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Editorial

Lipoprotein(a) as a Biomarker for Risk Stratification of Acute Myocardial Infarction

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ABBREVIATIONS

AMI: Acute Myocardial Infarction; aPTT, Activated Partial Thromboplastin Time; CCSP: Clinical Coronary Stenosis Progression; CK: Creatine Kinase; CRP: C-reactive Protein; CVD: Cerebrovascular Disease; CVP: Cerebral Vasculopathies; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; Lp(a): Lipoprotein (a); MACE: Major Adverse Cardiac Event; PAI-1: Plasminogen Activator Inhibitor-1; PT: Prothrombin Time; tPA: Tissue Plasminogen Activator; uPA: Urokinase Plasminogen Activator

EDITORIAL

The pathogenesis of acute myocardial infarction (AMI) is multifactorial; however, several studies have implicated impaired lipid metabolism as one of the crucial factors in the development of this disease [1-3]. We have found that a reduction in serum triglycerides does not prevent the risk of AMI, whereas a decrease in serum high density lipoproteins (HDL) and increase in C-reactive protein (CRP) strongly predispose the risky individuals to an AMI event suggesting the importance of HDL and CRP measurements for the assessment of a combined lipid-inflammation risk factor that could be a useful predictor of high risk individuals, as well as a prognostic marker in AMI patients [1]. Altered levels of carnitine, which is essentially required for the transport of long chain fatty acids into mitochondrial matrix for their oxidation to produce energy, have been reported in AMI patients [4]. Elevation of blood carnitine in AMI patients has been attributed to the poor uptake or increased leakage of carnitine through the ischemic myocardium [5]. Role of carnitine homeostasis in AMI was also supported by variations in blood carnitine levels due to the genetic polymorphism in carnitine palmitoyl transferase gene [6]. Khan et al. [7], observed a significant increase in total and differential leukocyte counts that was significantly correlated with CRP levels indicating a pro-inflammatory cascade in AMI patients. Interestingly, monocytes were found to be significantly increased in AMI patients but not in infected controls however serum creatine kinase (CK) was significantly increased in AMI patients and decreased in infected controls suggesting that differential trends of monocytes and CK in AMI and infective controls could be utilized for the prognosis of AMI patients [8].The markers of the extrinsic and intrinsic path ways of coagulation including prothrombin time (PT) and activated partial thromboplastin time (aPTT) were found to be significantly increased in AMI patients [9].

Lipoprotein-a [Lp(a)] is a subclass of lipoproteins that has recently gained biomarker importance due to its association with cardiovascular disease. Lp(a) is known to inhibit the fibrinolysis system and promote thrombus formation. Structurally, Lp(a) is composed of a low-density lipoprotein (LDL)-like particle and the specific apolipoprotein (a), which is covalently bound to apolipoprotein (b) of the LDL like particle. Serum Lp(a) levels are genetically determined and possess an average half-life of about 3 to 4 days. The desirable levels of plasma Lp(a) are below 14 mg/dL whereas the values of 14-30 mg/dL, 31-50 mg/dL and >50 mg/dL are considered as borderline, high and very high risk, respectively. Higher than normal values of Lp(a) are associated with a high risk for atherosclerosis, stroke, and heart attack. Although the mechanism through which Lp(a) promotes atherosclerosis is not clearly understood, proposed mechanisms include an increased Lp(a)-associated cholesterol entrapment in the arterial intima, inflammatory cell recruitment, carrying of pro inflammatory oxidized phospholipids, impairing fibrinolysis by inhibition of plasminogen activation and enhancing coagulation by inhibition of the tissue factor pathway inhibitor [10].

Because the structure of Lp(a) is quite similar to plasminogen, it competes with plasminogen for its binding site, leading to reduced fibrinolysis. Plasmin is an important enzyme present in blood that degrades many blood plasma proteins including fibrin clots (fibrinolysis). In circulation, plasminogen adopts a closed, activation resistant conformation whereas after binding with clots, plasminogen adopts an open form that can be converted into active plasmin by a variety of enzymes, such as tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). Deficiency in plasmin may lead to thrombosis as clots are not degraded adequately. Moreover, because Lp(a) stimulates secretion of plasminogen activator inhibitor-1 (PAI-1), it leads to thrombogenesis because the main function of PAI-1 is the inhibition of uPA, an enzyme responsible for the cleavage of plasminogen to plasmin. A combination of tPA and PAI-1has been suggested to be useful for assessing the prognosis of AMI [11]. Lp (a) also carries cholesterol and thus contributes to atherosclerosis [12,13]. In addition, Lp(a) transports the more atherogenic pro inflammatory oxidized phospholipids [14],

which attract inflammatory cells to vessel walls and leads to smooth muscle cell proliferation that facilitates plaque buildup [15].

Ikenaga et al. [16], measured Lp (a) 1 week after AMI and divided the patients into 2 groups based on high Lp (a) (>40 mg/dl) and low Lp (a) (≤ 40 mg/dl). The incidence of major adverse cardiac event (MACE) during 5 years was significantly higher in the high Lp(a) group than in the low Lp(a) group. This difference was primarily driven by a higher incidence of new lesions requiring revascularization in the high Lp(a) group [16]. Cho et al. [17], measured serum Lp(a) levels in 832 consecutive AMI patients on admission and divided them into tertiles according to serum Lp(a) levels including, Lp(a) <13.8, 13.8-30.6 and >30.6 mg/dL. The risk estimate for MACE at 1-year follow-up was significantly higher in tertile 3 than in tertiles 1 or 2 suggesting that high serum levels of Lp(a) were significantly associated with long-term adverse outcomes after AMI [17]. Morita et al. [18], determined serum Lp(a) levels in 130 AMI patients who underwent direct percutaneous coronary intervention and classified the patients on the basis of Lp(a) level at 1 month after the onset of AMI, into two groups: high Lp(a) (≥ 30 mg/dl) and low Lp(a) (<30 mg/dl) for evaluation of the clinical coronary stenosis progression (CCSP) rate. The findings showed that high serum Lp(a) level is a significant risk factor for CCSP but does not influence restenosis after stenting.

The Lp(a) levels were found to be significantly higher in patients with persistent occlusion compared with those with spontaneous recanalization of infarct-related arteries in the early phase of AMI [19]. Motta et al. [20], observed a positive correlation between mean serum Lp(a) values on day 1 and 7, and the size of the necrotic area in AMI patients, suggesting that Lp(a) has an atherogenic and prothrombotic role. Increased level of Lp(a) is closely related to the increase in the early morning incidence of AMI via a change in the prothrombotic state [21]. Elevated serum Lp(a) was associated with a history of prior myocardial infarction in patients with coronary spasm, suggesting that Lp(a) may play an important role in the genesis of thrombotic coronary occlusion and the occurrence of AMI subsequent to coronary spasm [22].

Postorino et al. [23], evaluated the relationship between the serum concentrations of Lp(a)] and AMI as well as cerebral vasculopathies (CVP) in elderly patients. The average serum levels of Lp(a) were 40.8 mg/dl in AMI, 46.7 mg/dl in CVP and 23.2 mg/dl in controls suggesting that an increased Lp(a) is of diagnostic value for the presence of both AMI and CVP and also represents a risk factor for developing CVP [23]. Nomura et al. [24], determined serum Lp(a) in 87 patients with AMI, 49 patients with cerebrovascular disease (CVD) and 85 healthy controls and correlated the Lp(a) levels with lesions in coronary and cerebral arteries. These results showed that a high Lp(a) value was linked to atherosclerosis of the cerebral and coronary arteries and also influenced the disease severity. However, Lp (a) was not found as a risk factor for the left ventricular thrombus in patients with AMI [25]. Although the serum levels of Lp(a) are usually not affected by lifestyle changes, treatment with atorvastatin [26], niacin [27] and aspirin [28] has been shown to reduce Lp(a) levels. In conclusion, Lp(a) measurements may provide more details about the risk for AMI but the added value of this biomarker beyond a routine lipid profile is yet to be standardized.

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