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Mini-Review

Lipoprotein (a): Current Status

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Abstract

Lipoprotein (a), also known as Lp(a), is one of the lipoproteins found in plasma. It is structurally related to low-density lipoprotein (LDL). The plasma level is mostly governed by genetics rather than diet or lifestyle measures. It has now been established as a risk factor for atherosclerotic cardiovascular disease (ASCVD) and senile valvular aortic stenosis. Statins do not reduce the Lp(a) level. However, niacin, plasma apheresis, proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) and antisense gene treatment lower the value meaningfully. Routine assessment of Lp(a) should be considered in the relevant population.

Keywords: Lipoprotein (a), ASCVD, aortic stenosis

Introduction

ASCVD is a major health problem all across the world. Some of the risk factors for ASCVD can be usefully modified by treatment, and the most important element to modify is dyslipidemia. LDL is the most important target for therapeutic intervention, along with triglyceride (TG), very low-density lipoprotein (VLDL), and apolipoprotein B (apoB), and low level of high-density lipoprotein (HDL). Lp(a) has got the focus of attention recently as an important risk factor for ASCVD and senile aortic stenosis (AS).

Epidemiology

A high plasma level of Lp(a), i.e., more than 50 mg/dL, has been found in approximately 1.43 billion people in 2018. Most people have Lp(a) levels in the range of 5 to 29 mg/dL. The prevalence varies with the geographical region, which conforms to a prehistoric migration of the human race, with rates of 25% in North America, 15% in South America and 10% in Central Asia.[1] On average, about 20% of the adult population have Lp(a) level above 50 mg/dL.[2] There are racial and ethnic variations in Lp(a) levels, with Afro-Caribbeans having higher levels of Lp(a) than Whites, Hispanic, or Asian individuals.

Genes determine the Lp(a) levels in the body. Some variants of the gene are very strongly related to ASCVD, more strongly than genes for LDL receptor, proprotein convertase subtilisin/kexin type 9 and apoE. Lifestyle measures do not affect the Lp(a) levels. Lp(a) size varies with the length of the apoA protein that wraps the fatty core. The structure of apoA involves looped segments called kringles that may be repetitive up to 40 times.[3] Smaller particles are associated with higher blood levels.

Pathophysiology

One standard deviation lower value of Lp(a) is associated with a lower incidence of CHD by 29%, PVD (peripheral vascular disease) by 31%, heart failure by 17%, stroke by 13%, chronic kidney disease by 9% and aortic valve stenosis by 37%.[4] This association is established on epidemiological meta-analyses,[5] Mendelian Randomization Studies[6] and Genome-wide

Association Studies.[7] Standard lipid analysis may miss up to 10% of people with a cardiovascular event, and only risk factor is high Lp(a). Lp(a) assessment changes the risk category to 40% of individuals as per a paper presented in the European Society of Cardiology (ESC) Congress in 2018.

Some LDL particles in the liver get covered with apoA and secreted as Lp(a) into the bloodstream. They deposit in the subendothelium and aortic valve leaflets. Some part is recycled in the liver. Lp(a) is pro-atherogenic, pro-inflammatory and pro-thrombotic in actions. It increases vascular smooth muscle cell proliferation, adhesion molecules, proteoglycan thrombotic matrix binding, foam cell and necrotic core formation, and lesion calcification. It also increases macrophage interleukin 8 expression, monocyte cytokine release, monocyte chemotaxis, oxidized phospholipids, PAI-1 expression and platelet responsiveness. It reduces plasminogen activation and fibrin degradation.

Because Lp(a) particles vary in size, the commonly used lab tests may be inaccurate. A more accurate approach is to measure the particle numbers by nanomoles per liter (nmol/L).[3] A blood level of 30 mg/dL may be associated with a Lp(a) concentration from 55 to 85 nmol/L.

It has been shown that the higher the value of Lp(a), the more the number of vascular beds affected. In the Odyssey Outcome trial, those with only coronary artery disease had an average Lp(a) value of 20.8 mg/dL, whereas when coronary and peripheral vascular bed were affected, the value was 25.5 mg/dL and when the cerebrovascular bed was also affected, the value was 29.4 mg/dL.[8] If Lp(a) level below 5 mg/dL is taken to confer 0% risk of heart attack, then a level of 5-29 mg/dL increases that risk by 20%, 30-76 mg/dL by 60%, 77-117 mg/dL by 90% and above 117 mg/dL by 160%.

In valvular aortic stenosis (AS), the progression of the disease was found to be significantly more if the Lp(a) was above 58.6 mg/dL. Event rates over 5 years were also significantly lower in the lower Lp(a) group. Statins increase Lp(a) and oxidized phospholipid apoB and accordingly reduce event-free survival in cases of valvular AS.[9]

Treatment for High Lipoprotein (a)

There are currently no approved medicines that directly target Lp(a). Statins do not reduce Lp(a). Niacin (vitamin B3) may reduce Lp(a) by 20% by reducing apoA transcription, but it is not a recommended therapy.[3] Large studies failed to show clinical benefit, and there may be serious side effects.

The American Heart Association (AHA) recommended a healthy lifestyle with a diet based on fruits, vegetables and protein and 40 minutes of exercise for 3 to 5 days a week to reduce the risk associated with high Lp(a), though not directly affecting the level.

The most effective available therapy for high Lp(a) is apheresis. This is expensive, requires weekly treatment, and involves certain risks. Apheresis may lower Lp(a) by about 70%, but it is not sustained.[3] Apheresis reduced annual major adverse cardiovascular event (MACE) by 86%, heart attack rate by 97%[10] and percutaneous coronary intervention by 65% and coronary artery bypass grafting by 88%.[11]

Recently, PCSK9 inhibitors have been shown to reduce Lp(a) by an average of 22% by up-regulation of LDL receptors.[12] In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Patients with Elevated Risk (FOURIER) trial, 27% of the total reduction of MACE was attributed to the reduction of Lp(a) when the baseline Lp(a) was above 60 mg/dL. Anti-sense gene modulation holds promise for the future. This approach targets and disrupts the messenger RNA that translates the LPA gene into Lp(a).[3] The anti-sense strand (siRNA) makes a complex with the target mRNA to form an RNA-induced silencing complex (RISC). It can reduce Lp(a) levels by 75-90%.

Guidelines

The 2018 American Heart Association/American College of Cardiology (AHA/ACC) Guideline on the Management of Blood Cholesterol[13] recognized the importance of Lp(a) testing for risk assessment. It is particularly indicated with a family history of premature ASCVD or personal history of ASCVD not explained by major risk factors. Its relevance in women is not determined. The 2019 ACC/AHA Guidelines on the Primary Prevention of Cardiovascular Disease[14] categorized Lp(a) as a risk enhancing factor above a value of 50 mg/dL, and especially at higher values.

The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines for the Management of Dyslipidemias[15] recommended measuring Lp(a) at least once in all adults to identify high inherited levels above 180 mg/dL, where

the risk of ASCVD is equivalent to heterozygous familial hypercholesterolemia (class IIa indication). It is also recommended in patients with a family history of premature CVD, and for reclassification of ASCVD risk.

A consensus statement from the EAS Consensus Panel published recently[16] recognized the role of triglyceride-rich lipoproteins or Lp(a) in ASCVD in some individuals. Whether LDL, Lp(a), and remnant particles cause atherosclerosis by the same mechanism is yet to be settled.

High Lp(a) level has been included in the International Classification of Diseases 10 (ICD-10) code as a separate disease entity in 2018.

Conclusion

Lp(a) has been recognized as an important and independent risk factor for ASCVD and senile aortic valve stenosis. Though the blood level is genetically determined, PCSK9i and anti-sense gene modulation can substantially reduce blood levels of Lp(a) along with clinical events. Apheresis is the presently accepted treatment, but not easily available or sustainable. The role of clinicians is to increase the awareness level of the importance of Lp(a).

Declaration of conflicting interests

The author declares no conflict of interest.

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