

DOI: 10.21767/2471-299X.1000020

# Lp-PLA2, a Novel Potential Biomarker Predicting Cardiovascular Disease in Type 2 Diabetes Mellitus

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Received date: Jan 22, 2016; Accepted date: Apr 25, 2016; Published date: Apr 29, 2016

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## Abstract

Cardiovascular disease (CVD) is the fatal complication of diabetes mellitus and it is a large economic burden of the world. Although there are a few biomarkers in predicting the cardiovascular disease, the disease is still far from being diagnosed and evaluated precisely in type 2 diabetes mellitus (T2DM) patients. Lp-PLA2 takes part in several links of the pathological mechanism in the diabetic cardiovascular disease. Researches have implied that the Lp-PLA2 has positive association with CVD severity in T2DM. Lp-PLA2 may be a novel biomarker diagnosing and evaluating CVD in T2DM.

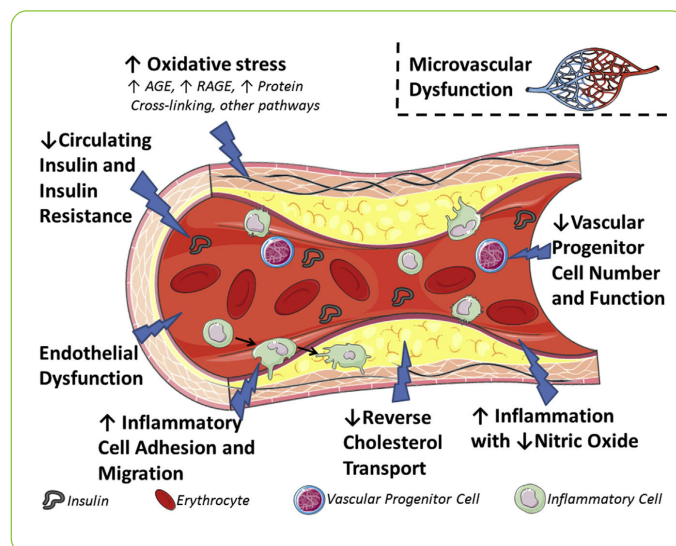
## Introduction

Nowadays, diabetes mellitus is sweeping the world as an epidemic. It has been a large burden of society [1]. Cardiovascular complication is the main cause of morbidity and mortality in diabetes patients. It is reported by World Health Organization, 50% of diabetes mellitus patients die from heart related disease, such as coronary heart disease, heart failure, ischemic heart disease, arrhythmia and sudden death [2]. Diabetes patients predispose to have cardiovascular disease, and more importantly, bear prone-rupture plague, leading to myocardial infarction and sudden death [3].

Biomarkers such as LDL-C, HDL-C have been well proved to predict CVD in population including T2DM patients. Some other traditional biomarkers have been applied in diagnosing and prognosing CVD, such as hs-CRP, IL-6, MCP-1, TNF $\alpha$ , VEGF [4]. There are also novel biomarkers especially reactive oxygen species raised up by the scientists, such as protein kinase C, nuclear factor-kB. Yet, there is still residual CVD hazard remaining uncovered. Recent studies show that part of men and women with low 1-year predicted risk have subclinical CVD. The phenomenon is not paid enough attention to [5,6].

In order to predict the risk and prevent the development of cardiovascular disease in diabetes mellitus patients, it is essential to study the pathological mechanism of vasculature in diabetes mellitus. Several of the major mechanisms have been discussed for diabetic cardiovascular disease, including

oxidative stress, progenitor cell dysfunction, microvascular dysfunction, and impaired reverse cholesterol transport (Figure 1) [7]. Among those process, Lp-PLA2, plays an important part in microvascular dysfunction, impaired reverse cholesterol transport, and also oxidative stress.



**Figure1:** Relationships between cardiovascular disease and diabetes.

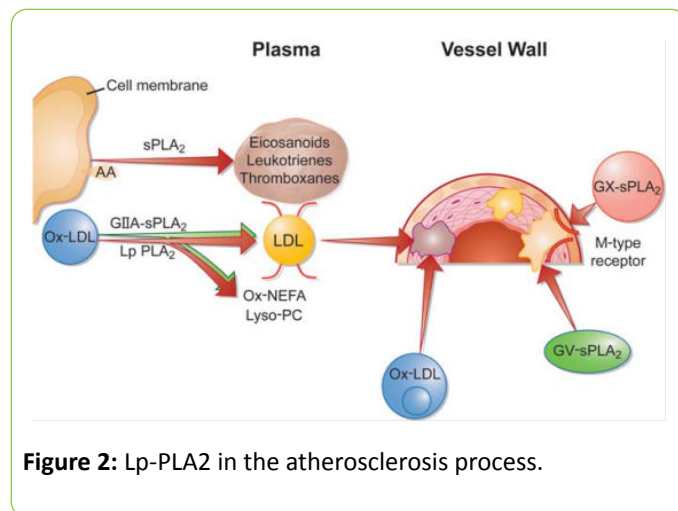
## Lp-PLA2 bio-chemical characteristic and physiology

Lp-PLA2, known as platelet activating factor acetylhydrolase (PAF-AH), belongs to Phospholipase A2 superfamily. Phospholipase A2 superfamily has five families: secretory PLA2 (sPLA2), cytosolic PLA2 (cPLA2), lysosomal PLA2; GVPLA2 (iPLA2) and lipoprotein-associated phospholipase A2. SPLA2 has several groups: IB, IIA, IIC, IID, IIE, IIF, III, V, X, and XI [8]. The Lp-PLA2 enzyme composes of 45 KDa molecular, secreted by monocyte, T lymphocyte, macrophages, mast cells, live cells, mostly by multiple inflammatory cells. Lp-LPA2 hydrolyzes fatty acids at sn-2 position into two polyunsaturated fatty acid and lysophospholipids which as marker of Lp-PLA2 activity, and specifically catalyzes the hydrolysis of oxidized LDL (ox-LDL) into lysophosphatidylcholine and oxidized fatty acid [9]. In the circulation, about 70% Lp-PLA2 binds to apoB transported by LDL and LP(a), apparently to the small dense LDL [10]. The

other 30% binds to apoA1 transported by HDL. However, in diabetes mellitus patient, it is reported the distribution is altered [11]. Recent study reports that Lp-PLA2 regulates the pro-inflammatory and anti-inflammatory process [12].

### Lp-PLA2 in the atherosclerosis process

Due to the property of Lp-PLA2, it accumulates lysophosphatidylcholine in situ and induces the expression of several inflammatory cytokines [13]. MacRitchie [14] reports that Lp-PLA2 inactivates potent lipid messengers, such as PAF and modified phospholipids in settings of oxidant stress, and has the susceptibility to oxidative attack. In hypercholesterolemic pigs with high fat diet, De Keyser points out that increased levels of oxidized LDL coming along with obvious increase in Lp-PLA2 activity [15]. In a 783 patients cohort study, it is reported Lp-PLA2 modulates LDL oxidation by hydrolysing oxidised phospholipids on particle surfaces. It is thought that the enzymes activity varies with genome type. It is strongly associated with genetic variants involved in lipid metabolism [16]. Under some circumstance, genetic depletion of Lp-PLA2 in mildly modified lipoproteins could enhance monocyte adhesion to endothelial cells comparing with lipoproteins that expressed normal activity levels [17]. *In vitro* experiment, exogenous Lp-PLA2 is able to inhibit endothelial cell apoptosis those induced by modified LDL particles (Figure 2) [18].



**Figure 2:** Lp-PLA2 in the atherosclerosis process.

During the oxidative stress, lipoprotein-associated phospholipase A2 increases ox-LDL particles; and allows for enhanced internalization into the macrophage [19].

### Studies on Lp-PLA2 in CVD and T2MD

A lot of epidemic studies have demonstrated that Lp-PLA2 is proposed as a predictive biomarker in CVD [20]. Mockel finds that Lp-PLA2 turns out to be a more effective risk marker than high sensitive CRP in acute coronary syndrome patients [21]. Also, by studying low risk coronary patients (classified by The Framingham risk score), Hargens discovers that Lp-PLA2 is significant independent predictor of those patients, while traditional risk markers such as lipids, glucose are not. It is suggested that the enzyme may valuable in earlier detection of

subclinical CVD [22]. In 2015, Lp-PLA2 is shown associated with CVD severity, having a positive correlation with the number of atherosclerosis plaques and diseased arteries [23,24].

As known, CVD develops faster and more serious in diabetes patients than non-diabetes [25]. Resent studies keep on looking for circulatory predictors of CVD in Diabetes. Wootton discovers that Lp-PLA2 activity is an independent predictor of CHD risk in a sample of subjects with diabetes mellitus [26]. Research on diabetes pathogenesis discloses that Lp-PLA2 associates with insulin resistance and predicts incidents in Diabetes among older adults [27]. Some clinical studies indicate Lp-PLA2 is significantly elevated in diabetic CVD before balloon angioplasty. The increase mass and activity of Lp-PLA2 may lead to the high risk of CVD during the early course [28,29].

Early in 2005, Zalewski concluded an obvious relation between Lp-PLA2 activity and Diabetes [30]. In some latest studies, Garg discovers there is positive correlation between LP-PLA2 and fasting glucose in diabetes mellitus patients while in the same group, positive correlation between oxLDL and plasma glucose. And the author suggests that reducing the LP-PLA2 might help decrease risk of CVD by intervening oxLDL in such group [29]. Nelson suggests that Lp-PLA2 activity is much more positive in T2DM than non-diabetes. Also the association is strongly positive in insulin resistance and Lp-PLA2 activity, and Lp-PLA2 mass is not positive in T2DM [27]. Fortunato concludes that Lp-PLA2 mass level is significantly higher in T2DM than non-diabetics, and the level is nearly 5 times higher than the normal group [28].

Hatoum concludes that LP-PLA2 activity is strongly related with incident CVD in T2DM, through observing 740 men and 777 women with confirmed diabetes enrolled in the Health Professionals Follow-Up Study and Nurses' Health Study. The phenomenon is obvious in the first 6 years. The author suggests that the LP-PLA2 activity is more positively related with the unstable lesions than the atherosclerosis alone [31]. Kanzuo points out, serum Lp-PLA2 activities has a positive relation with lysophosphatidylcholine contents in LDL in T2DM patients. Lysophosphatidylcholine is the production of Oxidized phospholipids in LDL hydrolyzed by Lp-PLA2. Lysophosphatidylcholine is increased in T2DM patients than the nondiabetic ones [32].

However, there is a contrast data against that LP-PLA activity and mass has positive relation with CVD. Nelson claims that the activity and mass has no difference between diabetes and non-diabetes group than expected [33].

## Discussion

It is essential for the medical industry to prevent the CVD in diabetes mellitus before struggling to find solution when it becomes severe. In order to diagnose the CVD in the early stage and evaluate the severity, circulating biomarkers are important parts in the procedure. Although there are a few biomarkers, it is still far from expectation. Lp-PLA2 is a novel biomarker empathized these days. A Lot of evidence proves

Lp-PLA2 to be a strong marker predicting the severity and outcomes of cardiovascular disease.

The endothelial cell layer is a barrier separating circulating stuff from the arterial intima. It is reported that macrophage infiltration enhances in diabetic mellitus patients' arterial wall [30]. Lp-PLA2 is secreted by macrophages mostly. Macrophage infiltrates the adipose tissue producing oxidative byproducts and also increases the production of Lp-PLA2. The free radical from oxidation of excess glucose could increase the oxidation of lipoproteins and therefor increase the substrate for Lp-PLA2. Whether Lp-PLA2 contributes to the oxidation itself or the just the byproduct, It means that Lp-PLA2 could imply the inflammation level. José L reports that intensified hypoglycemic therapy could decrease total Lp-PLA2 activity and redistribute Lp-PLA2 activity toward a higher proportion in high-density lipoprotein. The phenomenon hints Lp-PLA2 activity enhance in hyperglycemic people who intend to have high risk of CVD [34].

The Lp-PLA2 may be a crucial biomarker in diagnosing and evaluating CVD in diabetes mellitus patients. The pathological mechanism of cardiovascular disease in diabetes performs quite similar as in normal population, but it also has its own peculiarity. The Lp-PLA2 should be a potent biomarker in evaluating diabetic CVD, because the enzyme contributes to oxidative stress, progenitor cell dysfunction, microvascular dysfunction, and impaired reverse cholesterol transport. Recently, clinical researches already show encouraging results. Also, diabetic metabolic patients have higher levels of small dense LDL [35], which potentially offers better matrix for Lp-PLA2 transporting in circulation. Researches have proven it.

In conclusion, it is still essential to seek novel biomarker in order to prognose and diagnose the CVD in T2DM. Lp-PLA2 takes part in several process of atherosclerosis in diabetes patients. A lot of researches have proven that Lp-PLA2 might be a promised biomarker.

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