Editorial Commentary

Role of lipoprotein (a) in peripheral arterial disease

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Introduction

Lipoprotein (a) [Lp(a)] is a complex polymorphic lipoprotein synthesized by the liver, which is structurally similar to low-density lipoprotein (LDL). Like the LDL molecule, Lp(a) is composed of apolipoprotein B-100 (ApoB-100) but differs in that its ApoB-100 molecule is attached to apolipoprotein (a) [apo(a)], a polymorphic glycoprotein not found in the LDL molecule (1). Plasma levels of Lp(a) are primarily genetically determined by the LPA gene locus, independently of dietary or environmental factors (2).

Even though the physiological role of Lp(a) is not yet well understood, studies have shown that this lipoprotein may accelerate wound healing, promote tissue repair, and inhibit cancer growth and spread (3,4). It accumulates in endothelial injuries by binding to several components of the vascular wall and the subendothelial matrix, stimulates chemotactic activation of monocytes/macrophages, and modulates angiogenesis (4).

Lp(a) presents proatherogenic properties, mainly due to its capacity to transport pro-inflammatory oxidized phospholipids (OxPL), which are powerful predictors for the presence and progression of cardiovascular disease (CVD), as well as for future cardiovascular (CV) events (5). Furthermore, Lp(a) promotes secretion and expression of pro-inflammatory cytokines, enhances endothelial cell permeability, stimulates smooth muscle cell migration and proliferation, and stimulates the expression of adhesion molecules leading to monocyte recruitment and retention (6,7). In addition, Lp(a) also presents thrombogenic activities, as it promotes platelet aggregation, impairs plasminogen activation, and exerts inhibitory effects on fibrinolysis (6-8).

Several studies have described elevated Lp(a) levels as an independent causative risk factor for CVD (9,10).

In the Emerging Risk Factors Collaboration, which included 126,634 participants with no known history of pre-existing coronary heart disease (CHD) or stroke from 36 long-term prospective studies with 1.3 million person-years of follow-up, after adjustment for age, sex, lipids and other conventional risk factors, there was a 13% increased risk for CHD and a 10% increased risk for ischemic stroke for each 3.5-fold increase in Lp(a) concentration (9).

In the EPIC-Norfolk prospective population study, which included 18,720 participants with 212,981 person-years at risk, there was a 13% increased risk for coronary artery disease (CAD) and a 37% increased risk for peripheral arterial disease (PAD) for each 2.7-fold increase in Lp(a) concentration, and these associations were not modified by LDL-cholesterol levels (10).

In this review we aim to present and discuss the epidemiologic and clinical evidence pertaining to the effects of Lp(a) on PAD.

Lp(a) in PAD

PAD is a progressive atherosclerotic disorder characterized by narrowing and/or occlusion of large- and medium-sized arteries of the extremities with the lower extremity vessels being affected more commonly than those of the upper extremities. PAD has become a global health burden, as more than 200 million people worldwide have PAD (11). In addition, PAD is associated with a greatly increased CV morbidity and mortality, impairs quality of life, and is an important cause of amputation worldwide (12). Furthermore, among patients with CAD, those with PAD

have a greater vulnerability to adverse CV events and experience worse outcomes than those with CAD alone (13). In view of the above, it is essential to identify factors contributing in the initiation and progression of PAD, which could lead to an earlier detection, prevention of CV events, and decreased disability.

Several epidemiologic and clinical studies have described elevated Lp(a) levels as an independent causative risk factor for CVD, particularly CAD and stroke (9,14). On the other hand, the association of hyperlipoproteinemia (a) with PAD is not as straightforward and although most studies indicate a direct correlation between Lp(a) levels and PAD, in some others this association cannot be definitely confirmed.

In an earlier study, which was designed to determine the role of Lp(a) as a risk factor for PAD and included 100 white male patients with and without PAD, it was clearly shown that Lp(a) was the strongest significant individual predictor for the presence of PAD and this correlation was independent of other major risk factors for PAD (15).

In another small study, which studied 55 consecutive white men with premature PAD (onset at 45 years of age or earlier), it was demonstrated that the Lp(a) concentration was an independent discriminating risk factor for premature PAD with Lp(a) levels >30 mg/dL being associated with a 3.9-fold increased risk (16).

In a prospective case-control study, which included 200 patients with PAD and 200 age- and sex-matched control subjects, Lp(a) was proven to be a significant independent risk factor for PAD, and fasting Lp(a) levels >24 mg/dL incurred a 2-fold increase in the risk of PAD. Moreover, higher Lp(a) levels were associated with more severe forms of PAD (17).

In a cross-sectional study, which evaluated the correlation between serum levels of Lp(a) and PAD in 557 patients with type 2 diabetic mellitus, recruited consecutively from a diabetes clinic at the National Taiwan University Hospital, it was shown that Lp(a) levels of ≥30 mg/dL carried a 3 times higher risk of PAD. Furthermore, Lp(a) levels were also inversely correlated with the ankle-brachial index (ABI) values and were strongly predictive of the severity of PAD, particularly in patients with existent PAD or an ABI <0.9 (18).

In a longitudinal study, which examined the risk factors for large- and small-vessel PAD progression, it was demonstrated that there was a clear significant association between elevated Lp(a) levels and large-vessel PAD progression (19).

In another case-control study, after adjustment for several potential confounders, it was clearly demonstrated that increased Lp(a) concentrations (>19.5 mg/dL) were associated with a 3.73-fold increased risk for PAD. Furthermore, it was shown that low molecular weight (LMW) apo(a) phenotypes were also a significant predictor of PAD and were associated with a 2.21-fold increased risk (20). These findings were corroborated by another study, which analyzed the correlation of Lp(a) concentrations, LMW apo(a) phenotypes, and one single-nucleotide polymorphism (SNP) in the LPA gene (rs10455872) with PAD in three independent cohorts and performed a Mendelian Randomization approach using instrumental variable regression. The study showed a significant association of Lp(a) concentrations, LMW apo(a) phenotypes, and rs10455872 with symptomatic and asymptomatic PAD. The authors suggested that this association is most probably of causal nature, since the genetically determined apo(a) phenotypes and SNP alleles are in fact linked to PAD (21).

In the Edinburgh Artery Study, which prospectively evaluated the development of PAD in the general population over a17-year follow-up period, after adjustment for CV risk factors and baseline CVD, levels of Lp(a) were significantly associated with the development of PAD with a hazard ratio (HR) corresponding to an increase equal to the inter-tertile range of 1.22 (22).

The InCHIANTI study, a prospective, population-based, randomized study, evaluated the association of Lp(a) plasma levels with prevalent and incident lower extremity-PAD in 1,002 Italian subjects of 60–96 years of age over a 6-year follow-up period. The study found a significant cross-sectional association between higher plasma Lp(a) and lower extremity-PAD. In addition, there was a graded correlation between Lp(a) levels and ABI score, indicating a possible dose-response association between Lp(a) and severity of PAD in the lower extremities (23).

As it was mentioned earlier in this review, the EPIC-Norfolk study, a large prospective population study with 1.3 million person-years of follow-up, revealed a 37% increased risk for PAD for each 2.7-fold increase in Lp(a) levels, and this association was not modified by LDL-cholesterol levels (10). Furthermore, elevated Lp(a) plasma concentration was also associated with PAD-related hospitalization and mortality (10).

In the Factores de Riesgo y ENfermedad Arterial (FRENA), a prospective registry of consecutive outpatients with CAD, cerebrovascular disease or PAD, 1,503 stable outpatients were recruited. Patients with Lp(a) levels of 30–50 mg/dL presented a 3.18-fold higher risk for limb amputation, while those with Lp(a) levels >50 mg/dL were at a 22.7-fold increased risk for limb amputation (24).

On the other hand, as it was mentioned above, not all studies were able to definitely confirm the association between elevated Lp(a) levels and PAD. In the Novel Risk Factors for Systemic Atherosclerosis study, a nested case-control study involving 14,916 healthy men aged 40–84 years, the median plasma Lp(a) level in the 140 participants who developed PAD during a 9-year follow up period was 88.5 versus 75.1 mg/dL in 140 age- and smoking status-matched men who remained free of PAD. However, this numerical difference was not statistically significant and this study did not find enough evidence supporting Lp(a) as a predictor for PAD (25).

In another prospective cohort study, which evaluated 27,935 US healthy women ≥45 years of age over a median follow up period of 12.3 years, the association between Lp(a) levels and incident symptomatic PAD in women did not quite reach statistical significance (26). It is very possible, however, that the lack of statistically significant correlation between Lp(a) levels and PAD in the last two aforementioned studies may well relate to the low event rate.

Conclusions

There is extensive clinical evidence demonstrating a clear and strong association between elevated Lp(a) levels and CVD. Furthermore, from the above review of the epidemiologic and clinical data, it becomes evident that the vast majority of the clinical studies implicate Lp(a) as a strong independent predictor of PAD, although few studies do not definitely confirm this finding. In the future, the results of further large prospective, randomized controlled clinical trials are expected to shed light in this matter and more definitely determine the impact of Lp(a) on the incidence and progression of PAD.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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