Lipidaholics Anonymous Case 295: Elevated Lipoprotein(a) with normal lipid and lipoprotein concentrations

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Note from the author: This case is dedicated to all of the patients whose lives are affected by Lipoprotein (a) and the providers who are challenged to treat these cases effectively. Special thanks to the Lipoprotein (a) Foundation for its relentless patient support and educational offerings.

OVERVIEW:

Lipoprotein little “a”, abbreviated as Lp(a), is the oldest and strongest genetic risk marker for atherosclerotic CVD and finally seems to be gaining the respect it deserves as the most atherogenic lipoprotein that afflicts humans. Its prevalence is much higher than any of the familial hypercholesterolemia phenotypes, although many unfortunate folks have both FH and hyperlipoproteinemia (a).

Despite the numerous studies that seem to appear weekly, among many clinicians and for sure the public Lp(a) still is the most unrecognized, not tested for and least understood lipoprotein disorder. Unfortunately the new AHA/ACC Treatment of Blood Cholesterol Guidelines summary available as a free download on line in either Circulation or JACC does not mention Lp(a). The 260 page Full Panel Report Supplement (which few real world clinicians have seen or read) states:

“Elevated levels of Lp(a) are associated with an increased risk for premature ASCVD and often have a familial pattern, as plasma Lp(a) levels are determined to a great extent genetically. Renal failure also leads to Lp(a) elevations. Lp(a) is produced by the association of apolipoprotein(a), a protein that has substantial sequence homology with plasminogen, with apoB. It contains a variable number of a protein repeat called a kringle, and the number of kringles determines the molecular weight of Lp(a). Since the number of kringles may influence Lp(a) measurement, a kringle-independent assay should be used. Lp(a) levels are not affected by most pharmacologic therapies except for niacin and estrogen. Although niacin can reduce Lp(a) levels by 20%, LDL apheresis lowers Lp(a) levels by a substantially higher magnitude. However, no clinical trial data specifically show an outcome benefit associated with lowering Lp(a). Indeed, lower Lp(a) levels in AIM-HIGH did not result in improved outcomes, although it should be noted that lower LDL-C levels were achieved by statin therapy in that trial. The data are therefore insufficient to support the use of Lp(a) as a therapeutic target. Thus, the Panel continues to endorse statin therapy for ASCVD risk reduction in groups who can benefit from it, as noted elsewhere.”
I would note that despite what you often see reported, in reality no such isoform independent assay for Lp(a) exists for clinicians in the real world. An ongoing dilemma is that even experts disagree on what therapeutic advice to offer Lp(a) patients and what, if any, the goals of therapy should be. In that vein, this Lipidaholic’s Anonymous case brings forth a clinical challenge in a single woman with abnormal Lp(a) concentrations.

CASE DISCUSSION:

I had the opportunity to review the case of a perimenopausal woman, with an incredible healthy lifestyle who recently had lab testing done through Health Diagnostic Laboratory, Inc. that disclosed an elevated Lp(a) mass and Lp(a) particle count [Lp(a)-P] as well as an elevated lipoprotein phospholipase A 2 (Lp-PLA₂) level. There is some family history of CV events but it is not overly dramatic or premature. She is asymptomatic and is very active with cycling and running. She saw two generalists and the first told her to ignore the Lp(a) value in view of the normal lipid panel and her “protective” HDL-C (I want to cry when I hear docs say that!) and the other who at least knew the risk associated with Lp(a) suggested doing a coronary calcium test which in fact demonstrated subclinical atherosclerosis. She started to seek additional knowledge on Lp(a) and through online searching found the Lipoprotein (a) Foundation of which I am one of the advisors: (http://www.lipoproteinafoundation.org/). I met with the patient to (1) provide education and (2) suggest a referral because the patient’s case is unique and requires individualized advice from a clinical lipidologist.

The screening test panel revealed the following results:

![Screening Test Panel Results](image-url)
So we have a woman with a normal lipid panel, characterized by high HDL-C and a seemingly perfect apoB and total LDL-P. But the Lp(a) mass of 75 mg/dL and Lp(a)-P of 195 nmol/L are both elevated and although the inflammatory markers fibrinogen, MPO and hs-CRP are excellent, the lipoprotein phospholipase A2 (Lp-PLA2) was very high, especially for a woman, at 258 ng/mL. Recent data showed that Lp(a) measurements are not affected by fasting or inflammation.

**Lipoprotein(a) Concentration: Effect of fasting, nonfasting and inflammation**

![Graph showing lipoprotein(a) concentration over time](image)

Values are shown for the 20th, 50th, 80th, 90th, and 95th percentile

The rest of the panel including TSH, sterols, and IR/sensitivity markers were all normal. How would you advise this woman? Of course there are no “Level One” evidence based answers, so the current AHA/ACC cholesterol guidelines and their risk-assessment tool would tell her and her provider that all is well and she does not qualify for a statin or any other lipid-modulating therapy. Yet, even that statement stresses individualization of any therapeutic advice.

DAYSpring Analysis:

Lp(a) is by far the most common genetic lipoprotein disorder that results in atherosclerotic events. No other genetic lipid disorder, including familial hypercholesterolemia (FH) is even close in prevalence. One third of Americans have a high risk level defined as Lp(a) mass > 30 mg/dL or Lp(a)-P > 75 nmol/L. When a clinician sees elevated Lp(a) one then should do an exhaustive search for additional risk factors that would further worsen the prognosis such as hypertension, smoking, atherogenic lipoprotein abnormalities, diabetes or insulin resistance, other prothrombotic markers, hypothyroidism, hyperhomocysteinemia, low omega-3 index and inflammation. Since the Study of Women’s Health Across the Nation (SWAN) which evaluated middle-aged women transitioning to postmenopause showed Lp(a) was very modestly associated (r = -0.04) with insulin resistance and even after adjusting for ethnicity and BMI, and this association was not changed by including measures of thyroid status, androgens, or estrogen (Am J Cardiol 2003;92:533–537), I’d suggest more extensive biomarker testing on insulin resistance. The thorough work up I advise in persons with Lp(a) abnormalities is discussed in detail in Lipidaholic’s Case 292. At this point of the evaluation the patient only has one other risk factor but it is not a very desirable one – namely elevated lipoprotein phospholipase A₂ (Lp-PLA₂) which may be especially indicative of increased risk in patients with high Lp(a)-P than without (J Biological Chem 1995;270:31151-31157). Note, a phospholipase hydrolyzes (de-esterifies) one of the two attached fatty acids (acyl group) on a phospholipid creating a lysophospholipid (a PL with only one FA). Lipases capable of hydrolyzing the remaining fatty acid on lysophospholipids are called lysophospholipases. For a thorough review of phospholipids please see our lecture on Phospholipids, Part 1.

Lp-PLA₂ Activity of Lp(a) and LDL and Sensitivity to Oxidation

Results based on equimolar concentrations of lipoprotein particles indicate that the Lp(a)-associated acetylhydrolase activity exceeded those found associated with LDL by 6.9-fold.

Analysis of the data (8.9 nm (lyso-PAF)/min 3 mg protein for Lp(a) and 2.2 nm/min 3 mg for LDL) on the basis of equal protein concentrations affords a ratio of the activities of 4 (Lp(a)):1 (LDL)

Blencoe C et al. JBC 1995;270:31151-31157
Lp(a) conveys risk because it is an apoB-containing LDL particle capable of entering the arterial intima and the attached apo(a) has prothrombotic qualities as well as being a major trafficker of oxidized phospholipids. Oxidized phospholipids are created when the surface phospholipids on apoB particles enter the arterial wall and are exposed to free radicals. As seen in the above graphic once particle surface phospholipids (and maybe sterols) are exposed to arterial wall free radicals, the enzyme lipoprotein phospholipase A₂ (Lp-PLA₂) that traffics with the LDL hydrolyzes the phospholipids into oxidized fatty acids and lysophosphatidyl choline (simply a phospholipid that has lost one of its two fatty acids), both of which are potent signaling molecules that thus initiate the maladaptive inflammatory process in the artery wall with increased expression of vascular cellular adhesion molecules (VCAMs), selectins, monocyte chemotactic protein (MCP), etc. There are several studies showing that Lp(a) particles that traffic oxidized lipids, measurable using E06 antibodies, are significantly more atherogenic than those that do not. So I am quite suspicious that the combination of high Lp(a) and high Lp-PLA₂ in this person suggests that the apo(a) is carrying oxidized PL, but a more important question is does the high Lp-PLA₂ indicate the presence of any vulnerable plaque in this woman with subclinical atherosclerosis?

**Antibody Recognition of Oxidized Phospholipids in Blood**

![Image of antibody recognition]

Modified Lp(a) lipoprotein, which accumulates in atherosclerotic lesions, can be detected at higher levels in the blood with the use of E06, an antibody that recognizes oxidized phospholipids.

Berliner JA et al. NEJM 2005;351:9-11
It is also known that these oxidized lipid moieties are more prevalent in Lp(a) patients whose apo(a) is of the smaller size or lower molecular weight (MW). Note that the MW of apo(a) can vary between 275 and 800 kDa in different individuals. This is primarily due to a genetic polymorphism regulating the number of repeats of the kringle IV part of the molecule. Hepatic production of apo(a), which also determines the circulating concentration of Lp(a), is inversely related to the apo(a) size (Curr Opin Lipidol 2014, 25:289–296). Although this woman has not been tested for apo(a) isoform we can take an educated guess that she indeed has the small isoform. If one compares Lp(a) mass [the collective weight of the apo(a) proteins in her plasma] and compares it to the actual number of Lp(a) particles abbreviated as Lp(a)-P and sees discordance in favor of Lp(a)-P, the apo(a) isoform is small. Note her Lp(a) mass is high at 75 mg/dL but not super horrific but the Lp(a) -P is extremely high. This discordance where Lp(a)-P is much higher than that suggested by the Lp(a) mass means she has the small isoform. If she was producing mainly the large isoform, the Lp(a)-P would be much lower. In other words at any Lp(a) mass concentration there will be many more small, low MW apo(a) molecules than it does larger, higher MW apo(a) molecules. Thus, since each apo(a) attaches to an LDL particle, at any given Lp(a) mass, the person with the small apo(a) will have more Lp(a) particles than someone with the larger apo(a).

As recently discussed by Paul Durrington in Current Opinions in Lipidology (also referenced above) reporting Lp(a) as mass poses difficulty as the molecular mass of an individual’s Lp(a) is determined by the apo(a) size polymorphism expressed by that person. There is also a lack of clarity about whether the reported mass value refers to the particle mass [i.e. protein and lipid present in the Lp(a) particles], which would be less affected by the size polymorphism, or simply the protein mass [apoB and apo(a)] which will be much more variable. A different approach has been to quantify Lp(a) in terms of its cholesterol concentration which informs the clinician how much LDL cholesterol is actually in Lp(a). The emerging strategy is to measure Lp(a) particle concentration by the quantifying apoB component of the oxidized phospholipid:ApoB-100 ratio and Lp(a) lipoprotein levels to the extent of coronary artery disease (CAD) in 239 patients 60 years of age or younger than for patients older than 60 years.

Lp(a), there being only one apoB molecule per Lp(a) particle and apoB molecular mass being comparatively constant. Lp(a)-apoB is reported as Lp(a)-P. The slide below was also used in Lipidaholic’s Annoymous Case #292 but it is worth another look.

### Lp(a) Measurements

- Apo(a) mass is the amount or mass of apoprotein (a) in a dL of plasma
- Lp(a)-C is the cholesterol trafficked within all of the Lp(a) particles per dL
- Lp(a)-P is the # of LDL particles carrying apo(a), regardless of apo(a) size or MW that exist in a dL of plasma

So we can likely conclude she has too many Lp(a) particles with the smaller isoform of apo(a) and because of the elevated Lp-PLA₂ the odds are that the apo(a) is trafficking oxidized lipids. In patients producing apoprotein (a) the CV risk is most dependent on the number of oxidized Lp(small isoform a) particles. Because of her fantastic lifestyle, virtually all of her other biomarkers are fine. Although the good living has prevented any biomarker signals of IR, it would be wise to perform the full diabetes prevention and management panel on the next biomarker test.

The current approach to reducing risk in persons with elevated Lp(a) is normalize the LDL-C (which in my mind is simply a weak surrogate of which is LDL-P and apoB). In this case the apoB and LDL-P are concordant but interesting data presented by me at last year’s (2013) Scientific sessions of the NLA revealed that when LDL-P and apoB are discordant, the apoB is likely the more accurate way to count particles if Lp(a) mass is high (J Clin Lipidol 2013;7(#110):241-242).

### TREATMENT CONSIDERATIONS:

My thoughts were first to suggest consulting a nutritional consultant and/or naturopath for suggestions of any and all lifestyle ways of reducing oxidative/inflammatory issues that are at play. In view of the patient having subclinical CAD and elevated Lp-PLA₂, I also suggested seeing a cardiologist who well-schooled or certified in lipidology. I’d defer to that treating physician on providing an evaluation (stress-echo?) for an exercise prescription. The echo is also important because of the high association between Lp(a) and aortic stenosis.
I have seen clinical events related to Lp(a) in patients with unremarkable lipid (cholesterol) but high Lp(a)-P concentrations and it is my preference after in depth discussions with my patients that statin therapy is needed. Supporting this is the recent data from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) Study that statin use (rosuvastatin in this trial) reduced clinical CV events in patients who had above the mean Lp(a) to the same extent as those with below the mean Lp(a) concentrations (Circulation 2014;129:635-642). Recall that in JUPITER, normal LDL-C was present at baseline, yet statins were still prescribed. Also of great interest was the ability of a statin to reduce clinical events in persons with high Lp(a) mass despite the fact that the statin did nothing to the Lp(a) mass. Contrast this to the AIM HIGH study where niacin significantly reduced Lp(a) concentrations but did not reduce clinical events. One might speculate that in JUPITER despite the normal LDL-C apoB and LDL-P (quite responsive to statin treatment) was elevated whereas in AIM HIGH, because of aggressive statin and ezetimibe use LDL-P and apoB were well controlled.
So despite the normal LDL-P in this patient, I’d start with a low dose, well tolerated statin like pravastatin or pitavastatin. I’d start low (10 mg or 1 mg respectively) and see how it is tolerated keeping a close eye on glycemic markers and creatine kinase (CK). If one wanted to use rosuvastatin because that was the drug utilized in JUPITER, I’d go with 5 mg. The JUPITER data was also very similar to that from the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial (N Engl J Med 2011;365:2255-67) in supporting that Lp(a) acts as a CVD risk factor that is independent from LDL-C and also other CVD risk factors.

How far should the statin be pushed? I’d shoot for an LDL-P ~ 400 nmol/L but also keep a close eye on the desmosterol level (a cholesterol synthesis marker). The baseline desmosterol was normal in this patient and I would not want to over suppress cholesterol synthesis (reduce desmosterol too much). My reason for not chronically over-suppressing cholesterol synthesis is emerging evidence that both low cerebrospinal fluid and serum desmosterol concentration, which correlate well, are a risk factor for Alzheimer’s disease (J. Lipid Res. 2012; 53: 567-576). Whatever happens to her LDL-C likely tells us little about LDL-P or cholesterol homeostasis, meaning synthesis or absorption or the risk related to Lp(a)-P. Readily available cholesterol synthesis biomarkers like desmosterol/lathosterol now make this issue so easy to follow.

Because she is such a serious cyclist/runner I’d get a baseline CK level before using the statin. Even if somewhat high I’d still use the statin, but at least I’d have a baseline level for comparison. She should be advised to be cognizant of any muscular symptoms she is having prior to the start of the statin, so as not to attribute them to the statin henceforth. The potential for statin-related myopathic symptoms is increased in athletes especially in those with high level muscular activity like cyclists and the patient would need proper counseling on what symptoms to watch for such as the more serious weakness or dark urine (myoglobin) as well as proper hydration during exercise.
One thing to also keep in mind is that estrogen deficiency at perimenopause or menopause is associated with increases in Lp(a). Interesting is that the evidence showing that estrogen therapy may reduce clinical events in menopausal women with CAD who had elevated Lp(a) (HERS trial: Circulation, 2002;105:917-922). The very large Women’s Health Study showed higher Lp(a)-related CV risk in women not using hormone therapy compared to those who did. (J Am Coll Cardiol 2008;52:124–31) and also that Lp(a) concentrations are lower in women using menopausal hormone therapy. Slides on these two trials are in Lipidaholic’s Case 292, WHS and HERS.

### Women’s Health Study: Polymorphisms the Apolipoprotein(a) Gene

![Graph showing Kaplan–Meier estimates of the cumulative fraction of Caucasian women with a first ever major CVD event (myocardial infarction, ischemic stroke, or cardiovascular death) according to rs3798220 carrier status and treatment group.](Image)


### Heart & Estrogen/Progestin Replacement Study (HERS)

![Graphs showing incidence of events with E+P and Placebo for Lp(a) above and below median.](Image)


A downside to estrogen therapy is the potential side effect of venous thrombosis which has also been related to elevated Lp(a) in some studies. This patient is not having perimenopausal-related quality of life.
issues so estrogen use is not a consideration at this time but the topic needs to be discussed. The 
woman is also using aspirin and I think that should continue. There is good data that women with certain 
single nucleotide polymorphisms (SNPs) of apo(a) significantly do better with aspirin but those without 
the SNP do not. Since we cannot test for that, in view of the inflammation, I’d cover with ASA but in the 
future follow the AspirinWorks (urinary 11-dehydrothromboxaneB₂ which is a platelet reactivity test). If 
consistently normal, one could drop the ASA in this patient and see what happens to the test.

FOOD FOR THOUGHT

So the take home is in such a patient one could (1) follow the guidelines and because the risk 
assessment tool shows virtually no short-term risk, do nothing but advise her to continue her current 
lifestyle or (2) to do the extensive workup looking for other potentially treatable issues. In this case the 
Lp-PLA₂ and the coronary calcium (neither advocated by guidelines) subclinical atherosclerosis 
suggested a much more serious degree of risk is present. Finally I strongly advise all clinicians and their 
patients with Lp(a) issues to follow and support the Lp(a) foundation at 
http://www.lipoproteinafoundation.org/ or follow them at Twitter @LipoproteinaFDN

If you want to catch up with the many complex 
nuances of Lp(a) Dr Joseph McConnell and I have 
posted a review with updates at our Biomarker Bliki 
web site:

http://biomarkerbliki.org/articles/7#/section/24