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LIPOPROTEIN(a) AND CARDIOVASCULAR DISEASE

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ABSTRACT

Elevated lipoprotein (a) [Lp(a)] is an important risk parameter of cardiovascular disease (CVD). Its apoprotein, Apo (a), contains structural units similar to those present in plasminogen (a plasma protein that dissolves blood clots when activated). Lp(a) competes with plasminogen for binding with tissue plasminogen receptors and impairs the function of plasminogen. As a result minute clots grow large enough to cause blood vessel occlusion. Moreover, ox-Lp(a) is a potent stimulus of monocyte adhesion to endothelial cells, thus contributing to atherogenic changes in human blood vessels. Thus, higher serum levels (>30 mg/dl) of Lp(a) are deleterious and associated with an increased risk of CVD.

KEYWORDS: Lipoprotein (a), cardiovascular disease, plasminogen, atherosclerosis.

INTRODUCTION

Cardiovascular diseases (CVD) are a group of disorders of the heart and blood vessels and include: coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain.[1]

CVD are the most potent killers particularly so in the advanced countries of the world.[2] CVD accounts for approximately 30% of deaths worldwide, including nearly 40% in high income countries and about 28% in low and middle-income countries. For many years, CVD was considered to be more common in men than in women. In fact, the percentage of all deaths secondary to CVD is higher among women (43%) than among men (37%).[3] It is

responsible for 3% of all deaths in North America, being the most common cause of death in European men under 65 years of age and the second most common cause in women.[4] Elevated Lp(a) could be assessed along with lipid profile as screening test to identify the risk of CAD.[5] Among various reasons, dyslipidemias and elevated Lp(a) are significant causes for development of CVD in hypothyroidism. Study has been conducted to determine the serum lipid disturbances and significance of Lp(a) in hypothyroid patients in which majority were females in the age group 41-50years.[6]

Lipoprotein (a) [Lp(a)] is emerging as one of the important risk parameters of CVD. It is proposed to have atherogenic and thrombotic potentials.[2]Elevated Lp(a) has been proved as an independent risk factor for atherosclerotic coronary artery disease (CAD) and stroke, particularly in those with high low-density- lipoprotein cholesterol (LDL-C) or non-high-density-lipoprotein cholesterol (non-HDL-C) levels.[7,8] Lp(a) was first identified and classified as a "low density lipoprotein variant" over 40 years ago. Similar to LDL, but containing an additional protein, apo(a), Lp(a) has proven to be pathogenic in nature and involved in the development of CHD.[9]

The association of elevated Lp(a) with an increased risk of cardiovascular mortality and morbidity suggests that lowering Lp(a) using the therapeutic options available may be beneficial.[10]

STRUCTURE

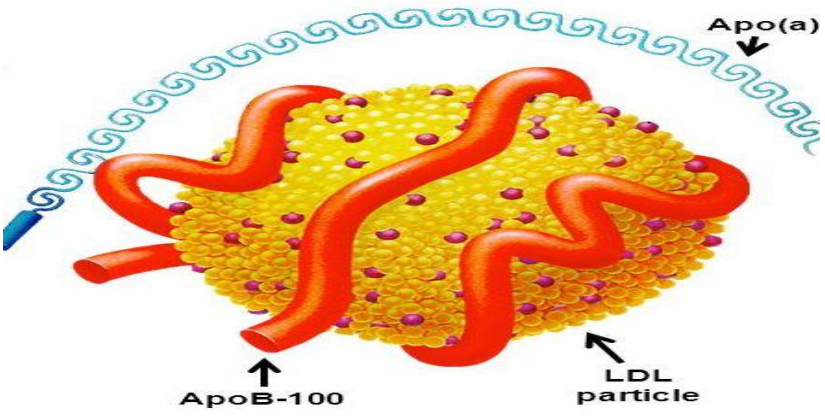

Fig. 1 : Structure of lipoprotein (a)

Lp(a) is a circulating lipoprotein composed of liver-derived apo(a) covalently bound to apoB, which is similar in lipid composition to apoB of LDL (Fig. 1). In 1963, Kare Berg reported the presence of Lp(a) in humans when searching for antigenic determinants of blood types by

observing that one-third of patients' plasma reacted to an antiserum from rabbits immunized with human LDL. Later, it was discovered that the Lp(a) gene, and the protein apo(a) are highly homologous to plasminogen (a plasma protein that dissolves blood clots when activated).[11,12,13] Because of this similarity to plasminogen, Lp(a) interferes with fibrinolysis by competing with plasminogen binding to molecules and cells.[14]

Lp (a) AND ATHEROSCLEROSIS

The transient increased serum levels of Lp(a) during myocardial infarction has been studied. The positive correlation between mean Lp(a) values on day 1 and 7 and the size of necrotic area suggested an atherogenic and prothrombic role of Lp(a). Moreover, elevated Lp(a) values were related to greater tissue damage. Some studies suggested that periodical determination of Lp(a) values in subjects with coronary disease may be useful in order to predict further acute vascular events.[15] Thus, several studies have found an independent and continuous association between Lp(a) and CVD.[7,8] Atherosclerosis is the dominant cause of cardiovascular disease (CVD) including MI, heart failure, stroke and claudication. Atherosclerosis is mainly located in the intima of many middle sized and large arteries, especially where the vessels divide. Most likely, this is influenced by the nature of the blood flow, since areas exposed to normal shear stress seem to be protected; here endothelial cells express atheroprotective genes.[16] Also, the adventitia may play a role in atherosclerosis development, and is characterized by lymphocyte infiltrates.[17] Inflammatory mechanisms play a central role in the pathogenesis of atherosclerosis and its complications.[18] It has been demonstrated that atherogenic lipoproteins such as apo(B-100), oxidized LDL, remnant lipoprotein (beta-VLDL), and Lp(a) play a critical role in the proinflammatory reaction.[14] Lp(a) competes with plasminogen for its receptors on endothelial cells, leading to diminished plasmin formation, thereby delaying clot lysis and favouring thrombosis. The high affinity of Lp(a) for fibrin provides a mechanistic basis for their frequent colocalization in atherosclerotic plaques.[19,20] Moreover, Lp(a) induces the monocyte chemoattractant, which leads to the recruitment of mononuclear phagocytes to the vascular wall.[21,22] Lp(a) particles can suffer oxidative modification and scavenger receptor uptake, with cholesterol accumulation and foam cell formation, leading to atherogenesis.[23] Oxidation of LDL and Lp(a) affects the catabolism of the lipoproteins, including changes in receptor recognition, catabolic rate, retention in the vessel wall, and propensity to accelerate atherosclerosis. Oxidative modification of apo(a) may have an influence on Lp(a) recognition by scavenger receptors of macrophages.[24] Moreover, ox-Lp(a) is a potent stimulus of monocyte adhesion

to endothelial cells, thus contributing to atherogenic changes in human blood vessels.[25] As the atherosclerotic plaque progresses, growth factors and cytokines secreted by macrophages and foam cells in the plaque stimulate vascular smooth muscle cell growth and interstitial collagen synthesis.[26] Thus, these effects on endothelial cell function may provide mechanisms by which Lp(a) contributes to the development of atherosclerotic lesions (Table 1).[14,9]

Table 1. Pathogenic activities of lipoprotein (a)

Atherogenic Activity	Thrombogenic Activity
↑ Permeability of EC layer	↓ Plasminogen activation
↑ Vascular adhesion molecule expression	↑PAI-1 expression
↑ Chemotaxis of monocytes	↓TFPI activity
↑ Foam cell formation ↑ SMC proliferation and de-differentiation	↑Platelet aggregation

EC, endothelial cell; SMC, smooth muscle cell; PAI-1, plasminogen activator inhibitor1; TFPI, tissue factor pathway inhibitor.

LABORATORY ESTIMATION

Currently used methods for Lp (a) measurement are –

- Turbidimetry
- Nephelometry
- RIA
- ELISA

Most of these assays, except ELISA, are based on use of polyclonal antibodies. Sandwich type ELISA are usually based on the use of combination of monoclonal and polyclonal antibodies to apo B and apo(a). At present, Lp (a) measurements are not well standardized, but a value of about 30 mg/dl of total Lp(a) particle mass has traditionally been used as a cut-off, above which increased concentration of Lp(a) are associated with increased risk of CVD. Because, Lp(a) values vary among ethnic groups, reference values ideally should be population based. For e.g., African Americans in general have significantly higher Lp(a) concentrations than Caucasians.[27]

MANAGEMENT

Lp(a) should be measured once in all subjects at intermediate or high risk of CVD/CHD who present with:[10]

- Familial hypercholesterolemia.
- Strong family history of CVD/or elevated Lp(a).
- Personal history of premature CVD.
- Recurrent CVD despite statin treatment.
- Inadequate response to statins.

Studies using niacin alone or in combination with, for example, statins have shown cardiovascular benefit. Niacin reduces Lp(a) levels by up to 30–40% in a dose-dependent manner and in addition exerts other potential beneficial effects by reducing LDL-cholesterol, total cholesterol, triglycerides, and remnant cholesterol and by raising HDL- cholesterol. Compared with LDL, Lp(a) is relatively refractory to both lifestyle and drug intervention. Other agents reported to decrease Lp(a) to a minor degree (≈ 10%) include aspirin, L-carnitine, ascorbic acid combined with L-lysine, calcium antagonists, angiotensin converting enzyme inhibitors, androgens, oestrogen and its replacements (e.g. tibolone), anti-estrogens (e.g. tamoxifen), and thyroxine replacement in hypothyroid subjects. Finally, in young or middle-aged patients with evidence of progressive coronary disease and markedly elevated plasma Lp(a), serious consideration should be given to instituting LDL apheresis which removes Lp(a) efficaciously; however, this form of treatment is prohibitively expensive and impractical for most patients and most clinical centres.[8]

CONCLUSION

The journey of Lp(a) as a clinically relevant lipoprotein over the last 50 years has evolved from an antigenic determinant in blood type, to a putative cardiovascular risk factor, to an independent, genetic risk marker of CVD. The independent residual risk of Lp(a) in mediating CVD is substantial and represents a significant opportunity and potential target of therapy in reducing the overall risk of CVD even further.[28]

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