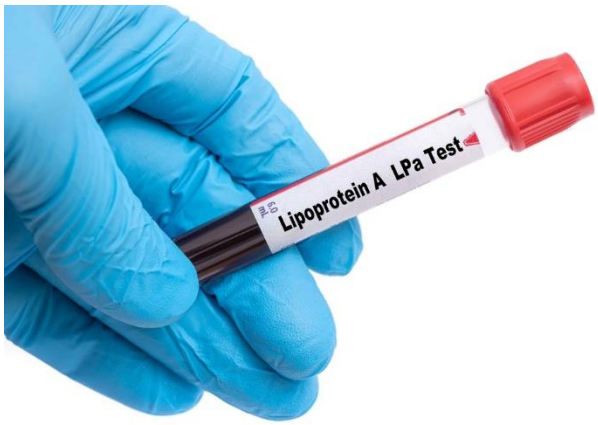

Lipoprotein (a)

What is it, why is it important, and how are elevations of it treated?

By

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Lipoprotein (a) (Lp(a)) elevation is an independent risk factor for cardiovascular disease. This article will discuss what Lp(a) is, why it is problematic and how to treat abnormally elevated levels.

Lp(a) was discovered in 1963 by Kare Berg who found it in the low-density lipoprotein (LDL) fraction of serum. He discovered the connection between abnormal elevations of Lp(a) and the presence of coronary artery disease.[1]

Lp(a) is a lipoprotein that contains apolipoprotein B100 (apoB) which is bound to apolipoprotein(a) (apo(a)). ApoB has an LDL-like lipid core and is proatherogenic. There are a number of different subtypes of apo(a) to which proinflammatory and proatherogenic phospholipids can bind.[1] Apolipoproteins are proteins that bind to lipids to form lipoproteins

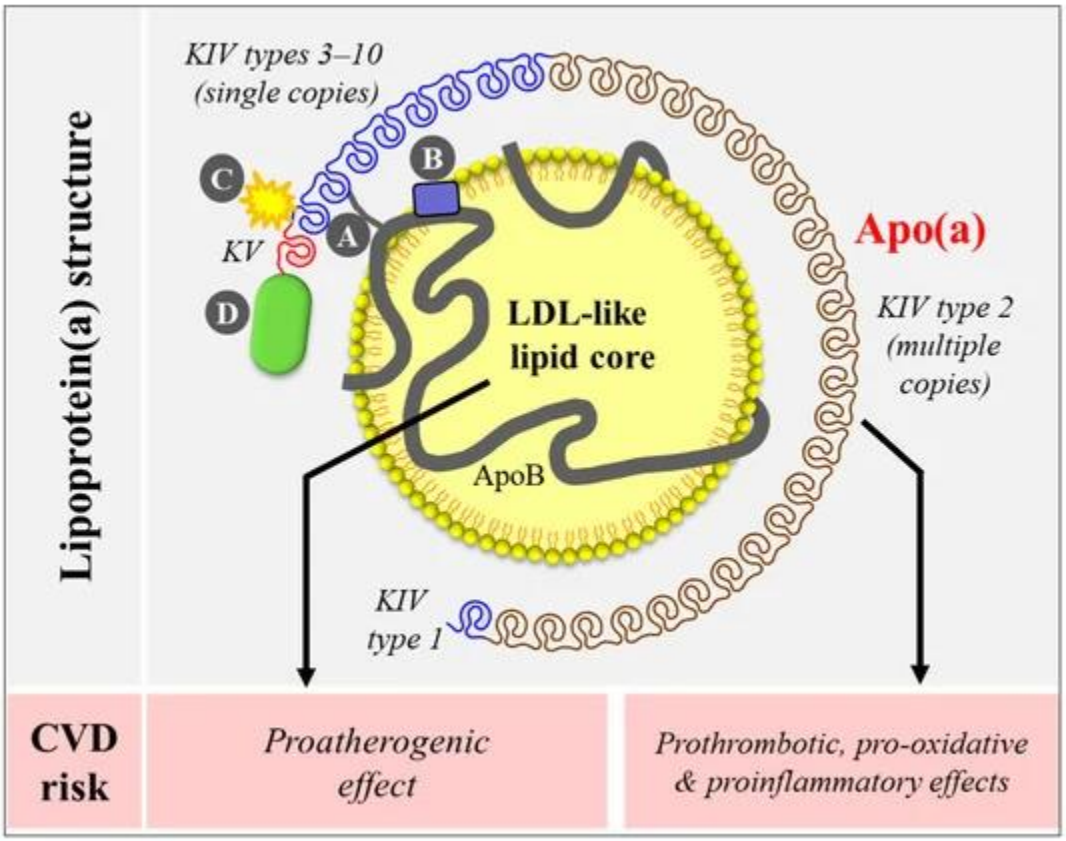
Genetic Variation

70% to over 90% of Lp(a) production is genetically determined, although environmental factors and medical conditions may also play a role.[1] Abnormally high Lp(a) levels can

differ depending on ethnicity and the type of assay used, making standardization of normal ranges difficult. Blacks of African descent and South Asians have been found to have generally higher median Lp(a) levels than Whites or East Asians.[1]

Lp(a) blood levels are dependent on 2 *LPA* gene alleles. Other gene loci are involved to a much lesser extent in regulating Lp(a) levels. The *LPA* gene is thought to have evolved from the gene for plasminogen. There can be more than a 1000-fold range of Lp(a) concentrations between individuals, from less than 0.1 mg/dL (milligrams per deciliter) to more than 300 mg/dL. Lp(a) blood levels are not greatly influenced very much by age, gender, fasting state, diet, or physical activity.[2]

Lipoprotein (a) Structure



[3]

Lp(a) has an LDL-like core. Apo(a) binds to apoB-100 via a single disulfide bond (A) at a location near the LDL receptor binding site (B). Apo(a) has kringle structures KIV and KV. There are 10 variants of apo(a) KIV of which type 2 is present in multiple copies. Apo(a) binds to proinflammatory and proatherogenic oxidized phospholipids (C). Apo(a) also has a protease domain (D) that lacks proteolytic activity.

Lp(a) is produced in the liver. Lp(a) concentrations are dependent on the number of kringle IV (KIV) repeats in an individual's apo(a), which is controlled by the *LPA* gene. A kringle is named after a Scandinavian pretzel-like pastry they resemble. It is a protein folded in on itself in a loop that becomes part of a larger molecule.

There are ten different genetic variants of Kringle IV but one, KIV type 2, can be repeated from 2 to 40 times in apo(a). The number of KVI type 2 repeats are thought to be responsible for most of the genetic variation seen. Individuals having smaller apo(a) molecules with less than 22 KVI type 2 repeats have, on average, markedly higher Lp(a) concentrations than individuals having larger apo(a) isoforms with more than 22 KIV type 2 repeats. There is also a kringle V (KV) that can be found in Lp(a), but it only appears once and does not repeat like the KIV type 2.[2]

Adverse Effects

The apoB part of Lp(a) is thought to be atherogenic because of its similarity to LDL. Although there are much fewer circulating plasma Lp(a) particles than LDL particles, Lp(a) may be selectively retained in the arterial wall through binding of apo(a) to extracellular matrix proteins. Lp(a) also carries endogenous oxidized phospholipids which stimulate the immune system and can trigger sterile inflammation and calcification. Apo(a) interacts with fibrin/fibrinogen and endothelial cells through its lysine-binding site and is found in human atheromas and calcified aortic valves.[1]

Cardiovascular Events

One study found that each doubling of the Lp(a) level is associated with 22% greater risk of myocardial infarction.[4] A meta-analysis found that high Lp(a) levels are an independent risk factor for cardiovascular disease with an odds ratio of 2.57.[5] Another large study found that the development of heart failure increased with increasing levels of Lp(a).[6]

While there appears to be a linear relationship between Lp(a) levels and cardiovascular outcomes, an Lp(a) level of 30–50 mg/dL is frequently used as the cut-off for concern about cardiovascular disease (CVD).[5] The European Atherosclerosis Society Consensus Panel guideline states that the desired Lp(a) level for the prevention of CVD is less than 50 mg/dL.[7] A large Scandinavian study postulated that based on their findings, to reduce major adverse cardiovascular events in a population of patients with existing CVD by 20%, Lp(a) levels would need to be reduced a median of 50 mg/dL (105 nmol/L (nanomoles per liter)) for five years in that population.[8]

Aortic Valve Calcification

Patients with elevated Lp(a) levels have more rapid aortic valve calcification progression on serial computed tomography scans, and worse clinical outcomes.[1] One study found accelerated progression of aortic stenosis in individuals in the top third of measured Lp(a) levels.[1,9] It was also found that in patients with diagnosed aortic stenosis, elevated Lp(a) levels and elevated numbers of oxidized phospholipids attached to the Lp(a) molecules were associated with more rapid aortic stenosis progression and need for aortic valve replacement.[9] Another study identified a single mutation of the *LPA* gene to be associated with the presence of aortic-valve calcification with an odds ratio of 2.05.[10] The same study found evidence that suggested lifelong elevations in Lp(a) levels lead to a markedly increased prevalence of aortic-valve calcification in adulthood.[10] A meta-analysis looking at calcific aortic valve disease (CAVD) found an association between Lp(a) levels ≥50 mg/dL and CAVD, but there was insufficient evidence to link Lp(a) levels between 30 mg/dL and 50 mg/dL similarly to CAVD. The authors suggested that the magnitude of the Lp(a) concentration might have a dose-response relationship with CAVD.[11]

Stroke

Lp(a) elevation is thought to possibly be a stroke risk but at a lower level of risk than for cardiac disease, but the data is conflicting. One large study found subjects whose Lp(a) levels were an average of 28 mg/dL lower than a comparison group with higher Lp(a) levels, had 13% less stroke events.[1,12] However, a meta-analysis found evidence that Lp(a) elevation caused CVD but found no evidence of a relationship to stroke.[13]

Thrombosis

Because of Lp(a)s similarity to plasminogen, and the fact that apo(a) inhibits plasmin-mediated fibrinolysis in vitro, the question of whether elevated Lp(a) levels can lead to thrombotic events has been investigated. Although some data from trials suggest a positive association of Lp(a) level and risk of venous thromboembolism,[14-16] the literature is mixed. Another study found no effect of Lp(a) on venous thromboembolism[17]. Meta-analyses have been both positive and negative for a correlation between Lp(a) levels and venous thrombosis.[18-20]

Diabetes Mellitus

An inverse association of very low Lp(a) levels and type 2 diabetes mellitus has been discovered with very low levels of Lp(a) associated with a higher risk of developing diabetes. Lp(a) levels of less than 4 mg/dL were associated with approximately a 20% to 50% higher relative risk of diabetes development, with Lp(a) levels of less than 1 mg/dL having the highest risk.[21] This was confirmed by a number of other studies.[22,23] One of them also found that prediabetes, insulin resistance, and hyperinsulinemia were all increased in subjects with very low levels of Lp(a).[22]

Testing

The National Lipid Association recommends that testing for Lp(a) levels be considered when there is a significant family history of premature ASCVD (arteriosclerotic cardiovascular disease) in first-degree relatives, personal history of premature ASCVD, or severe primary hyperlipidemia. The American College of Cardiology and American Heart Association screening guidelines mention Lp(a) testing as an optional risk enhancer measurement.[24] The European Society of Cardiology has a general recommendation to screen Lp(a) levels at least once in a person's lifetime.[25.26]

One of the difficulties in standardizing testing for Lp(a) is that there a number of different assays. The gold standard is considered to be the ELISA test (enzyme-linked immunosorbent assay). The ELISA test measures the true number of Lp(a) particles and is reported in nanomoles per liter (nmol/L). Other immunoassay tests may overestimate or underestimate true Lp(a)levels due to calibration in milligrams/deciliter (mg/dL). Mg/dL is a weight-based measure, that does not fully take into account the variability in size of the apo(a) segment due to the differing numbers of attached kringle units. However, recent improvements in immunoassay testing have been able to increase the precision of mg/dL testing methods.[1] A significant portion of the medical literature on Lp(a) has been reported in mg/dL units but there have been recommendations that nmol/L per liter, be selected as the standard in the future.[1] One suggested method of converting Lp(a) nmol/L units to mg/dL units is to divide the nmol/L result by 2.15.[27]

Ethnicity

Abnormally high Lp(a) levels can differ depending on ethnicity, making standardization of normal ranges difficult. Blacks of African descent and South Asians have been found to have generally higher median Lp(a) levels than Whites or East Asians.[1] In another study of subjects with familial hypercholesterolemia, mean Lp(a) levels were 30-33%

higher in Druze, Christian-Arabs, and Jewish-Ashkenazi groups than the control group who were family members without hypercholesterolemia. Lp(a) levels were increased over control levels by 110% in the Jewish-Sephardic subject group in that trial.[28]

What to do with this information when treating patients is unclear as the literature is sometimes conflicting and more definitive research is needed. Blacks have median Lp(a) levels two to three times higher than Whites, and there are conflicting study findings that elevated Lp(a) levels in Blacks both cause and don't cause harm.[29-32] Part of this may be that Blacks predominantly carry the larger apo(a) isoform which is less atherogenic. However, one study found 26% of African-Americans carried the more atherogenic smaller apo(a) isoform. Not controlling for different apo(a) isoforms within an ethnic group may explain some of the conflicting findings of different studies.[33]

Treatment

There are data to support that lowering the Lp(a) can reduce adverse cardiovascular events.[1] Results from studies of dietary intervention show only very modest effects on reducing Lp(a) levels.[1,3] A clinical goal, especially when adverse events occur even after aggressively lowering the LDL cholesterol and apoB levels is to secondarily attempt to lower the Lp(a) level if elevated.[1]

Lipoprotein Apheresis

The most effective intervention for Lp(a) lowering is lipoprotein apheresis. Blood is withdrawn from one intravenous line by a blood pump and the plasma is then separated out and filtered to remove LDL and Lp(a). Both the treated plasma and the rest of the blood components are returned to the patient's circulation by a second intravenous line. It is typically performed every 2 weeks as Lp(a) levels return to previous levels after that time period. The Food and Drug Administration approval for Lp(a) lowering using lipoprotein apheresis is for a Lp(a) level greater than 60 mg/dL and LDL greater than 100 mg/dL with either documented coronary artery disease or documented peripheral artery disease.[34] During a 3- to 4-hour apheresis session, the Lp(a) level typically is lowered by about 50% to 85%. There is also a reduction in oxidized phospholipids, as well as lowering LDL concentrations by 60% to 85%. There is clinical data suggesting that Lp(a) lowering with lipoprotein apheresis may reduce the risk of cardiovascular events.[1] In one study, patients with Lp(a) above the 95th percentile who continued to have major adverse coronary events (MACE) despite being on maximally tolerated lipid-lowering therapy, were started on lipoprotein apheresis. In the study group Lp(a) levels were

lowered 73% and the MACE rate decreased 86% compared to a pre-apheresis phase of the study used as the control.[2,35] Another similar trial demonstrated that lipoprotein apheresis effectively lowered the incidence of MACE by 78%.[36] In a different study, subjects with an Lp(a) over 50 mg/dL who were treated with apheresis plus statin for 18 months had significantly more regression of coronary atherosclerosis lesions when compared to a statin only group.[2,37]

Statins

Standard hyperlipidemia treatments such as statins have minimal Lp(a)-lowering efficacy, and some statins may increase Lp(a) levels.[1] One meta-analysis found that statins significantly increased baseline plasma Lp(a) levels 8.5% to 19.6%.[38] The mechanism is not well understood but the authors postulated that statin-induced increased production of apo(a) may lead to increased plasma levels of Lp(a). Another possible mechanism may depend on statin mediated increase in plasma proprotein convertase subtilisin/kexin type 9 protein (PCSK9) levels, which may further increase Lp(a) production.[38] Another meta-analysis and systemic review found that statin therapy does not cause clinically significant changes in Lp(a) levels and may not change Lp(a) associated cardiovascular risk.[39]

PCSK9 Inhibiting Medications

Trials of monoclonal antibodies that inhibit PCSK9 demonstrated that besides lowering LDL levels, those medications can also reduce Lp(a) levels by 25% to 30%.[1,40] In the ODYSSEY trial, cardiac patients on statins with LDL maximized to 70mg/dL or lower started using alirocumab, which caused a lowering of Lp(a) levels that independently reduced the risk for MACE compared to controls. The investigators found that each 1mg/dL reduction in Lp(a) was associated with a 0.6% decrease in the risk of MACE events.[41] The FOURIER trial found that evolocumab reduced Lp(a) levels by 26.9% and the risk of coronary heart disease, death, myocardial infarction, or urgent revascularization by 23%.[42]

Another PCSK9 directed medication is inclisiran, which is a small interfering RNA that blocks PCSK9 messenger RNA. In clinical trials it has been found to decrease Lp(a) levels by 18.6–25.6% while reducing LDL levels close to 50%. One of the advantages of inclisiran is that it is long-lasting and after a second dose administered at 3 months, recommended dose intervals are then every 6 months.[43,44]

Antisense Oligonucleotides

Newer medications, still in testing trials, are antisense oligonucleotides which inhibit the production of apolipoprotein(a) in the hepatocyte, the source of Lp(a). One drug, known as APO(a)-L_{Rx}, has been found to reduce Lp(a) levels up to 80%.[45]

Niacin

Niacin when taken daily has been shown to lower Lp(a) by 20% to 45% as well as raising HDL and lowering LDL. Niacin by itself has been found in one 15-year study to decrease mortality 11%,[46] and in another meta-analysis niacin reduced MACE 25%.[47] However, niacin when added to statins has not been associated with improved cardiac outcomes in a number of trials and appears to add no benefit to statins alone.[1,2,48-50]

Hormonal drugs

Hormonal drugs may improve Lp(a) levels but are not necessarily associated with improved cardiovascular outcomes. Estrogen can improve Lp(a) levels but is not currently used as a therapy to improve lipid markers. Estrogen also does carry other potential risks and is unlikely to become an established treatment.

Testosterone replacement therapy has also been shown to lower Lp(a) levels, but more research is needed. Testosterone replacement therapy can lower HDL levels, which may elevate the risk of atherosclerosis.[26]

Conclusion

Lp(a) elevation is a known genetic risk factor for both cardiovascular disease and aortic calcification. Unfortunately, diet and lifestyle changes do not affect Lp(a) levels to any significant degree.

There are differences in median Lp(a) levels in different ethnic groups which may need to be taken into consideration. There are a number of tests for Lp(a) but ELISA is considered the most accurate. Mg/dL is frequently used as the reported value for Lp(a) levels in the literature but there have been recommendations to switch to nmol/L, which is thought to provide a more accurate measurement.

At a minimum, patients with premature CVD, recurrent CVD despite being on statin therapy, high risk of fatal CVD, a family history of hypercholesterolemia, elevated Lp(a), or premature CVD should probably have Lp(a) levels checked.[2]

Niacin lowers Lp(a) but has not been shown to improve outcomes when added to statin therapy. Statins may actually raise Lp(a) levels and may not be completely effective in preventing MACE in patients with Lp(a) elevations. PCSK9 inhibitors and PCSK9 small interfering RNA drugs lower Lp(a) levels and have demonstrated improved cardiac outcomes. Antisense oligonucleotides, which dramatically decrease Lp(a) levels, are currently being evaluated. Lipoprotein apheresis is a definitive treatment usually reserved for patients with an Lp(a) level over 60 mg/dL.

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