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SURVEILLANCE

Enigmatic lipoprotein (a) and cardiovascular disease

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Abstract: Lipoprotein (a), (LPA) consists of a low density lipoprotein (LDL)-like particle with a lipid core encircled by a large protein, the apo-B-100. A very large glycoprotein, the apoprotein (a) (apoA) is firmly linked to apo-B-100 by two covalent disulfide bonds. The metabolic role of LPA until very recently has been shrouded in mystery. Individuals who have no LPA or a very low level are not known to be affected with any specific disorder. Naturally, this does not mean that LPA above normal is likewise without clinical impact. Elevated LPA is a well known risk factor for atherosclerosis. Amount of LPA in the organism is genetically determined and it is also because of this that medical intervention has not been very successful in modifying this prominent risk metabolite *(Fig. 3, Tab. 1, Ref. 37)*. Full Text in free PDF *www.bmj.sk*.
Key words: lipoprotein (a), apoprotein (a), low density lipoprotein, cardiovascular diseases, genetics

Interest in blood lipoproteins dates back to the mid-20th century. The function of lipoprotein particles is to transport water-insoluble lipids and cholesterol around the body in the blood. Lipoproteins were subclassified into several groups: chylomicrons, which take up lipids from the small intestine, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). The extent of atherosclerosis correlates significantly and positively with VLDL, IDL and LDL cholesterol, and negatively with HDL cholesterol. Studies performed later (1963) isolated the LPA (1).

Composition and metabolism of LPA and apoprotein (a)

LPA consists of a LDL-like particle with a lipid core encircled by a large protein, the apo-B-100. A very large glycoprotein, apoprotein (a) (apoA) is firmly linked to apo-B-100 by two covalent disulfide bonds (Fig. 1). Circulating apoA is synthesized by the liver as a precursor with a lower molecular mass which is processed into the mature form and then secreted into the blood stream. Promptly after secretion, free apoA binds to circulating LDLs to generate complete LPA particles. The assembly of LPA occurs almost exclusively extracellularly, as no apoA-apoB-100 complexes can be detected within cells. A large and highly glycosylated protein constituent of apoA has very little affinity for lipids but forms disulfide-linkage to apo-B-100. apoA has serine proteinase activity and can be of varying sizes from 400- to 800-kDa. It is homologous to plasminogen and can modulate thrombosis and fibrinolysis. It is highly heritable.The human apoA gene is located in a gene cluster within 400 kb of genomic DNA on the telomeric region of chromosome 6 (6q26-27) (2,3). apoA proteins vary in size due to a size polymorphism.

The half-life of LPA in the circulation is about 3 to 4 days. LPA is an unusual molecule in that its concentrations vary widely, over one thousandfold between individuals, from < 0.2 to > 200 mg/100 ml. LPA plasma concentration is two- to threefold higher in persons of African and South Asian ancestry compared to other populations. More than 90% of this variability is determined by inherited DNA sequence variation (4).

Interestingly, when comparing different animal species, LPA was identified only in humans, in the old world primates, in the hedgehog and in guinea pigs rendered vitamin C deficient (5). According to Linus Pauling (6) adequate ascorbate saturation

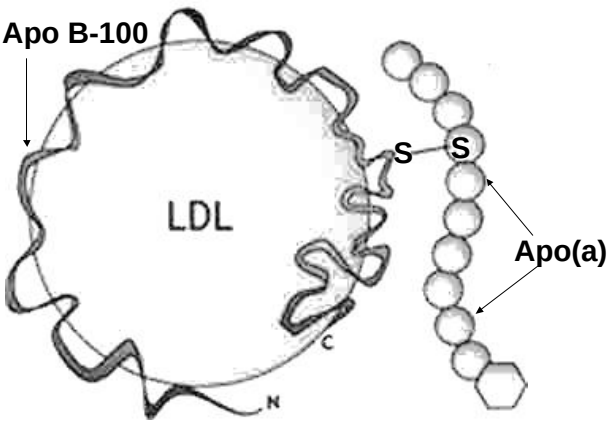

Fig. 1. Schematic structure of lipoprotein (a). A very large glycoprotein, apoprotein (a) (apoA) is firmly linked to apo-B-100 by covalent disulfide bonds.

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prevents in the guinea pigs LPA accumulation in the arteries and subsequent atherosclerosis. Although the role of ascorbic acid as an antioxidant is interesting, the hypothesis that LPA is a surrogate for ascorbate in humans is unlikely. More tempting is the possibility that LPA may not be vital but just evolutionary advantageous under certain environmental conditions. LPA offered an evolutionary advantage to humans by promoting or accelerating the healing of wounds and the repair of tissue injuries (7).

Catabolism of LPA is also unclear. Uptake via the LDL receptor is not a major pathway of LPA metabolism. The kidney has a potential role in LPA clearance from plasma (8)). We are not aware of nutritional or pharmacological interventions with decisive effect on plasma LPA. LPA is not associated with the level of LDL, HDL, total plasma cholesterol, fibrinogen, trigycerides, serum creatinine,urine protein output or by hypertension, body mass index or smoking. Because of this, LPA remains an enigmatic metabolite with unclear participation in the metabolic pathways and with an obscure function. Individuals with no identifiable LPA in their organism are seemingly entirely healthy.

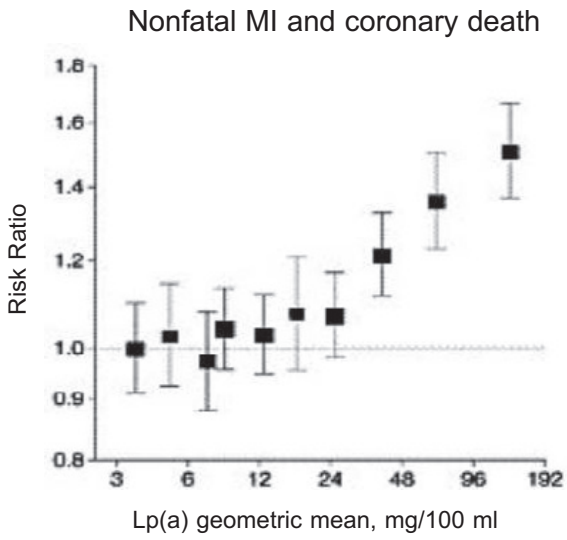

Fig. 2. Relation of the risk of myocardial infarction with LPA level. This data result from 30 prospective studies and over 106,000 individuals (20). Error bars represent 95 % confidence intervals.

LPA and cardiovascular disorders

Soon after LPA was discovered it was proposed that it may have a role in the process of atherogenesis, being structurally similar to LDL. First reports on the association between coronary artery disease and LPA were published in 1972–5 (10, 11). Elevated levels of LPA have been associated with a family history of myocardial infarction in asymptomatic individuals (12) as well as in patients sufferring from infarction (13), coronary artery disease (14, 15) and restenosis of coronary artery vein grafts (16). The subjects in these studies have generally presented with evidence of specific cardiac or cerebrovascular conditions. The association of LPA with atherosclerotic disease, coronary atherosclerosis or atherosclerosis in the extracranial carotid arteries (17) was also described. A sophisticated experiment described the mixing of autologous ^{131}I-LPA and ^{125}I-LDL and reinjecting these intravenously 3 hours before elective surgical removal of the arterial intima. There was a positive association between the intimal clearance of LDL and that of LPA. This indicates that high plasma levels of LPA may share with LDL the potential for causing lipid accumulation in the arterial intima in humans (18). LPA is considered an independent risk factor for intima-media carotid thickening in individuals free of prevalent cardiovascular disease (19).

Emerging Risk Factors Collaboration group (20) reviewed a large sample of prospective studies, focusing on the association between LPA level, major cardiovascular (CV) adverse events and mortality in over 100,000 individuals. There was a continuous dependence of coronary heart disease on LPA level (Fig. 2). It appears that the risk of CV mortality mildly increases at 15 mg/100 ml LPA but at higher level it steeply goes up. At LPA around 400 mg/100 ml the CV risk almost doubles. The decade-to-decade consistency of LPA levels in adults is very high, considerably higher than that of blood pressure, serum lipid levels, and C-reactive protein concentration.

Based on these and many more recently published reports of CV risk related to the level of LPA (21–27), these data are summarized in Table 1. The threshold values given below are applicable only to Caucasians, not for black or South Asia people. LPA laboratory diagnosis is in urgent need of standardization (e.g. immunoturbidometry). The frequency distribution of LPA level in healthy middle-aged white men is shown in Figure 3. Obviously, almost 80 % of the population belongs to LPA range of normal or only mild CV risk, while 20 % have LPA associated with a prominent risk (28). Remarkably, in Africans and South Asians the LPA values are clearly in the higher range.

Initially the assumption was that the atherogenic effect of LPA resembles the LDL by depositing cholesterol in the arterial wall. Later on, further possible mechanisms were proposed for the atherogenic role of LPA. In advanced atherosclerosis, LPA is an independent risk factor not dependent on LDL. LPA represents a coagulant risk of plaque thrombosis (29). apoA contains domains that are very similar to plasminogen. The main function of plasminogen is to dissolve fibrin blood clots. LPA accumulates in the vessel wall and inhibits binding of plasminogen to the cell surface. This inhibition of plasminogen by LPA also promotes proliferation of smooth muscle cells. These unique features of LPA suggest it causes generation of clots and atherosclerosis. Further possible mechanisms for apoA atherogenicity include proinflammatory, oxidized phospholipids that

Tab. 1. Desirable and risk values of LPA blood levels in Caucasian ethnicity.

Group	Values in mg/100 ml	Values in nmol/L
Desirable	< 14	< 35
Borderline risk	14 – 30	35 – 75
High risk	31 – 50	75 – 125
Very high risk	> 50	> 125

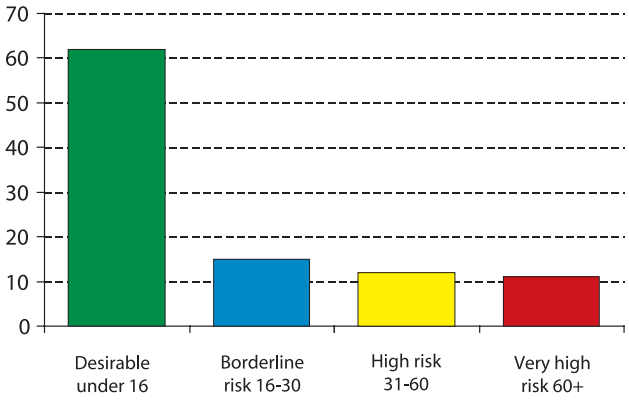

Fig. 3. Distribution of LPA levels in middle-aged healthy white men. According to (28).

are covalently bound to apoA (30). The presence of oxidized phospholipids in LPA, potentially being taken up by the vessel wall, could also accelerate development of atherosclerosis.

Discussion

In assessing appropriate cardiovascular preventive measures, one needs to consider how clinically effective is an intervention to lower LPA. Our current level of understanding would suggest that LPA lowering might be beneficial in patients with high LPA but we still are accumulating satisfactory evidence on how to define subgroups with regard to LPA levels, apoA size and presence of other risk factors. Additionally, the lack of knowledge of LPA metabolism, both regarding its formation and catabolism raises considerable challenges in devising strategies to lower LPA. Because apoA synthesis is of major importance in regulating LPA, interference in LPA particle formation may offer intervention possibilities. Absence of a well-defined metabolic pathway for LPA has prevented any progress regarding agents that might interfere with either formation or catabolism.

At present, nicotinic acid is the only major hypolipidemic agent that has proven efficacy in lowering LPA (31). However, the published research on this subject suffers from a lack of uniformity in results. Nicotinic acid therapy may be associated with troubling side effects such as skin itching and flushing similar to hot flashes.

Tempting is the assumption that some naturally occurring antioxidants may have a potential to inhibit generation of LPA. Ascorbic acid has been in focus ever since Rath and Pauling (5) reported the essential role of ascorbate depletion associated with atherosclerotic plaques in deficient guinea pigs. Linus Pauling, the double Nobel prize winner exagerrated the role of ascorbic acid in the management of malignancy and further research in relation to LPA was halted. LPA which originates from the LDL outside of the hepatocytes is covalently bound with disulfides to apoA. High saturation with antioxidants reduces the rate of conversion of the sulfhydril –SH groups to disulfidic –SS. It was confirmed that a potent antioxidant, coenzyme Q 10 prominently inhibits LPA in patients with coronary artery disease (32). It is of considerable importance to explore the effect on LPA synthesis of other naturally occurring substrates: grape polyphenols (especially resveratrol), phenolic acids, anthocyanins and flavonoids, alone or in combination with the ascorbic acid.

Novel productive contribution to resolving the enigma of LPA metabolism stems from the cooperation of two seemingly unrelated medical fields: ethnic-geographic medicine and genetics. Recently, Clark et al. (27) used a novel gene chip containing 48,742 single-nucleotide polymorphisms (SNPs) in 2,100 candidate genes to test for associations in 3,145 patients with coronary disease and 3,352 control subjects. Three chromosomal regions (6q26–27, 9p21, and 1p13) were strongly associated with the risk of coronary disease. The LPA locus on 6q26–27 encoding LPA had the strongest association. Two LPA variants were strongly associated with both an increased level of LPA and an increased risk of coronary disease. These findings provide support for a causal role of LPA in coronary disease.

Comprehensive analysis of genomic variation in the LPA locus and its relation to plasma LPA reported marked differences among European Caucasians, the Chinese and the South Asians (33). South Asians appear to be affected by the risk of LPA for CV disease more than the Chinese. Malayans who had elevated serum LPA were at a higher risk for peripheral vascular disease (34). However, direct comparison of various ethnic groups regarding the risk of CV disease is complicated by the presence of other confounding factors besides the LPA: hypertension, obesity, diabetes mellitus and smoking (35).

Given the failed attempts to control excessive level of LPA with diet or lipid lowering medications, recent success with the extracorporeal elimination using lipid apheresis (36) provides direct evidence for a causal role of LPA in coronary heart disease (37). Patients with coronary artery disease and higher LPA levels when subjected to apheresis had significant reduction of major adverse coronary events in an apporoximate five-year follow up.

Conclusion

Though of high theoretical and practical interest, many aspects of the metabolism, function, evolution and regulation of plasma concentrations of LPA are presently unknown, controversial, or enigmatic. Plasma LPA in white patients appears to be a major coronary risk factor with a predictive value approaching that of the level of LDL or HDL cholesterol. Presently, medical science is not capable to practically modify high levels of LPA or apoA since these are strongly affiliated with the genotype. Heroic measures like plasmapheresis seem to be indicated in individuals with the highest risk. We have to wait for controlled studies using natural substances with a strong antioxidizing potential that may inhibit the generation of disulfide bonds between the apo B-100 and the apo A.

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