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EDITORIAL

Lipoprotein-associated phospholipase A2 as a predictive biomarker of sub-clinical inflammation in cardiovascular diseases

Manole COJOCARU, MD, PhD, EurClinChem[a];
Inimioara Mihaela COJOCARU, MD, PhD[b]; Isabela SILOSI, MD, PhD[c]

[a]Department of Physiology, Faculty of Medicine,
"Titu Maiorescu" University of Medicine and Pharmacy,
Center for Rheumatic Diseases, Bucharest, Romania
[b]Department of Neurology, Colentina Clinical Hospital,
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[c]Department of Immunology, Faculty of Medicine,
University of Medicine and Pharmacy, Craiova, Romania

ABSTRACT

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a predictor biomarker for incident atherosclerotic disease. Lp-PLA2 has been identified in atherosclerotic plaques, however, its role in atherosclerosis is still under investigation. Lp-PLA2 belongs to the superfamily of phospholipase A2 enzymes. It is produced by macrophages that appears to play a role in the atherosclerotic vessel wall. Emerging data seem to suggest that Lp-PLA2 may be proatherogenic, which is an effect thought to be mediated by lypophosphatidylcholine and oxidized nonesterified fatty acids, two mediators generated by Lp-PLA2. Phospholipase A2 plays an essential role in metabolism of membrane phospholipids, it is related to inflammatory reactions, secretion of amyloid precursor protein. Several studies have documented the strong association of Lp-PLA2 with coronary heart disease and stroke in the general population. Lp-PLA2 may be a stronger predictor of recurrent stroke risk. Inflammatory markers have been associated with ischemic stroke risk. Their relationship to prognosis after stroke is unsettled. The present review article focuses particularly on the characteristics of the Lp(a)-associated Lp-PLA2 and discusses the possible role of this enzyme in view of the new data.

Key words: lipoprotein-associated phospholipase A2, sub-clinical inflammation, predictive biomarker, cardiovascular disease risk

Address for correspondence:
Manole Cojocaru MD, PhD, EurClinChem, 5 Thomas Masaryk Street, Zip Code 020983, Bucharest, Romania
email address: manole_cojocaru@yahoo.com

It has been estimated that up to 80% of premature heart attacks and strokes are preventable. In recent years, atherosclerosis has become recognized as an inflammatory disease whose activity can be assessed by circulating biomarkers. Along with C-reactive protein (CRP), lipoprotein-associated phospholipase A2 (Lp-PLA2) may now be considered as a biomarker with sufficient accumulated evidence to support its application in clinical practice. CRP is a well-known marker for inflammation. Patients with elevated levels of CRP have an increased risk for heart attack stroke, sudden death and vascular disease. Studies have shown a strong correlation between this enzyme and an increased risk for coronary and stroke events, independent of the traditional cardiovascular risk factors. Furthermore, Lp-PLA2 as a risk predictor has been shown to be independent of and complementary to high-sensitivity CRP (1-3).

Lipoprotein-associated phospholipase A2 is among the multiple cardiovascular biomarkers that have been associated with increased cardiovascular disease (CVD) risk. Lp-PLA2 appears, however, to be relatively unique in its high specificity for vascular inflammation as opposed to systemic inflammation, its low biologic variability, and its direct role in the causal pathway of plaque inflammation (4-6).

Approximately 80% of Lp-PLA2 (a subtype of the PLA2 family) circulates bound to LDL, whereas the other 20% is bound to high-density lipoprotein (HDL) and remnant lipoprotein particles. It has been shown that the distribution of Lp-PLA2 between LDL and HDL depends on the extend of its glycosylation, which can affect plasma Lp-PLA2 activity (7).

Lipoprotein(a) [Lp(a)] is composed of a low-density lipoprotein (LDL)-like particle to which a large, highly glycosylated apolipoprotein(a) [apo(a)] is linked by a single disulfide bridge. The physiological role of Lp(a) is largely unknown. Lp(a) is an atherogenic lipoprotein and it is present in atherosclerotic but not in normal vessel walls. Platelet-activating factor (PAF) acetylhydrolase primarily exhibits a Ca2+ -independent phospholipase A2 activity and is complexed to lipoprotein in plasma; thus, it is also referred to as lipoprotein-associated phospholipase A2 (Lp-PLA2). Lp-PLA2 is associated with Lp(a) (8,9). Substrates for Lp-PLA2 are the proinflammatory phospholipid platelet activating factor, as well as phospholipids containing oxidatively fragmented residues at the sn-2 position (oxidized phospholipids; ox-PLs). Such phospholipids are thought to play key roles in inflammatory reactions and particularly in vascular inflammation and atherosclerosis. Like LDL, Lp(a) is susceptible to oxidation, and oxidized Lp(a) is enriched in lysophosphatidylcholine (lyso-PC), which is formed by hydrolysis of oxPL, a reaction catalysed by the endogenous Lp-PLA2. Lyso-PC plays important roles in plaque formation, thus, it is considered as an important proatherogenic phospholipid. Thus by mediating the hydrolysis of oxPL and the generation of lyso-PC, the Lp(a)-associated Lp-LPA2 may significantly influence the biological activities of oxidized Lp(a) in the artery wall, which are mediated by both oxPL and lyso-PC. A similar role has been described for the LDL-associated Lp-PLA2.

Phospholipase A2 (PLA2) belongs to a family of enzymes that catalyse the cleavage of fatty acids. Pathological data suggest that Lp-PLA2 may be proatherogenic, because it is present within atherosclerotic plaques and co-localizes with macrophages. In advanced lesions, Lp-PLA2 staining is intense in regions abundant in lipids and oxidation products. Lp-PLA2, is also present in thin-cap fibroatheromas, in necrotic cores of human ruptured plaques, and in apoptotic macrophages. This suggests that it is at least associated with plaque progression and vulnerability, although its exact role is not fully defined (10,11).

There are more than 19 different isoforms of PLA2, but recent studies have focused on three major groups, namely, the group IV cytosolic PLA2, the group II secretory PLA2 (sPLA2), and the group VI Ca2+-independent PLA2. These PLA2s are involved in a complex network of signalling pathways that link receptor agonists, oxidative agents, and proinflammatory cytokines to the release of arachidonic acid and the synthesis of eicosanoids (12).

Recent clinical studies showed that Lp-PLA2 is a predictor for incident atherosclerotic disease (13-15).

Lp-PLA2 is associated mainly with apolipoprotein B (apoB)-containing lipoprotein and primarily with low-density lipoprotein (LDL), whereas a small proportion of circulating enzyme activity is also associated with high-density lipoprotein (HDL) (16). In addition to LDL, and HDL, another carrier of Lp-PLA2 in plasma is Lp(a) (enriched in Lp-PLA2 compared with

LDL). However, Lp(a) can influence the distribution of Lp-PLA2 between LDL and HDL in plasma (17).

Platelet-activating factor-acetylhydrolase in plasma is complexed to lipoproteins; thus it is also referred to as Lp-PLA2. Lipoprotein-associated phospholipase A2 is associated mainly with apolipoprotein B (apoB)-containing lipoproteins and primarily with LDL, whereas a small proportion of circulating enzyme activity is also associated with HDL.

Lipoprotein-associated phospholipase A2 has been shown to be an independent risk factor for coronary heart disease and ischemic stroke in several studies (18).

Lipoprotein-associated phospholipase A2 is a proinflammatory enzyme secreted by macrophages that is primarily bound to LDL in the circulation. It hydrolyzes oxidized phospholipids to generate lyso-PC and oxidized fatty acids, which have proinflammatory properties, and its activity is increased in small dense LDL. In this regards, it is suggested that this enzyme might have an anti-inflammatory role because it degrades and inactivates proinflammatory PAF and oxidized phospholipids; other studies showed that Lp-PLA2, may have a proinflammatory and proatherogenic role because it generates lyso-PC and bioactive oxidized fatty residues (19).

Several epidemiologic studies have demonstrated an association between plasma Lp-PLA2 concentration and risk of subsequent cardiovascular events (2,11,20).

Elevated levels of Lp-PLA2 have been shown to indicate greater risk of plaque formation and rupture and can indicate increased risk of cardiac events. sPLA2 (secretory) enzymes mediates the hydrolysis of membrane phospholipids to arachidonic acid and are effective in neurotransmission, immune response, digestion and signal transduction When sPLA2 activities are increased in pathological conditions, the oxidative metabolism of arachidonic acid by the lypooxygenase and cyclooxygenase pathways lead to free radical generation. Cyclooxygenases which are produced from arachidonic acid in forward steps are known to be effective in angiogenesis. The most studied enzyme is the sPLA2 in this enzyme family. It plays a direct role in cell proliferation, angiogenesis and apoptosis. (13,16).

High levels of Lp-PLA2 believed to trigger a cascade of inflammatory events in atherosclerosis can independently predict increased risk of stroke. High levels of an enzyme – Lp-PLA2 believed to trigger a cascade of inflammatory events in atherosclerosis can independently predict increased risk of stroke (5). Lp-PLA2 was not clearly associated with stroke severity but was related to stroke recurrence, suggesting it is more closely linked to vascular disease pathology. Elevated levels of Lp-PLA2 were independently predictive of coronary events in men with moderately elevated cholesterol (21).

A meta-analysis showed that Lp-PLA2 is significantly associated with CVD and the risk estimate appears to be relatively unaffected by adjustment for conventional CVD risk factors (19, 22). However, the clinical value of HDL-cholesterol Lp-PLA2 as a potent inhibitor of the atherosclerotic process remains to be established (23,24).

A significant interaction between Lp-PLA2 and LDL was found for individuals in the high LDL group (25).

The determination of Lp-PLA2 should be used in conjunction with clinical evaluation and patient risk assessment to assist in predicting patient risk of cardiovascular disease (5,14).

The following patients are candidates for Lp-PLA2 testing: intermediate-risk persons with one to two traditional risk factors; high-risk coronary risk equivalent patient, even if treated, to see if their plaque is still unstable; borderline lipid patients; borderline hypertension in apparently healthy patients.

Lipoprotein-associated phospholipase A2 is associated mainly with apolipoprotein B (apoB)-containing lipoproteins and primarily with low-density lipoprotein (LDL), whereas a small proportion of circulating enzyme activity is also associated with high-density lipoprotein (HDL). The majority of the LDL-associated Lp-PLA2 activity is bound to the atherogenic small-dense LDL (sdLDL) particles and recently it was shown that the enzyme activity is a marker of sdLDL particles in plasma (4,16).

Among the LDL subfractions, Lp-PLA2 activity is preferentially associated with the atherogenic small, dense (sdLDL) particles in vitro. In plasma of either normolipidemic volunteers or patients with various types of dyslipidemia, the majority of the LDL-associated Lp-PLA2 activity was bound to sdLDL particles (12).

Lipoprotein-associated phospholipase A2 has been identified in atherosclerotic plaque,

however, its role in atherosclerosis is still under investigation. In this regard, it is suggested that this enzyme might have an anti-inflammatory role because it degrades, and inactivates proinflammatory platelet activating factor (PAF) and oxidized phospholipids; other studies showed that Lp-PLA2 may have a proinflammatory and proatherogenic role because it generates lysophosphatidylcholine (lysoPC) and bioactive oxidized fatty residues (11,18).

The Lp(a)-associated Lp-PLA2 may play an important role in the metabolism of oxidized phospholipids in humans, in view of emerging data showing that oxidized phospholipids in plasma are preferentialy sequestered on Lp(a). The type of dyslipidemia and the underlying defect significantly influence the enzyme distribution among lipoprotein subspecies (5,17).

Plasma Lp-PLA2 activity is a marker of sdLDL in human plasma. However, serum triglyceride concentrations are a better predictor of sdLDL. In fact, an increased plasma triglyceride concentration is biochemically a prerequisite for the formation of sdLDL particles. Thus, other than triglyceride concentrations, the total plasma Lp-PLA2 activity appears to be the best marker of sdLDL in plasma (16,25,26).

Despite the small contribution of the Lp(a)-associated Lp-PLA2 in the plasma enzyme pool, the overall contribution of this enzyme in the inflammatory processes in the artery wall could be significant, especially in patients exhibiting high levels of Lp(a) in plasma, because Lp(a) accumulates preferentially to LDL within lesions, and much of is very tightly bound to lesion components (12,17).

Future studies should determine whether selective inhibition of Lp-PLA2 or reduction and whether statins and/or fibrates are more effective for stroke prevention in patients with elevated levels of Lp-PLA2 (27,28). ❑

CONCLUSION

It is now well established that Lipoprotein-associated phospholipase A2 (Lp-PLA2) is intimately associated with Lp(a). Lp-PLA2 can be used to determine cardiovascular risk, both of coronary heart disease and cerebrovascular disease. Lp-PLA2 is an enzyme that has been identified as a novel risk factor for coronary events and stroke. Lp-PLA2 activity is an independent predictor of coronary heart disease and ischemic stroke in the general population.

Elevated of Lp-PLA2 are indicative of vascular inflammation associated with the formation of plaque within the arteries. This may play an important role in triggering a stroke.

Elevated levels of Lp-PLA2 provides information beyond traditional risk factors for identifying middle-aged individuals at risk for ischemic stroke. The enzyme mass is preferentially distributed on sdLDL particles. However, the Lp-PLA2 activity in these particles is much less than that expected from the enzyme mass carried by sdLDL particles. ❑

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