



In search of a physiological function of lipoprotein(a): causality of elevated Lp(a) levels and reduced incidence of type 2 diabetes¹

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“Shallow (wo)men believe in luck or in circumstance. Strong (wo)men believe in cause and effect.” (Ralph Waldo Emerson, *The Conduct of Life*, 1860).

Assigning causality to complex, multifactorial phenotypes, such as incident T2D, is difficult. Assigning causality by the relative lack or an absence of a putative causal mediator is nearly impossible without the benefit of rigorous mechanistic studies and randomized trials where confounding variables can be controlled. Yet this is where we find ourselves in 2018, with several reports suggesting an association of very low lipoprotein(a) [Lp(a)] levels (<10 mg/dl or <25 mmol/L) and incident T2D or, interpreting alternatively, elevated Lp(a) levels with lower risk of incident T2D. These associations were derived from large prospective epidemiological cohorts with robust durations of follow-up, including the Women’s Health Study in 2010 (1), Copenhagen cohorts in 2013 (2), EPIC-Norfolk in 2014 (3), and a Turkish study in 2017 (4) and the Bruneck Study in 2017 (5) (Table 1). These studies included 134,707 people followed prospectively for 5–20 years and have a weighted odds ratio for incident T2D of 0.75 for high levels versus low levels of Lp(a). In almost all of the studies, this association was present with mean/median Lp(a) levels in quartile 1 of <5 mg/dl compared with the comparator quartile 5 with Lp(a) levels 44.6–69.0 mg/dl.

In the latest cross-sectional study reported in the current issue of the *Journal of Lipid Research*, Mu-Han-Ha-Li et al. (6) investigated the association of Lp(a) concentrations, LPA KIV₂ repeats, and T2D in a Chinese population of 1,863 consecutive patients undergoing coronary angiography. Evaluating the data by tertiles, they showed that the risk of prevalent diabetes (i.e., T2D present on admission to the hospital) was approximately 25% less in subjects in the top tertile [median (range) 67.9 (35.3–318.5) mg/dl] of Lp(a) versus those in the bottom tertile [median (range) 7.4 (0.6–12.9) mg/dl]. The study showed that the prevalence of T2D was 41.6%, 37.6%, and 35.1% in Lp(a) tertiles 1, 2, and 3, respectively, showing the risk

is mainly in the low Lp(a) individuals. Moving closer to causality, an association was also noted between the larger number of KIV₂ repeats and prevalent T2D. A similar study suggested likewise, that the association is with a larger number of KIV₂ repeats and not necessarily low Lp(a), as recently suggested in the Copenhagen City Heart Study (7). The Lp(a) values of risk are quite similar to the prospective studies noted above. The importance of this observation is that large numbers of KIV₂ repeats, which are associated with lower levels of Lp(a), and vice-versa, are also genetically determined and therefore cannot be confounded by environment.

The study by Mu-Han-Ha-Li et al. has strengths and limitations. First, it adds to the database that, irrespective of the underlying mechanisms, low Lp(a) levels are associated with higher risk of both prevalent and incident T2D. Second, it expands the observation to nonCaucasians, who were primarily under-represented in the other studies, so that the robustness of the observation is more certain. Third, it is the second report to suggest that large numbers of KIV₂ repeats are also associated with prevalent T2D (7), which makes it a more intriguing observation that should stimulate more fundamental research into causality. Fourth, the diagnosis of T2D was made by several accepted methods and appears not to be a major confounding variable in the study methodology. Finally, the Lp(a) assay used appears to be adequate, and there did not appear to be an imbalance of younger age (less T2D) or statin use (more T2D) among tertiles of Lp(a).

Limitations of the present study include that this was a confirmatory study, as other studies have shown relationships of Lp(a) and prevalent T2D (a nonexhaustive list is

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TABLE 1. Association of Lp(a) levels and incident T2D

First Author	Year	Cohort	Patients, n	Duration of Follow-up	Lp(a) Levels* Q5 vs. Q1	OR Q5 vs. Q1	Weighted OR
Mora (1)	2010	WHS	26,746	Median 13.3 years	44.6 vs. 3.9	0.78	0.155
Mora (1)	2010	CCHS	9,652	Not provided	54.0 vs. 4.4	0.58	0.042
Kamstrup (2)	2013	CCHS/CGPS	77,901	Not provided	69.0 vs 3.0	0.79	0.457
Ye (3)	2013	EPIC-Norfolk	17,908	Mean 9.8 years	53.5 vs. 3.9	0.63	0.084
Kaya (4)	2017	Turkish	1,685	Mean 5 years	Mean 9.3–11.9 vs. 7.1–7.6	0.84	0.011
Paige (5)	2017	Bruneck	815	Median 20 years	51.9 vs. 2.3	0.73	0.004
Total			134,707				0.75

Lp(a) values are in mg/dl. The weighted odds ratio is based on the summation of the relative contribution of the study size and the odds ratio in that study. WHS, Women's Health Study; CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study.

shown in **Table 2**). It was also a cross-sectional study with a highly selected population undergoing coronary angiography, and therefore, local practice patterns and unconscious selection bias may have contributed to a skewed population that may not represent patients as a whole. A second major limitation of this study, and also of the Copenhagen studies and all studies that use polymerase chain reaction technology to quantitate number of KIV₂ repeats (8), is that allele-specific numbers of KIV₂ repeats cannot be determined, and the data are reported as a summary of both alleles. For example, if it is measured that there are a total of 60 repeats, it cannot be known if this is due to a patient having 30 KIV₂ repeats on each allele, or 15 and 45 on each allele. This may have implications in appropriate interpretation of the data, as it is known for cardiovascular disease that the smaller of the two isoforms is usually responsible for most of the plasma Lp(a) levels. Future studies trying to link large isoforms to T2D should use the gold standard methodology, which is agarose gel electrophoresis with appropriate standards to confirm these associations (9). The PCR method has only modest correlation to gel electrophoresis and is not precise enough to make firm conclusions (8). Because gel electrophoresis is laborious and not time- or expense- conducive to large scale investigations, more efforts should be made to develop allele-specific PCR methods to determine isoform size.

A more critical question that has not yet been addressed is whether it is low levels of Lp(a) or a large number of KIV₂ repeats that are associated with T2D, or the opposite; that is, whether high levels of Lp(a) and small numbers of KIV₂ repeats are protective. This is a crucial question that cannot be answered with the current epidemiological studies, and we must go to the laboratory to address this question with mechanistic studies. The recent National Heart, Lung, and Blood Institute Working Group on Lp(a) (10) proposed that development of more appropriate

transgenic Lp(a) models are needed to provide new insights into Lp(a) pathophysiology. In this instance, models expressing small and large isoforms, along with the native *LPA* promoter, can assess glucose metabolism, insulin resistance, and the relationship to changes in Lp(a) levels that would provide more certainty with regard to whether these epidemiologic associations are causal.

The issue of reverse causality is a very real possibility in these associations. T2D can have a lag phase of 10–20 years before it is diagnosed, and in the preceding timespan, patients will develop insulin resistance and elevated insulin levels. Several studies have shown an inverse association between insulin levels and Lp(a) levels (11), even before a frank diagnosis of T2D is made (12, 13). Furthermore, physiological doses of insulin have been suggested to suppress apolipoprotein(a) mRNA and protein production in cynomolgous monkey hepatocytes (14). Although Mendelian randomization studies are thought to protect against reverse causality, it is possible that confounding variables may be present. For example, an unrelated and unknown genetic influence may be in high correlation with the instrumental variable (in this case, KIV₂ repeats) being assessed. Additionally, it is possible that prediabetes insulin levels may have a disproportionate suppressive effect in subjects with large isoforms, thereby making this association appear to be causal.

Ultimately, the physiological function Lp(a), if any, will need to be determined and understanding this may be useful in the current dilemma. Lp(a) is an unusual lipoprotein that is a combination of an LDL-like particle to which is covalently attached an evolutionarily modified, remodeled, and proteolytically inactive plasminogen-like molecule called apolipoprotein(a) (15, 16). The apolipoprotein(a) component of Lp(a) is not a lipoprotein per se, as it has no lipid binding domains, yet through its evolutionary lifetime has somehow found a way to covalently attach to apolipoprotein B-100, so that Lp(a) circulates as a lipoprotein. Apolipoprotein(a)

TABLE 2. Association of Lp(a) levels and prevalent T2D

First Author	Year	Journal	Patients, n	Lp(a) Levels in DM vs. NonDM
Schernthaner (34)	1992	Atherosclerosis	155	No difference
Haffner (35)	1993	Diabetes	264	13.6 mg/dl vs. 16.1 mg/dl men
Haffner (35)	1993	Diabetes	332	12.6 mg/dl vs 15.9 mg/dl women
Csaczar (36)	1993	Diabetologia	483	No difference
Saely (37)	2006	Eur. J. Clin. Invest.	587	11 mg/dl vs. 16 mg/dl
Fraley (38)	2009	J. Am. Coll. Cardiol.	2342	10.9% vs. 12.2%
Mora (1)	2010	Clin. Chem.	26,746	9.5 mg/dl vs. 11.7 mg/dl WHS
Mora (1)	2010	Clin. Chem.	9,652	15.7 mg/dl vs. 17.4 mg/dl CCHS
Arsenault (39)	2016	Am. J. Cardiol.	1,424	14 mg/dl vs. 15 mg/dl

is also not present in animals other than the hedgehog, African monkeys with tails, apes, and humans (17), but it appears to have undergone several modifications of remodeling from the plasminogen gene. First, KIII of plasminogen evolved in the hedgehog and is attached to apoB as a lipoprotein. Then, many millions of years later, in African monkeys, KIV of plasminogen duplicated itself in multiple copies but lost its fibrin binding activity. It also had an intact protease domain present but with loss of its protease activity, but also had no KV. Then, both fibrin-binding deficient KIV and KV appeared in apes, and finally fibrin-binding competent KIV and KV appeared in humans. Additionally, thus far, only plasminogen of all species tested and human apo(a)/Lp(a) have been documented to contain measurable levels of oxidized phospholipids (17). Whether these are all chance events or if there are yet-to-be-discovered evolutionary advantages of these changes, and how this might relate to incident T2D, remain to be determined.

As best as we can tell, Lp(a) has no known physiological function in modern society, although etiologically, it may have evolved to protect the host in many ways. Although speculative, there have been suggestions that Lp(a) can contribute to wound healing via its lysine-binding component that can attach to lysine molecules at injured sites and deliver cholesterol for generation of new cell membranes (18, 19). Like many other examples of evolutionary advantage of proteins that were modified in Africa, such as altered hemoglobin that protects against malaria but causes sickle cell anemia and apolipoprotein L1 that protects against African sleeping sickness but is associated with renal failure (20), it is possible that because Lp(a) arose in Africa and the highest concentrations are in people of African descent, higher levels may protect against an unknown parasitic infection. However, the closest explanation of Lp(a) biology, but not necessarily the correct one, likely has to do with the fact that the *LPA* gene has duplicated itself from the plasminogen gene, either to further enhance plasminogen activity or to act as a yin-yang balance to plasminogen pathophysiology. In fact, we have shown that the oxidized phospholipids that are primarily present on Lp(a) are associated with increased cardiovascular risk (21, 22), but that the oxidized phospholipids present on plasminogen are associated with enhanced fibrinolysis in vitro and that higher levels are present post-myocardial infarction (23–25), a putative beneficial function to prevent thrombus propagation. In line with these relationships, several members of the plasminogen-related coagulation cascade, including tissue plasminogen activator that activates plasminogen to plasmin, are also associated with higher risk of incident T2D (26–29), another action that is seemingly opposed by elevated Lp(a) levels.

An additional clinically relevant issue that may have an impact if these associations are causal is whether drugs that lower Lp(a) can also induce the development of T2D. It can be extrapolated that levels of Lp(a) <5 mg/dl are present in ~10% of the world's population (30); therefore, over 700 million people already have Lp(a) levels where low levels may have broad population effects. Niacin and

PCSK9 inhibitors lower Lp(a), and whereas niacin is associated with insulin resistance, the large PCSK9 inhibitors outcomes trials have not reported increases in incident T2D (31). Antisense oligonucleotides are much more potent in reducing Lp(a) (32, 33), but the level where the association of Lp(a) and T2D is evident is usually <5 mg/dl; therefore, this is unlikely to be an issue if the treatment is aimed at reducing levels to what is considered normal; that is, <30 mg/dl. Finally, if the Mendelian randomization studies are accurate, they suggest it is not necessarily low Lp(a) levels but large isoforms that may be causal (7). Because patients with large isoforms have very low Lp(a) levels, they are unlikely to be recruited in Lp(a) lowering trials, as recently observed (32, 33).

The search for causality of Lp(a) and T2D, whether it is low levels versus high levels, or large isoforms versus small ones, now needs to transition to mechanistic studies. Understanding these associations not only will help define Lp(a) biology but may also bring new insights and new therapeutic targets to the burgeoning epidemic of T2D. **RESEARCH**

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