiological data, a relative risk of 1.5 has been reported involving those patients with mean Lp(a) values of 50 mg/dL, especially in patients with premature coronary disease (51). Continuous associations of Lp(a) with the risk of coronary artery disease have been reported and this association is similar regarding to coronary death and non-fatal myocardial infarction (52-54). This association is not significantly affected by sex, non-HDL or HDL cholesterol, triglycerides, blood pressure, diabetes, or body mass index. These results are consistent mainly in Caucasians but studies in non-Caucasians are needed to corroborate also this issue in other populations (33). The association of Lp(a) concentrations with CHD is only slightly reduced after adjustment for long-term average levels of lipids and other established risk factors. This situation increases the likelihood that Lp(a) is an independent risk factor for CHD (53). The strength of Lp(a) as coronary risk factor is relatively modest as compared with non-HDL cholesterol. This is somewhat different when the level of Lp(a) is very high leading to a proportionally most important role for Lp(a) as CHD risk factor (52). Trying to associate fibrinolysis and myocardial ischemic disease, it has been suggested that Lp(a) may inhibit fibrinolysis of coronary artery thrombus (55). This is because higher levels of Lp(a) have been reported in survivors of myocardial infarction in whom recanalization of infarct artery failed as compared with patients with a patent artery (56). Other prospective studies have not shown relationship between high levels of Lp(a) or apo(a) isoforms and cardiovascular risk (57-59) contributing to some degree of controversy.
- **Stroke:** Serum Lp(a) concentration is also associated independently with risk of ischemic stroke (60,61). Current data in relation to Lp(a) concentration and stroke are sparse but seem to be similar than those for CHD. Serum Lp(a) level was demonstrated to predict stroke in elderly people in a large longitudinal (62) and in a case-control study (63). It has been shown that high levels of Lp(a) are associated with ischemic stroke in patients with atrial fibrillation especially when left atrial thrombus is present (64). Unhealthy dietary fat intake and a high serum Lp(a) level have been shown to predict fatal and nonfatal stroke or transient ischemic attack independently of established risk factors in a study of a community-based sample of middle-age men (65). Lp(a) has also been detected in intraparenchymal cerebral vessels suggesting a potential inflammatory role in acute stroke for Lp(a) (66). Other studies have not found statistical relationship between higher level of Lp(a) and thrombotic stroke (67).

6. Special situations

There are some common medical conditions that may be influenced by the level of Lp(a). Conversely, serum Lp(a) levels can be modified by the existence of some medical disorders. These medical conditions are summarized as follows:

- **Lp(a) and dialysis:** It is well known that atherosclerosis is more prevalent among patients with end-stage renal disease (68). Hemodialysis procedure “per se” has been shown to modify serum levels of Lp(a) increasing them after hemodialysis procedure (69). It has been proposed that inflammation, a very important condition in hemodialysis patients, could play an important role in this Lp(a) increase (70-72). Basal serum levels of Lp(a) are increased in dialysis patients and the level is elevated in almost 70% of patients (73). Even more, in patients with continuous ambulatory peritoneal dialysis, Lp(a) level is significantly higher as compared with patients on hemodialysis (74) pointing to a possible modulating effect of Lp(a) concentration by the different dialysis procedures. Particularly, high serum Lp(a) levels and the low molecular weight apo(a) phenotype have been associated with adverse clinical outcomes in dialysis patients (75).
- **Lp(a) and atrial fibrillation:** Higher serum Lp(a) level in ischemic stroke patients associated with atrial fibrillation and left atrial thrombus formation or in acute myocardial infarction has been reported (76,77). Lp(a) elevation and reduced left atrial appendage flow velocities have been shown to be independently risk factors for thromboembolism in chronic nonvalvular atrial fibrillation (55). Probably, the association of Lp(a) is stronger in the presence of atrial thrombus instead of atrial fibrillation itself, because of the plasminogen inhibitory action of Lp(a) (64). In this sense, other studies have not found association between higher levels of Lp(a) and non-valvular atrial fibrillation (78).
- **Lp(a) and blood coagulation:** the genetic homology in the cDNA sequence of human apo(a) with plasminogen, the zymogen for the major fibrinolytic serine protease plasmin (79), has been related with the cardiovascular pathogenicity of Lp(a) (80). There is a major difference in the kringle structure between plasminogen and Lp(a) that is a single aminoacid exchange (R560S) that prevents apo(a) from enzymatic cleavage such as the action of tissue-type plasminogen activator (t-PA) or urokinase plasminogen activator (u-PA). This molecular mimicry between plasminogen and Lp(a) contribute to the role of Lp(a) in atherogenesis binding Lp(a) to the tissue factor pathway inhibitor (TFPI), docking to diverse lipoprotein receptors (especially those affecting LDL or very low density lipoprotein (VLDL) and by the entrapment of Lp(a) into extracellular matrix proteins (81). This situation leads to a retention of Lp(a) and recruitment of monocytes, upregulating the expression of the plasminogen activator inhibitor 2 in these monocytes (82). It has also been reported that Lp(a) modulates endothelial cell surface fibrinolysis contributing to the increase in atherosclerotic risk (83).
- **Lp(a) and alcohol intake:** Many epidemiological and clinical studies have shown that light-to-moderate alcohol consumption is associated with reduced risk of CHD and total mortality in the middle-age and elderly of both genders (84,85). Lipid levels are modified by alcohol in different forms but it is not completely clear the way they are. In alcohol abuse patients, levels of Lp(a) have been reported to decrease and this has been related to the time of abstinence (86). In other study an increased level among table wine drinkers has been described (87). A special situation is the association of alcohol intake, Lp(a) level and vascular disease. In this sense, high serum Lp(a) concentration and heavy drinking were found independently associated with larger infrarenal aortic diameters (88) and abdominal aortic aneurysms (89), probably due to the capability of Lp(a) to inhibit elastolysis in the vessels wall (90).

7. Treatment

Treatment possibilities are scarce at present when the aim is to reduce Lp(a) plasma concentration. Only niacin, in a dose dependent fashion, and certain inhibitors of cholesteryl ester transfer protein have shown limited effect ranging between 20%-40% lowering from baseline levels (91,92). Other drugs such as acetylsalicylic acid and L-carnitine can decrease mildly elevated Lp(a) concentrations (91,93,94). Contradictory findings have been reported with statins (95-98). Promising molecules like mipomersen, an antisense oligonucleotide directed to human apoB₁₀₀ have been shown to reduce Lp(a) concentrations by 70% in transgenic mice (99). Similar molecules such as eprotirone, tibolone and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors can also decrease Lp(a) concentrations being currently under development (91,100-102). Nevertheless, the most dramatic change in Lp(a) concentrations can be achieved with regular lipid apheresis (103,104). Table 2 shows the efficacy of different treatment options in reducing Lp(a) plasmatic level.

<i>Treatment</i>	<i>Change in Lp(a) concentration (%)</i>
Diet and exercise	0
Resins	0
Fibrates	5-10
Statins	5
Nicotinic acid	35
Neomicine	25
Estrogen substitutive therapy	15-40
Apheresis	40-60

Table 2. Effect of different pharmacological therapies on Lp(a) serum concentration.

8. Controversies

The risk associated to Lp(a) concentration is only about one-quarter of that seen with LDL cholesterol so any clinical implication of this moderate association currently appeared limited. The role of specific Lp(a) subtypes could help to clarify the vascular risk. Particularly, smaller apo(a) isoforms could act associated with other factors such as small-dense LDL and oxidized LDL particles in the vessel wall increasing inflammation and accelerating atherosclerotic disease. This fact needs for more investigation.

Studies reporting association of apo(a) isoforms size variations with the risk of vascular disease have reported divergent relative risks, involve wide confidence intervals and the number of individuals included has been small. If smaller apo(a) isoforms are relevant to

vascular disease independent from Lp(a) concentration is not completely clear at present. Moreover, many studies have used different cut-offs to define smaller apo(a) size.

The effect of the change in Lp(a) level and its relation with inflammation as well as its influence on endothelial function are unknown at present.

It has been suggested that Lp(a) is associated with CHD only at very high concentrations but this affirmation remains somewhat controversial making very important to identify possible ethnical differences as well as an adequate cut-off level we can rely on.

9. Conclusions

Lp(a) results from the association of apo(a) and LDL particles. Since first studies linking Lp(a) and cardiovascular disease, an important amount of clinical and laboratory evidences have supported the fact that Lp(a) is an independent cardiovascular risk factor, especially in younger people with premature cardiovascular disease.

Many ethnical differences and variations in apo(a) size have been reported. Moreover, small apo(a) size isoforms have been related with an increased cardiovascular risk. Its relation with the number of KIV repeats determines genetically variation in apo(a) size. Several studies including methanalysis have related higher levels of Lp(a) with CHD and stroke.

It seems also that Lp(a) is elevated in patients under dialysis, and possibly in those with atrial fibrillation increasing the cardiovascular risk of these patients, normally already high.

An interesting link between laboratory and clinical effects of Lp(a) is its action modulating the fibrinolytic system because of the great homology between Lp(a) and plasminogen.

The association between higher levels of Lp(a) and alcohol intake remains more controversial at present.

Current treatment options are not very useful except for niacin and plasma apheresis but both therapies are not easy to use because of toxicity, tolerability and availability.

Finally, large prospective studies are needed focusing on Lp(a)-associated small apo(a) isoforms and cardiovascular disease, and also in order to ensure treatment approaches.

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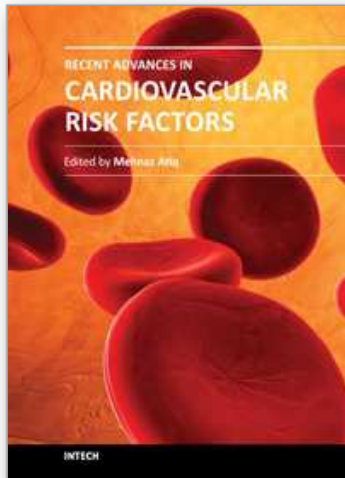
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Recent Advances in Cardiovascular Risk Factors

Edited by Prof. Mehnaz Atiq

ISBN 978-953-51-0321-9

Hard cover, 522 pages

Publisher InTech

Published online 21, March, 2012

Published in print edition March, 2012

Among the non-communicable diseases, cardiovascular disorders are the leading cause of morbidity and mortality in both the developed and the developing countries. The spectrum of risk factors is wide and their understanding is imperative to prevent the first and recurrent episodes of myocardial infarction, stroke or peripheral vascular disease which may prove fatal or disabling. This book has tried to present an update on risk factors incorporating new research which has thrown more light on the existing knowledge. It has also tried to highlight regional diversity addressing such issues. It will hopefully be resourceful to the cardiologists, general practitioners, family physicians, researchers, graduate students committed to cardiovascular risk prevention.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

José Antonio Díaz Peromingo (2012). Lipoprotein (a) and Cardiovascular Risk, Recent Advances in Cardiovascular Risk Factors, Prof. Mehnaz Atiq (Ed.), ISBN: 978-953-51-0321-9, InTech, Available from: <http://www.intechopen.com/books/recent-advances-in-cardiovascular-risk-factors/lp-a-and-cardiovascular-risk>

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