



CASE REPORT

Lipoprotein(a) and Atherosclerosis: A Case Report and Literature Review

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Clinical Scenario

A 61-year-old man presented with central chest and vague left shoulder pain precipitated by a brisk walk up a steep hill. His pain resolved with rest. He has never had this pain before and had no associated symptoms. He has no other medical problems. He is known to have three vessel coronary artery disease (CAD) based on two previous cardiac catheterizations. His initial catheterization was conducted to evaluate the cause reversibility on an exercise stress test using radioisotope technetium 99M for imaging of myocardial perfusion. Due to a family history of heart disease, the stress test was done at age 50. He gets more than 40 minutes of cardiovascular exercise at least four days a week, has no history of tobacco or drug use, and does not have diabetes. His blood pressure is 110/65, resting heart rate 64, and body mass index (BMI) is 23. The patient takes 40 mg of Atorvastatin, and 81 mg of aspirin, both daily. High-density lipoprotein (HDL) is 65 mg/dl and low-density lipoprotein (LDL) is 50 mg/dl. Repeat cardiac catheterization reveals greater than 95% occlusion of his left main coronary, left circumflex, left anterior descending, and posterior descending arteries. His right main coronary artery is approximately 50% occluded. After being treated with four-vessel coronary artery bypass grafting surgery, he returned to his functional baseline of vigorous exercise without angina.

Introduction

An otherwise healthy 61-year-old male presented with stable angina without traditional risk factors for coronary artery atherosclerosis. Lack of traditional risk factors was the impetus for a more extensive workup,

including specific lipoproteins, including Lp(a). The patient's workup revealed an Lp(a) level of 230 nmol/L, which is in the highest quartile [1]. Lp(a) levels > 30 mg/dl or > 75 nmol/l are considered elevated. Around 25% of the global population has levels this high, which is over 1 billion people. Importantly, there is no ICD-10 coding option for increased Lp(a) which greatly limits epidemiologic and other studies [2].

Pathophysiology and Genetics

Lp(a) is a low density lipoprotein that has a lipid core and a protein component. The lipid core is the same as LDL, and the protein component consists of apoB-100 and apoA. The apoA in the protein component of Lp(a) is similar to plasminogen. Both have the kringle K-IV and K-V and protease domains of plasminogen. The 34 isoforms of Lp(a) are differentiated by the number of K-IV kringle repeats. The more repeats of K-IV, the less Lp(a) in the blood. Other genetic factors including lipoprotein metabolism can affect Lp(a) levels [3]. The effect of Lp(a) can partially be explained by its inhibition of plasminogen activation. Lp(a) competes with plasminogen and t-PA by binding to fibrin (Figure 1); consequently, clot breakdown is inhibited [4]. Lp(a) also interacts with macrophages in blood vessels introducing another pathway to atherosclerosis. Foam cells form and initiate an inflammatory cascade [5].

Patient behaviors (e.g. smoking) are among the most powerful risk factors for atherosclerosis. However, 90% of an Lp(a) level is determined by the allele of the apoA gene [6]. The genetic determination for Lp(a) level has also been demonstrated in the study of twins [7,8].



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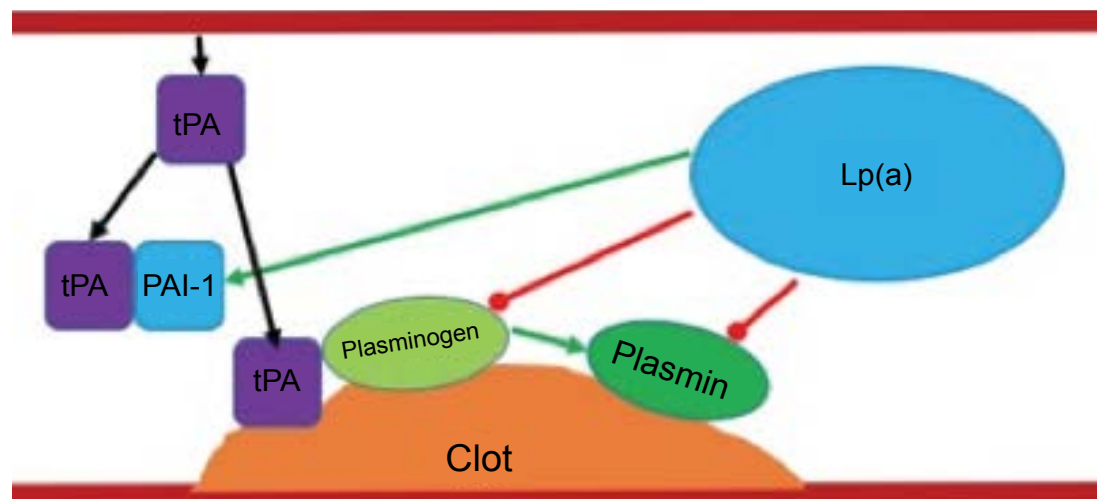


Figure 1: The pathophysiology of Lp(a). Lp(a) potentiates PAI-1 which inhibits tPA. Lp(a) blocks plasminogen and plasmin.

A Risk Factor for Atherosclerosis?

In 1986, Rhoads and colleagues showed that Lp(a) levels above the 75th percentile correlated with a higher odds of myocardial infarction (MI). He wrote that drugs such as neomycin and niacin may lower Lp(a). Further, Lp(a) could be used to screen younger patients for MI risk, since Lp(a) levels remain stable throughout a patient's life [9]. These possible treatments and surveillance plans have not been widely validated or implemented as of 2018.

In 1993, a prospective study of 296 middle aged white men found no association between Lp(a) and risk of future MI [10]. This finding supported not screening patients for Lp(a) levels to determine risk of CAD. The authors reported that while their results differed from most retrospective studies, an earlier large prospective study also demonstrated no relationship between Lp(a) and MI [11]. However, they noted that the results could not be extrapolated to other races. In part, these studies contributed to a shift of attention away from investigating Lp(a) as a cause of atherosclerosis, screening of Lp(a), and treatment of high levels of Lp(a).

Maher and colleagues randomized 146 men younger than 63 with CAD, elevated apoB and a family history of CAD to either an AHA diet and lovastatin plus colestipol, niacin plus colestipol or placebo (plus colestipol of LDL > 90th percentile). Subjects were followed for 2.5 years. The researchers concluded that Lp(a) increases the risk of atherosclerosis, and that the risk can be mitigated by aggressive medical LDL attenuation despite persistent Lp(a) elevation [12]. The findings of this study may be limited since niacin has never shown to have a cardioprotective benefit when combined with statins; however, niacin lowers Lp(a) levels on its own. Also, since the niacin/colestipol and placebo group were not treated with a statin, today's standard of care, the study is further limited.

A prospective study of 2047 patients, who had suffered an MI or died of CHD during the study period

showed that Lp(a) was an independent risk factor for CAD [13]. Lp(a) levels were consistent over time, and as Lp(a) increased so did the risk for coronary disease. The odds ratio when comparing the upper to lower third of Lp(a) levels was 1.60 (1.38-1.85) for coronary disease.

Clarke and associates demonstrated that three specific chromosomal areas are strongly associated with coronary artery disease risk, one of which contained the LPA coding locus (6q26-27) [14]. Two main genetic variants at the Lp(a) locus had to odds ratios for coronary disease of 1.70 (1.49-1.95) and 1.92 (1.48-2.49) respectively. The odds for coronary disease increased from 1.51 (1.38-1.66) to 2.57 (1.80-3.67) if the patient had two copies of the variant allele instead of one. After controlling for Lp(a) level, the odds ratio difference did not exist. This result implies that Lp(a) has a genetically determined, causal relationship with CAD.

In a review article of 36 prospective studies (126,634 patients) the Emerging Risk Factors Collaboration concluded that there are, "continuous, independent, and modest associations of Lp(a) concentration with the risk of CHD" [1]. Patients were followed for a combined 1.3 million person years with endpoints that included CHD, stroke, and death. The risk ratio for CHD adjusted for patient age and sex was 1.16 (1.11-1.22) for every 3.5 times increase in Lp(a) concentration. The study suggested that CHD risk increases curvilinearly with Lp(a) level. Importantly, the researchers showed that Lp(a) increased the risk for ischemic stroke, but, did not increase risk for non-vascular death. These findings agree with the suspected pathophysiology of vascular disease caused by Lp(a).

Zhu and colleagues conducted a cross-sectional study of 679 patients with CAD in the Han Chinese population [15]. With adjustments for CAD risk factors, they found that Lp(a) levels were independently associated with the number of stenotic coronary vessels. Lp(a) was also independently associated with the Gensini, a measure of the severity of artery blockage.

A study of 228 menopausal women in Italy looked at the association between high Lp(a) and an increase in small dense-low density lipoprotein (sd-LDL) [16]. This study excluded women with metabolic syndrome and showed that there was a slight increase in sd-LDL if there was elevation in Lp(a), which they conclude may partially explain why Lp(a) leads to premature atherosclerosis.

In summary, although initially debatable, the literature shows that Lp(a) is an independent, causal, risk factor for coronary artery disease. Now we turn to ways of identifying and decreasing Lp(a) levels, and consequently, coronary artery disease risk.

Screening

There is currently not a consensus for Lp(a) screening. The European Atherosclerosis Society consensus panel recommended screening for anyone at an intermediate or high risk of CVD/CHD with an Lp(a) goal level of < 50 mg/dl [17]. The panel also advised using niacin as pharmacotherapy for meeting that goal.

Treatment

Currently there is no standard treatment to reduce Lp(a), and no studies have been conducted to assess the impact therapeutic Lp(a) reduction on CAD. The main goal of treatment is to address other known risk factors for CAD, including aggressive LDL lowering.

Chasman and associates established the Lp(a) genotype of 25,131 Caucasian women. Some women (3.7%) carried the minor allele. With nearly 10 years of follow up, this group had an age-adjusted hazard ratio of 2.21 (1.39-3.52) compared to non-carriers. However, if treated with 81 mg aspirin, their hazard ratio was 0.44 (0.20-0.94) compared with placebo treated carriers. Aspirin did not significantly alter the cardiovascular risk for non-carriers. This study suggests that aspirin has a profound effect on coronary artery disease risk in patients with variant allele Lp(a), and that such patients with elevated Lp(a) should be treated with aspirin to help mitigate risk [18]. However, risk is not being altered by lowering the amount of Lp(a), but by decreasing Lp(a) effects on clotting.

Nicotinic Acid (niacin) lowers Lp(a). However, niacin has never been shown to decrease coronary artery disease risk or improve patient outcomes. Nonetheless, it is reasonable to consider niacin therapy in patients with high Lp(a) as niacin is safe and usually well tolerated. Carlson and colleagues reported a mean decrease in Lp(a) of 38% (28-47%) in 31 patients treated with 4 g of niacin, daily, for six consecutive weeks. Additionally there was also a decrease in LDL [19]. More recently, Guyton and associates treated 72 patients with a 2 g bedtime dose Niaspan (extended-release niacin). The mean Lp(a) decrease was 20%, and other lipid and fibrinogen levels were favorably affected [20]. These

studies suggest that niacin is an effective treatment to decrease Lp(a) levels; however, such decreases have not been shown to lead to clinical improvement and there is no agreed upon target Lp(a) level.

Statins do not lower Lp(a) [21]. However, statin therapy is essential for patients with increased Lp(a) to mitigate additional CAD risk.

PCSK-9 inhibitors decrease Lp(a) levels. A systematic review and meta-analysis of 6,566 patients found that the mean Lp(a) reduction was 26% [22]. The study also showed a reduction in myocardial infarction and all-cause mortality, but these benefits were not independently attributable to Lp(a) reduction. The proposed mechanism of such reduction is increased uptake by the low-density lipoprotein receptor (LDLR) due to decreased circulating LDL. Since there is less LDL circulating, the LDLR uptakes more Lp(a) [23]. These authors do not rule out that PCSK 9 inhibition might decrease Lp(a) synthesis, although increased uptake seems more likely. Regardless, PCSK-9 inhibition should be considered in patients with elevated Lp(a) as an adjunct treatment to address their entire lipid profile.

Apheresis is another option for patients with very high Lp(a). Khan and associates studied the effect of lipoprotein apheresis on patients with refractory angina and Lp(a) greater 500 mg/L [24]. In this crossover randomized controlled trial of apheresis versus sham procedure, myocardial perfusion reserve increased by 0.63 with apheresis and decreased by 0.16 with the sham procedure. This small study showed apheresis to be a viable option for patients with refractory angina and very high Lp(a). However, this treatment is costly and burdensome.

Lastly, Ionis Pharmaceuticals has a drug in development designed to lower Lp(a) with an antisense ribonucleic acid (RNA) injectable treatment. A randomized, double-blind, placebo-controlled Phase 1 study of 47 patients demonstrated a dose-dependent 77.8% decrease in Lp(a) levels with six treatments of 300 mg [25]. Antisense therapy is a potential medical treatment of atherosclerosis, including high Lp(a).

Conclusions

Lp(a), a genetically determined, causal risk factor for coronary atherosclerosis is an emerging treatment target for CAD. Common drug therapies (e.g. aspirin, statins) for high Lp(a) aim to mitigate other risk factors. Niacin and PCSK-9 inhibitors decrease Lp(a), but this decrease in Lp(a) has never been shown to be clinically meaningful. Antisense RNA therapy is a new approach to Lp(a) reduction. Further research is needed to determine universal screening protocols and if decreasing Lp(a) medically can be translated into improved patient outcomes.

Clinical Scenario Revisited

The patient continued to do well for 8 years. At age

69 he had shortness of breath and some mild mid sternal chest pain, again from walking briskly uphill. Coronary catheterization showed his right coronary artery (RCA) to be 90% stenosed. His bypass grafts had multiple patches of stenosis, with a suspected culprit lesion in the venous graft to the left circumflex artery at 35%. A drug-eluting stent was placed in the RCA and the patient began dual antiplatelet therapy (DAPT). After meeting with a metabolic lipid specialist, the patient was started on evolocumab (Repatha), in addition to DAPT and high-intensity statin therapy, the combination which has shown to reduce cardiac events [26]. He was able to resume high-intensity aerobic exercise shortly after stenting. Three months later, his Lp(a) had decreased 25% from before starting Repatha. It is not clear if this reduction have any therapeutic benefit.

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Conflicts of Interest

We have no conflicts of interest, funding, or disclosures.

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