

## LIPOPROTEIN(A) IN CEREBRAL STROKE: A REVIEW

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*[Lipoproteina (a) nell'ictus cerebrale. Review]*

### ABSTRACT

Lipoprotein(a) [Lp(a)] and apolipoprotein(a) [apo(a)] levels may be risk factors for cerebrovascular diseases. Lp(a) can accumulate in the arterial walls of cerebral vessels. This happens because apo(a) can bind proteoglycans, glycosaminoglycans and fibronectin, which are important connective tissue elements. Lp(a) is implicated in the activation of endothelial uptake, oxidative modification and foam cell formation, suggesting that these processes could play an important role in atherosclerosis.

Endothelial dysfunction represents a common link in many diseases induced by elevated plasma concentrations of Lp(a) ranging from chronic inflammation to atherosclerosis and including ischemic stroke. The role of Lp(a) as a risk factor for ischemic stroke has been assessed in several studies.

The results support the hypothesis that elevated Lp(a) is a risk factor for ischemic stroke and especially for stroke caused by large artery atherosclerosis.

**Key words:** Lipoprotein(a), apolipoprotein(a), atherosclerosis, stroke, cardiovascular disease.

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### Introduction

Lipoprotein(a) was described in 1963 by Berg in the electrophoretic band of prebeta lipoprotein. It has a diameter of 25-30 nanometers and molecular weight ranging between 280,000 and 700,000 daltons. It consists of a low-density lipoprotein (LDL)-like particle, combined with a chain of apolipoprotein(a) or apoprotein(a)<sup>(1)</sup>. Apoprotein(a) [Apo(a)] is linked to apolipoprotein B100 (ApoB100) by a single disulphide bridge<sup>(2)</sup>.

The apo(a) gene is a member of the plasminogen superfamily of evolved genes. The apo(a) gene has been described in primates and the hedge-hog<sup>(3)</sup>.

Although the relation between Lp(a) and atherosclerosis has been reported in numerous studies, little is known about whether Lp(a) would exacerbate the complicated lesion formation in vivo<sup>(4)</sup>.

Clinical importance of Lp(a), as reported in several studies, is due to its role as a risk factor for

cardiovascular diseases. It has been suggested that the atherogenic property of Lp(a) may be associated with its structural similarity to plasminogen<sup>(5)</sup>. Moreover, lipoprotein(a) may interfere in clot lysis by competing for the same binding sites as plasminogen.

Lp(a) is implicated in the activation of endothelial uptake, oxidative modification and cell formation, and it has been suggested that these processes play an important role in atherosclerosis. Lp(a) can accumulate in the arterial walls of coronary and cerebral vessels<sup>(6)</sup>. This happens because apo(a) can bind proteoglycans, glycosaminoglycans and fibronectin, which are important connective tissue elements<sup>(7)</sup>. Some studies demonstrate that serum Lp(a) concentrations correlate significantly with plasma fibrinogen levels<sup>(8)</sup>. Plasma fibrinogen level has been recognized as an independent risk factor for atherosclerosis and its thrombotic complications in adults<sup>(9)</sup>. Fibrinogen enhances platelet

activity, and elevated plasma fibrinogen concentrations are predictors of vascular events. Fibrinogen promotes the binding of apo(a) to the vessel walls in vivo and it is necessary for its resulting pathological effects involved in the generation of atherosclerosis<sup>(10)</sup>. Moreover, fibrinogen is an independent risk factor for ischemic atherothrombotic stroke<sup>(11)</sup>.

Elevated Lp(a) levels (>25–30 mg/dl) have been linked to an increased risk of atherothrombotic diseases<sup>(12,13)</sup>. Metabolic abnormalities and pharmacological agents can influence the concentrations of Lp(a). These values can be elevated in diabetes mellitus<sup>(14)</sup>, chronic renal failure<sup>(15)</sup>, nephrotic syndrome<sup>(16)</sup>, cancer<sup>(17–19)</sup>, hypothyroidism<sup>(20)</sup> and as part of the acute phase response<sup>(21)</sup>. Lp(a) values are low in liver failure<sup>(22)</sup> and hyperthyroidism<sup>(23)</sup>. The values for Lp(a) serum levels are between 0.1 and 300 mg/dl; mean values are 18.4 mg/dl<sup>(24)</sup>.

Elevated serum lipoprotein(a) is an independent predictor of coronary artery disease (CAD) and myocardial infarction<sup>(25–27)</sup>, intermittent claudication<sup>(28)</sup> and cerebrovascular disease<sup>(29)</sup>.

Motta et al studied the transient increased serum levels of this lipoprotein during acute myocardial infarction (AMI). The positive correlation between mean Lp(a) values on day 1 and 7, and the size of the necrotic area, suggest that Lp(a) has an atherogenic and prothrombotic role. Moreover, elevated Lp(a) values were related to increased tissue damage. The study suggests that periodical determination of Lp(a) values in subjects with coronary diseases is useful in order to predict further acute vascular events<sup>(30)</sup>.

### Serum levels, structure and isoforms

Biophysical studies of Lp(a) have revealed aspects of its structure. Lp(a) particles examined by electron microscopy appeared to be roughly circular, with no apparent differences from images of LDL (31). Cryoelectron microscope studies showed Lp(a) particles to be roughly spherical with a low-density core surrounded by a higher density shell, and some particle averages showed a toroidal structure<sup>(32)</sup>. However, it was not possible to relate these observations to other properties of Lp(a).

Apo(a) shows a specific structure, different by apoB100 with low content of aspartate, leucine, isoleucine, phenylalanine and lysine, while proline, threonine, arginine and glycine are elevated. The high content in proline, serine and threonine in the apo(a) suggests the frequent presence of  $\beta$ -sheet.

Moreover, serine and threonine represent glycosylation sites<sup>(33,34)</sup>

While in the apoB100 carbohydrates represent 5–10% of the protein weight, in the apo(a) this value can be 40%. The percentages of carbohydrates are: 26% galactose, 9% mannose, 16% galactosamine, 12% glucosamine and 37% sialic acid.

High carbohydrates and proline levels in the apo(a) cause less structural order compared to apoB100. Apo(a) contains 8% of alpha-coil, 21% of beta-sheet and 71% of random coil, apoB100 40, 30 and 30% respectively<sup>(35)</sup>.

The apo(a) product contains several sequential tertiary polypeptide coils called kringles, that are homologous with the kringle IV region of plasminogen. Some of the kringle IV units appear to contain either strong or weak lysine binding sites that contribute to the structure of the Lp(a) particle<sup>(36)</sup> and to its (sub)cellular distribution<sup>(37)</sup> and metabolism<sup>(38)</sup>. The number of sequential kringles for repeats is highly variable, comprising the primary basis for the genetic polymorphism and size heterogeneity found in humans<sup>(39)</sup>.

The serine-proteinase region of apo(a) contains the same residues that constitute the potential active site in plasminogen, however, a Serine substitution at the Arginine-Valine activation cleavage site makes apo(a) insensitive to plasminogen activators<sup>(40)</sup>.

Dieplinger et al discovered six different isoforms (F, B, S1, S2, S3 and S4 according to different electrophoretic mobilities) that vary in size from 300 to 800 kDa<sup>(41)</sup>. More recently, a seventh isoform category, S5, has been described. Improved techniques at higher resolution revealed >20 protein isoforms. The isoforms can be grouped into low (LMW) and high molecular weight (HMW) isoforms, according to the number of kringle IV repeats in the apo (a) molecule. In healthy subjects, LMW isoforms are associated with high levels of Lp(a) and HMW isoforms with lower levels of Lp(a). Lp(a) levels are not significantly affected by age or sex, diabetes, dietary cholesterol or HMG-CoA-reductase inhibitors<sup>(42)</sup>.

### Genetics of Lp(a)

The genetic nature of the Lp(a) lipoprotein variations in human serum was realized and reported by Berg in 1963. Single gene control was postulated and later confirmed in numerous studies, including a major study from Hawaii<sup>(43)</sup>. The gene

for the Lp(a) apolipoprotein, the LPA gene, has evolved from the gene for plasminogen, which is a much smaller protein<sup>(44)</sup>. Lp(a) concentrations exhibit only a very small amount of variation in any given individual. Classical linkage studies between segregating high Lp(a) lipoprotein levels and plasminogen polymorphism (the polymorphism in the gene that the LPA gene developed from) has confirmed an extremely close linkage.

This very strong linkage, between segregating high Lp(a) lipoprotein levels and plasminogen, by itself proves that Lp(a) level is controlled by the LPA locus on chromosome 6 or by regions very closely linked to the LPA gene. The discovery that the LPA gene has evolved from the plasminogen gene made it plausible to hypothesize that LPA genes could influence components or processes related to thrombogenesis or thrombolysis in various ways.

Berg showed the interrelationship between fibrinogen levels and Lp(a) levels; LPA genes appear to affect both the level and variability of fibrinogen; they may have “level gene” as well as “variability gene” effects on fibrinogen.

The effect of LPA genes on absolute fibrinogen level may be more pronounced at higher age than at young age. The same may be true with respect to the “variability gene” effect of LPA genes and this effect may also be stronger in women than in men<sup>(45)</sup>.

### Lp(a) and stroke

Apart from the well established risk factors for stroke (such as increasing age, hypertension, diabetes, smoking, or the presence of vascular diseases), the possibility that Lp(a) may be a risk factor for ischemic stroke has been assessed in several (mainly retrospective) studies<sup>(46)</sup>. Milionis et al. suggested that determination of Lp(a) levels and Apo(a) isoform size may be important in identifying elderly individuals at risk of ischemic stroke independently of other risk factors and concurrent metabolic derangements<sup>(47)</sup>.

Petersen et al in 2007 investigated whether elevated Lp(a) is more frequent in ischemic stroke related to atherothrombosis than in other etiologies of stroke. Because of the close structural homology between Lp(a) and plasminogen, they also studied the role of plasminogen in different stroke subtypes and whether a dependency on Lp(a) plasma levels exists. The results support the hypothesis that ele-

vated Lp(a) is a risk factor for ischemic stroke and especially for stroke caused by large artery atherosclerosis. Low plasminogen activity may play a role in the pathogenesis of cerebrovascular diseases, especially for the development of cardioembolic stroke<sup>(48)</sup>.

The relationship between Lp(a) and hemostatic profile was demonstrated in other studies which documented that Lp(a) seems to be more associated with coagulation markers of thrombosis<sup>(49)</sup>. Many studies documented the relationship between Lp(a) and symptomatic stroke. Nevertheless, asymptomatic, “silent”, cerebral infarction has also attracted interest. A silent stroke is usually detected on incidental imaging (computed tomography scan, magnetic resonance imaging) in patients with no localised neurological signs. In most cases of silent infarction, lacunar strokes of less than 1 cm in size are detected in the basal ganglia in apparently healthy elderly individuals. These lesions are associated, in most reports, with advanced age and hypertension, and constitute a major cause of dementia.

Kario et al reported that silent multiple lacunar strokes in 178 asymptomatic, high risk, elderly Japanese patients (aged 44 to 93 years) were associated with a hypercoagulable state, endothelial damage, and significantly raised Lp(a) concentrations.

The authors further subdivided the silent lacunar group into subgroups based on the number of lacunes (few lacunes, 1–2; moderate number, 3–4; numerous lacunes, 5). Raised Lp(a) values (and particularly those > 300 mg/litre) were more common in the “numerous lacune” than the “few lacune” subgroups (50). On the other hand, there are studies that do not support Lp(a) as a risk factor for stroke. Hobbs and White proposed several factors that might contribute to the existing confusion in attributing risk to Lp(a).

#### *These included:*

- 1) small sample sizes unable to determine the relation between apo(a) phenotypes and Lp(a) concentrations,
- 2) different ethnic groups,
- 3) the influence of oestrogens in women participating in studies,
- 4) plasma storage before Lp(a) determination,
- 5) inappropriate methods of data analysis, and
- 6) selection bias<sup>(51)</sup>.

However, on balance, there is evidence that raised circulating Lp(a) concentrations are associated with an increased risk of vascular events.

Furthermore, other risk factors (such as dyslipidaemia or raised homocysteine values) enhance the risk attributed to Lp(a). Therefore, the association between high Lp(a) values and atherosclerotic complications might be weaker in prospective studies than in cross sectional studies.

In the latter, the presence of the disease is a prerequisite and, thus, other risk factors could significantly contribute to the atherosclerotic burden<sup>(52-57)</sup>.

## Conclusions

Lp(a) lipoprotein is an emerging finding in the development of atherothrombosis. Moreover, Lp(a) is an important predictor of several other diseases<sup>(58-59)</sup>. Lp(a) seems to be associated with coagulation markers of thrombosis and recent studies suggested that an increased Lp(a) level could represent a risk factor for ischemic stroke. Further studies are needed to investigate the role of Lp(a) as an established risk factor for stroke.

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