Lipoprotein-Associated Phospholipase-A2 in Diabetic Kidney Disease

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Abstract

Background: Diabetic kidney disease, or kidney disease attributed to diabetes, occurs in 20–40% of patients with diabetes and is the leading cause of end-stage renal disease (ESRD). Diabetic nephropathy is a clinical syndrome characterized by the persistent albuminuria (>300mg/day or >200µg/min) that is confirmed on at least 2 occasions 3-6 months apart, progressive decline in the glomerular filtration rate (GFR) and elevated arterial blood pressure (> 130/90). Diabetic nephropathy is the leading cause of chronic kidney disease in the United States and other Western societies. It is also one of the most major long-term complications in terms of morbidity and mortality for individual patients with diabetes. Diabetes is responsible for 30-40% of all end-stage renal disease (ESRD) cases in the United States.Recent researches indicate that increased plasma level of Lp- PLA2 is associated with incidence and development of DKD in T2D patients. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a proinflammatory enzyme that has been confirmed to be independently associated with atherosclerosis .Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a proinflammatory enzyme that has been confirmed to be independently associated with atherosclerosis and the plasma Lp-PLA2 is a marker for inflammation in the vessel wall. Considering the potential proinflammatory effect of Lp-PLA2, a number of studies were carried out to determine the role of this enzyme in DR. A recent epidemiologic study showed that the activity of plasma Lp-PLA2 is higher in diabetic patients with Proliferative diabetic retinopathy than in healthy individuals and diabetic patients with non- proliferative diabetic retinopathy. In addition, the increase in Lp-PLA2 was correlated with the severity of diabetic retinopathy.Several studies indicated that atherosclerosis and endothelial dysfunction, which are related to inflammation caused by hyperglycemia, were also involved in DKD, as well as macrovascular complications. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a pro- inflammatory enzyme that has been confirmed to be independently associated with atherosclerosis.

Keywords: I Lipoprotein-associated phospholipase- A2, Diabetic Kidney Disease

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Introduction

The term diabetes mellitus describes a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs **(1).**

Diabetic kidney disease, or kidney disease attributed to diabetes, occurs in 20–40% of patients with diabetes and is the leading cause of end-stage renal disease (ESRD) **(2).**

Diabetic nephropathy is a clinical syndrome characterized by the persistent albuminuria (>300mg/day or >200µg/min) that is confirmed on at least 2 occasions 3-6 months apart, progressive decline in the glomerular filtration rate (GFR) and elevated arterial blood pressure (> 130/90) **(3).**

Proteinuria was first recognized in diabetes mellitus in the late 18th century. In the 1930s, Kimmelstiel and Wilson described the classic lesions of nodular glomerulosclerosis in diabetes associated with proteinuria and hypertension. By the 1950s, kidney disease was clearly recognized as a common complication of diabetes, with as many as 50% of patients with diabetes of more than 20 years having this complication **(3).**

Diabetic nephropathy is the leading cause of chronic kidney disease in the United States and other Western societies. It is also one of the most major long-term complications in terms of morbidity and mortality for individual patients with diabetes. Diabetes is responsible for 30-40% of all end-stage renal disease (ESRD) cases in the United States **(3).**

Diabetic nephropathy (DN) is a common cause of end stage renal disease that characterized by the accumulation of extra cellular matrix in glomerular mesangium, formerly known as glomerulosclerosis, and kidney interstitial tissue that eventually leads to renal failure **(4).**

Epidemiology:

Since the 1950s, kidney disease has been clearly recognized as a common complication of diabetes mellitus (DM), with as many as 50% of patients with DM of more than 20 years' duration having this complication **(5).**

Diabetic nephropathy rarely develops before 10 years' duration of type 1 DM. Approximately 3% of newly diagnosed patients with type 2 DM have overt nephropathy. The risk for the development of diabetic nephropathy is low in a normo albuminuric patient with diabetes' duration of greater than 30 years. Patients who have no proteinuria after 20-25 years have a risk of developing overt renal disease of only approximately 1% per year. In terms of diabetic kidney disease in the United States, the prevalence increased from 1988-2008 in proportion to the prevalence of diabetes. Among people with diabetes, the prevalence of diabetic kidney disease remained stable **(5).**

Lipoprotein-associated phospholipase- A2 in diabetic kidney disease

- **Introduction**

Recent research indicates that increased plasma level of Lp- PLA2 is associated with incidence and development of DKD in T2D patients. **(6)**

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a proinflammatory enzyme that has been confirmed to be independently associated with atherosclerosis **(7)**

Lp-PLA2 is a marker for inflammation in the vessel wall.
(8)

Lp-PLA2 hydrolyses oxidized low-density lipoproteins into proinflammatory products that are implicated in endothelial dysfunction and plaque inflammation. **(9)**

Lp-PLA2 was considered as a therapeutic target to prevent retinal vasopermeability and macular edema during diabetes. **(10)**

Lp-PLA2 is an enzyme that is highly expressed in

macrophages. It is a mediator of the inflammatory response, The Lp-PLA2 circulating in serum mainly binds to low-density lipoprotein particles, and it is responsible for the hydrolysis of oxidized phospholipids on LDL particles. **(11)**

- **Lipoprotein-associated phospholipase A2: structure and biology**

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase (PAF-AH), belongs to the phospholipase A2 superfamily. **(11)**

The major sources of Lp-PLA2 in plasma are T lymphocytes, mono- cytes/macrophages, activated bone marrow-derived mast cells, and liver cells. **(12)**

The secreted Lp-PLA2, circulates in plasma in active form. It predominantly binds to LDLs, and in a much smaller extent to HDLs, Lp(a), lipoprotein remnants, and platelet-borne microparticles. **(13)**

- **Function of LP-PLA2**

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a proinflammatory enzyme that has been confirmed to be independently associated with atherosclerosis and the plasma Lp-PLA2 is a marker for inflammation in the vessel wall. **(9)**

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is principally secreted by macrophages and circulates in the blood in the form of a complex with low-density lipoprotein (LDL) and high density lipoprotein (HDL). **(14)**

Lp-PLA2 was originally named plasma platelet-activating factor acetylhydrolase (pPAFAH), due to its hydrolytic action on platelet-activating factor (PAF). **(15)**

In addition to PAF, Lp-PLA2 could hydrolyze oxidized LDL into two bioactive products, lysophosphatidylcholine (lysoPC) and oxidized nonesterified fatty acids (oxNEFAs). LysoPC seemingly represents the majority of Lp-PLA2-derived proinflammatory effects.Furthermore, lysoPC was recently demonstrated to induce the pericytes loss in the central nervous system (CNS), which is indicative of an injured). **(16)**

Because of the proinflammatory effects and high distribution in blood, together with the observation that elevated plasma Lp-PLA2 levels were associated with a number of vascular diseases in epidemiological studies. **(17).**

- **Role in atherosclerosis**

Atherosclerosis, the underlying cause of the majority of clinical cardiovascular events, is a systemic disease process involving a combined effect of inflammation and immunological factors. **(18)**

Exposure of endothelial cells to damaging stimuli, as smoking, arterial hypertension, diabetes mellitus, dyslipidemia can induce qualitative changes that are collectively defined as “endothelial activation” and are currently postulated regarded as one of the earliest events in atherogenesis. **(19)**

An “activated” endothelium expresses adhesion molecules and chemotactic substances, increases its permeability to macromolecules with ensuing variation of the subendothelial extracellular matrix composition. As a result, low-density lipoproteins (LDLs), particularly those that are smaller and denser and therefore more pro-atherogenic, penetrate the vessel wall and remain trapped in the sub-intimal space, where they undergo oxidative changes. Oxidized LDLs induce recruitment of monocytes by vascular cells and promote their differentiation into macrophages. **(20)**
The latter are well-established triggers of the inflammatory cascade, *via* stimulation of endothelial cells expression of adhesion molecules and cytokines, induction of chemotaxis of monocytes and leucocytes, and promotion of their entry in the sub-intimal space of the arterial walls. **(21)**

The accumulation of lysophosphatidylcholine and oxidized fatty acids in the sub-intimal space contributes to the development of the plaque lipid “core”. Moreover, these substrates once

taken up by macrophages promote their conversion into foam cells. **(21)**

In addition, lysophosphatidylcholine induces the production of reactive oxygen species, such as superoxide, by activating the endothelial nicotinamide adenine dinucleotide phosphate oxidase and by inducing the endothelial nitric oxide synthase (eNOS) "uncoupling". **(22)**

- **Role in Diabetic kidney disease (DKD)**

DKD is usually classified as a noninflammatory glomerular disease. However, previous studies consistently indicated that DKD was associated with increased and persistent expression of inflammation associated genes and pathways. **(23)**

Several studies indicated that atherosclerosis and endothelial dysfunction, which are related to inflammation caused by hyperglycemia, were also involved in DKD, as well as macrovascular complications. Albuminuria, the earliest indicator of kidney damage in diabetes, is widely considered to reflect underlying endothelial dysfunction and is an independent predictor of cardiac vascular disease. **(24)**

Endothelial dysfunction has been demonstrated in T2D, in both the peripheral and coronary circulation.Elevated levels of circulating biomarkers, indirect indices of endothelial cell damage, activation and inflammation, are found in type 2 diabetic patients. **(25).**

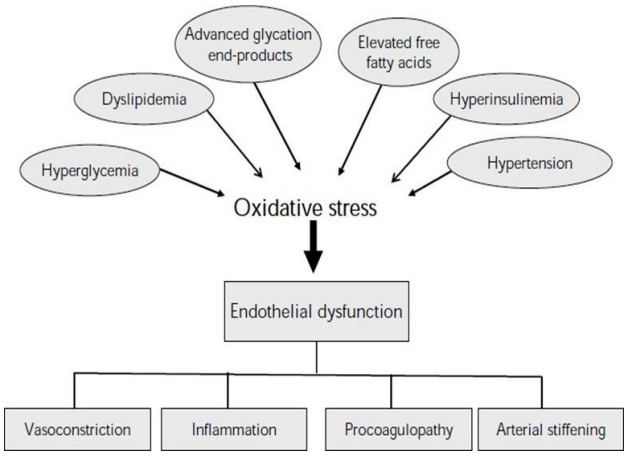

FIGURE (1): Pathogenesis and consequences of endothelial dysfunction

DKD and diabetic retinopathy are both diabetic microvascular complications with similar pathologic basis, and frequently develop in the same patients. **(26)**

Lp-PLA2 as a therapeutic target

It is well known that lipid-altering medications, including statins, fenofibrate, prescription of omega-3 fatty acids, for weight loss, have been shown to reduce Lp-PLA2 levels. The degree of its reduction correlates with the extent of lipid lowering. Lp-PLA2 was identified as a potential novel target of therapy. The most used therapy targeting Lp-PLA2 in plasma in advanced stages of clinical investigation is darapladib. Darapladib is a selective, potent, reversibile, oral inhibitor of lipoprotein-associated phospholipase A2. The basic idea of applying darapladib is to improve patient outcomes in addition to evidence-based treatments and potentially reduce cardiovascular and cerebrovascular events by decreasing cytokines concentrations, stabilizing atherosclerotic plaque, inhibiting macrophage infiltration, and thickening of the connective tissue cap. **(27)**

(The SOLID-TIMI 52) was a randomized, double-blind, placebo- controlled, multicenter, and event-driven trial that determined the clinical benefit of direct inhibition of Lp-PLA2 activity with darapladib in patients after an acute coronary syndrome (non-ST-elevation or ST-elevation myocardial infarction). Direct inhibition of Lp-PLA2 with darapladib added to optimal medical therapy and initiated within 30 days of hospitalization did not reduce the risk of major coronary events.Darapladib is a selective Lp-PLA2 inhibitor that is under investigation for its potential to stabilize high-risk atherosclerotic plaques and potentially reduce cardiovascular events. **(28)**

Research about LP-PLA2

Recent research has revealed that LP-PLA2 is involved in the pathogenesis of many diseases explored in animal models or clinical trials such as Atherosclerosis, Alzheimer, diabetic retinopathy, cancers and other diseases.In 2014, the Food and Drug Administration approved the Lp-PLA2 test for patients without existing coronary disease measure a person's risk of heart disease, cardiac arrest, and the potential for other heart problems. **(29)**

The European Society of Cardiology recommended Lp-PLA2 as part of a refined risk assessment in patients at high risk of a recurrent acute athero-thrombotic event, and the American Heart Association/American Stroke Association recommended that measurement of the Lp-PLA2 in patients without CVD might be helpful in identifying patients at an increased risk of stroke. The epidemiological investigations on the relationship between Lp-PLA2 activity and Alzheimer yielded inconsistent results. Two studies demonstrated no significant association between plasma Lp-PLA2 mass and AD. **(30).**

It was observed that plasma Lp-PLA2 activity was not associated with a diagnosis of AD, since no strong correlations were found between Lp-PLA2 activity and cerebrospinal fluid (CSF) markers of Alzheimer. **(311)**

Even though the epidemiological results could not determine the role of Lp-PLA2 in dementia, the nonclinical and clinical studies attributed the alleviation of AD progression to Lp-PLA2 inhibition. Remarkably, the beneficial effect of Lp-PLA2 inhibitors might result from preventing BBB breakdown in a cerebral amyloidosis-independent manner. Lp-PLA2 inhibition might be a promising approach to treat intestinal malignancies. **(11)**

Plasma Lp-PLA2 activity is predominantly up regulated in patients with antiphospholipid antibodies, suggesting a prognostic biomarker role for Lp-PLA2 in managing the antiphospholipid syndrome. Lp-PLA2 might be a biomarker of vascular damage among patients with Rheumatoid arthritis. **(32)**

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