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Lipoprotein-associated phospholipase A2 is a risk factor for diabetic kidney disease

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ABSTRACT

Aims: This study aimed to determine the association between lipoprotein-associated phospholipase A2 (Lp-PLA2), a marker for inflammation in the vessel wall and independently associated with atherosclerosis, and the incidence of diabetic kidney disease (DKD) in patients with type 2 diabetes (T2D).

Methods: A total of 1452 patients were enrolled in this retrospective cross sectional study. We recruited patients with T2D who were tested for glycated hemoglobin, fasting and 2 h post-meal serum C-peptide, blood lipid profile, 24 h urine albumin excretion rate (UAER), blood creatine, blood albumin, uric acid, and Lp-PLA2.

Results: Among the patients with T2D, 40.3% were diagnosed with DKD and the correlation between DKD and Lp-PLA2 was the most significant one compared to other diabetic complications (odds ratio = 1.651, $P < 0.001$). Plasma Lp-PLA2 level in patients with DKD was significantly higher and increased Lp-PLA2 level was independently associated with the incidence of DKD after adjustment for age, gender, duration of diabetes, glycated hemoglobin, body mass index, blood lipids, blood pressure, presence of coronary heart disease and carotid plaque, and use of statins (odds ratio = 1.545, $P = 0.013$). Lp-PLA2 was found to be positively correlated with UAER ($r = 0.123$, $P < 0.001$) and negatively correlated with estimated glomerular filtration rate (eGFR) ($r = -0.71$, $P = 0.009$).

Conclusions: Increased plasma level of Lp-PLA2 is associated with incidence and development of DKD in patients with T2D. Lp-PLA2 should be considered as a biomarker for early detection and follow-up of DKD.

Trial registration: clinicaltrials.gov, No. NCT03362112, Registered 30 November 2017, retrospectively registered.

Abbreviations: Lp-PLA2, lipoprotein-associated phospholipase A2; T2D, type 2 diabetes; DKD, diabetic kidney disease; UAER, urine albumin excretion rate; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; TC, total cholesterol; HDL-c, high density lipoprotein cholesterol; TG, triglycerides; LDL-c, Low density lipoprotein cholesterol; BMI, body mass index; MDRD, Modification of Diet in Renal Disease study; CV, coefficients of variation; AACE, American Association of Clinical Endocrinolgists; OR, odds ratio; SD, standard deviation; T1D, type 1 diabetes; PAF, platelet-activating factor

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1. Introduction

The prevalence of type 2 diabetes (T2D) has increased rapidly in recent years, and the number of patients with T2D is expected to rise to 552 million by 2030 [1]. Diabetic kidney disease (DKD), one of the most frequent complications of diabetes, is a major cause of the development and progression of chronic kidney disease and end-stage renal disease [2]. However, beyond angiotensin II-receptor blockers and angiotensin-converting enzyme inhibitors, therapeutic options to block the progression of DKD are limited and other strategies to preserve kidney function are needed [3].

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 [4–7]. Recently, several studies indicated that atherosclerosis and endothelial dysfunction, which are related to inflammation caused by hyperglycemia, were also involved in DKD [8–10], as well as macrovascular complications. Functional destruction of endothelium is regarded as an early event that lays the groundwork for the development of renal microangiopathy and subsequent clinical manifestation of nephropathic symptoms [8]. 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 [11]. Despite their well-recognized association, the mechanism by which endothelial dysfunction may result in albuminuria is incompletely understood.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a proinflammatory enzyme that has been confirmed to be independently associated with atherosclerosis [12,13] and the plasma Lp-PLA2 is a marker for inflammation in the vessel wall [13]. Lp-PLA2 hydrolyses oxidized low-density lipoproteins into proinflammatory products that are implicated in endothelial dysfunction and plaque inflammation [14,15]. Previous studies found that Lp-PLA2 levels increased in both patients and rats with diabetic retinopathy [16,17]. Moreover, Lp-PLA2 was considered as a therapeutic target to prevent retinal vasopermeability and macular edema during diabetes [16,18,19]. DKD and diabetic retinopathy are both diabetic microvascular complications with similar pathologic basis, and frequently develop in the same patients [20]. However, the relationship between Lp-PLA2 and DKD was unknown.

To investigate the relationship between Lp-PLA2 and DKD, we checked plasma Lp-PLA2, 24 h (hrs) urine microalbumin and blood creatinine in patients with T2D, and we found Lp-PLA2 was strongly associated with urine microalbumin.

2. Materials and methods

2.1. Patients

A total of 1713 Chinese patients with T2D who visited the Department of Endocrinology, Nanjing First Hospital, Nanjing Medical University between Jan 2015 and Aug 2016, were included in this retrospective cross-sectional study. All of the patients with T2D were diagnosed by the admitting physician, and the diagnostic criterion of T2D was according to the World Health Organization in 1999 [21]. Patients were excluded due to pregnancy, use of systemic steroidal anti-inflammatory drugs, acute metabolic diabetic complications such as ketoacidosis or hyperosmolar state (coma), or acute infection.

Patients were diagnosed as having DKD if they met one of the following criteria or both: 1. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. 2. Urine albumin excretion rate (UAER) > 30 mg/24 hrs [2]. DKD was defined according to the UAER and eGFR tested in this study or the medical history of patients.

This study was approved by the Institutional Ethics Committee of Nanjing First Hospital, Nanjing Medical University. The methods were carried out in accordance with the Declaration of Helsinki guidelines, including any relevant details. All subjects gave and signed written informed consent before study initiation.

2.2. Data collection

The patient's age, sex, height, weight, blood pressure (BP) and duration and treatment of diabetes were recorded. Data regarding glycated hemoglobin (HbA1c), fasting and 2 hrs post-meal serum C-peptide, lipids (total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), triglycerides (TG), Low density lipoprotein cholesterol (LDL-c), 24 hrs UAER, blood creatine, hemoglobin, and uric acid levels were collected. The initial body mass index (BMI) of the patients was calculated as weight in kilograms divided by height in meters squared. eGFR was calculated using Modification of Diet in Renal Disease study (MDRD) equation: eGFR (mL/min/1.73 m^2) = $(175 \times (\text{Creatinine})^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female).

2.3. Measurement of Lp-PLA2

Plasma Lp-PLA2 was detected with a commercially available turbidimetric immunoassay kit (Lp-PLA2 TestKit, Norman Cat No. 14082101, Norman Inc., Nanjing, CN). The intra- and inter-assay coefficients of variation (CV) were 3.68% and 7.94%, respectively, when the Lp-PLA2 concentration was 174 ng/mL, and the intra- and inter-assay CV were 3.22% and 6.58%, respectively, when the Lp-PLA2 concentration was 445 ng/mL.

2.4. Statistical analysis

Analyses were performed using the SPSS 16.0 (SPSS, IL, USA) statistical package. All variables were tested for normal distribution of the data. Data are presented as means (standard deviation [SD]) or percentages. Differences between the studied groups examined using the student's unpaired *t*-test for parametric data or the Mann-Whitney *U* test for non-parametric data, respectively, or using univariate tests. The categorical data were examined with chi square test.

The relationship between Lp-PLA2 and diabetic complication was analyzed by logistic regression. Influencing factors of Lp-PLA2 were found by linear regression analysis. All comparisons were 2-sided at the 5% significance level. P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Participants' characteristics

From the 1713 patients enrolled in the study, 91 patients were excluded because of an acute infection, and a total of 170 patients, with missing data regarding 24 hrs UAER, were also excluded. The final study population consisted of 1452 patients. The patients, aged 20 to 92 years (mean age, 58.5 ± 12.5 years), included 895 males (61.6%), and 585 (40.3%) of the patients were diagnosed with DKD.

3.2. The relationship between Lp-PLA2 and chronic diabetic complications

We divided the patients into normal and high Lp-PLA2 groups according to the clinical cutoff associated with increased cardiovascular risk (<200 or ≥200 ng/mL for Lp-PLA2), which was proposed in American Association of Clinical Endocrinologists' (AACE) Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis Endocrine Practice [22]. Binary logistic regression showed that correlation between DKD and Lp-PLA2 was the most significant one compared to other diabetic complications (Table 1). Lp-PLA2 was also correlated with carotid plaque as expected.

3.3. The incidence of DKD and clinical characteristics in the normal and high Lp-PLA2 groups

As shown in Table 2, patients in high Lp-PLA2 (≥200 ng/mL) group had higher BP, BMI, HbA1c, C-peptide, TC, TG, LDL-c, and uric acid levels and lower HDL-c levels than patients with normal Lp-PLA2 (<200 ng/mL) level. The duration of diabetes was longer in the normal group than in the high Lp-PLA2 group. Additionally, older people and female were more in the high Lp-PLA2 group than in the normal group. The incidences of hypertension and carotid plaque were higher in the high Lp-PLA2 group compared with the normal group (P < 0.05 and 0.01, respectively). The incidence of DKD, as well as 24 hrs UAER and Creatinine, was significantly higher in the high Lp-PLA2 group than those in the normal group, while eGFR decreased in the high Lp-PLA2 group.

3.4. Comparison of clinical data and Lp-PLA2 among patients with or without DKD

Age, duration of diabetes, BP, BMI, HbA1c, fast C-peptide, TG, uric acid, UAER, Creatinine, Lp-PLA2 and the incidences of hypertension, coronary heart disease (CHD) and carotid plaque increased, while hemoglobin, eGFR and HDL-c decreased in patients with DKD, see in Table 3.

3.5. The correlations between Lp-PLA2 and DKD

According to the binary logistic regression analysis, Lp-PLA2 was positively associated with presence of DKD after adjustment for age, gender, duration of diabetes, HbA1c, BMI, TC, HDL-c, TG and LDL-c (odds ratio [OR] 1.327); comparing the high Lp-PLA2 group with the normal Lp-PLA2 group (P = 0.026). Per SD increase in Lp-PLA2 was also strongly associated with DKD (P = 0.029), see in Table 4. After adjusted for presence of coronary heart disease and carotid plaque, use of statins, and systolic/diastolic blood pressure, the high Lp-PLA2 remained positively correlated with presence of DKD (OR = 1.545, P = 0.013).

We divided the patients into 3 groups according to the 24 h UAER: normal group (UAER < 30 mg/24 hrs, n = 908), microalbuminuria group (UAER range from 30 to 300 mg/24 hrs, n = 419) and macroalbuminuria group (UAER > 300 mg/24 hrs, n = 125). The Lp-PLA2 levels in different groups are shown in Fig. 1a. Age, gender, duration of diabetes and BMI were adjusted by univariate tests. Lp-PLA2 increased in microalbuminuria and macroalbuminuria groups compared to normal group (both P < 0.05 and 0.01, respectively), and was higher in macroalbuminuria group than in microalbuminuria group (P < 0.05). The Lp-PLA2 level also increased when the eGFR < 60 mL/min/1.73 m^2 (P < 0.01), as seen in Fig. 1b.

Spearman correlation analysis showed that Lp-PLA2 was positively correlated with UAER (r = 0.123, P < 0.001) and negatively correlated with eGFR (r = −0.71, P = 0.009). The correlations between UAER and Lp-PLA2 were significant in the patients with different ages or durations of diabetes. However, the correlations between eGFR and Lp-PLA2 were only significantly in older patients (≥60 years) or patients with long duration of diabetes (≥10 years). The correlations between Lp-PLA2 and UAER/eGFR were similar for different genders and

Table 1 – Binary logistic regression for the relationship between Lp-PLA2 and chronic diabetic complications.

Complications	P value	OR	95% Confidence interval	
			Lower	Upper
DKD	<0.001	1.651	1.316	2.072
Neuropathy	0.477	0.892	0.65	1.223
Retinopathy	0.099	0.781	0.582	1.048
Carotid plaque	0.005	1.290	1.078	1.543

Lp-PLA2, lipoprotein-associated phospholipase A2.
DKD, diabetic kidney disease.
OR, odds ratio.

Table 2 – Characteristics of patients in the normal and high Lp-PLA2 group.

Items	Lp-PLA2 < 200 ng/mL	Lp-PLA2 ≥ 200 ng/mL	P value
Patients (number)	633	819	
Gender (male n(%))	406(64.1)	489(59.7)	0.048
Age (year)	57.7(11.6)	59.2(13.2)	0.021
Duration of diabetes (year)	7.4(6.7)	6.9(6.9)	0.037
Systolic pressure (mmHg)	129.8(14.1)	132.2(15.7)	0.006
Diastolic pressure (mmHg)	78.8(8.9)	80.2(9.8)	0.011
BMI (kg/m^2)	24.3(3.2)	25.1(3.5)	<0.001
HbA1c (%)	8.9(2.1)	9.3(2.1)	<0.001
FPG (mmol/L)	8.7(0.1)	8.8(3.0)	0.127
Fast C-peptide (ng/mL)	1.8(1.2)	2.0(1.3)	0.003
C-peptide 120 min (ng/mL)	4.2(2.8)	4.4(3.0)	0.333
Total cholesterol (mmol/L)	4.7(1.1)	4.9(1.2)	<0.001
Triglyceride (mmol/L)	1.9(1.6)	2.2(2.2)	0.002
HDL-c (mmol/L)	1.4(0.4)	1.3(0.4)	0.011
LDL-c (mmol/L)	2.4(0.8)	2.6(0.7)	<0.001
Uric acid (umol/L)	315.5(93.9)	339.2(106.7)	<0.001
UAER (mg/24 h)	84.1(263.4)	114.2(261.7)	<0.001
Creatinine (umol/L)	70(22.8)	74.8(31.8)	0.016
eGFR ($mL/min/1.73\ m^2$)	106.0(30.3)	100.5(33.1)	0.002
DKD (n(%))	212(33.5)	373(45.5)	<0.001
Hypertension (n(%))	319(50.4)	462(56.4)	0.026
CHD (n(%))	84(13.3)	121(14.8)	0.448
Carotid plaque (n(%))	363(57.4)	540(65.9)	0.001
Use of statins (n(%))	39(6.2)	55(6.7)	0.747

Lp-PLA2, lipoprotein-associated phospholipase A2.
BMI, body mass index.
FPG, fasting plasma glucose.
HDL-c, high density lipoprotein cholesterol.
LDL-c, Low density lipoprotein cholesterol.
UAER, urine albumin excretion rate.
eGFR, estimated glomerular filtration rate.
DKD, diabetic kidney disease.
CHD, coronary heart disease.
Continuous variables were described as mean (standard deviation).
Categorical variables were described as sample (n) and percentage (%).

HbA1c levels (Table 5). We also performed correlation analysis in patients with hypertension history, and we found that the correlations between UAER/eGFR and Lp-PLA2 were significant in patients with hypertension, but there were no significant correlations in patients without hypertension (Table 5).

3.6. *Influencing factors of Lp-PLA2*

To validate the accuracy of Lp-PLA2 levels, Spearman analysis was performed between Lp-PLA2 and LDL-c, and the Lp-PLA2 level was positively correlated with LDL-c level ($r = 0.141$, $P < 0.001$).

To confirm the factors that influenced Lp-PLA2, the relationships betweenLp-PLA2 and age, duration of diabetes, HbA1c, BMI, blood pressure, blood lipid, UAER, eGFR, smoking history, and white blood cells (WBC) were analyzed using linear regression analysis. Among the factors, BMI, HbA1c, age and WBC were all positively correlated with LP-PLA2 ($P < 0.05$ for all). In the patients with short duration of diabetes (<10 years), the Lp-PLA2 level was most correlated with HbA1c ($\beta = 11.704$, $P < 0.001$) in linear regression analysis; however, the most correlated factors of Lp-PLA2 was BMI ($\beta = 7.797$, $P = 0.007$) in patients with long duration of diabetes (≥10 years).

4. Discussion

The novel finding of our present study is that plasma Lp-PLA2 in patients with DKD is significantly higher and increased Lp-PLA2 level is independently associated with the incidence of DKD in patients with T2D. The dysregulated metabolic milieu (including hyperglycemia, hypertension, hyperlipidemia, and insulin resistance) initiates DKD [23]. Our present study reveals that in patients with T2D, the rate of DKD is about 40%. As compared to patients without DKD, the ones with DKD had more co-morbidities such as more elderly, fatter, longer duration of T2D and had higher HbA1c, blood pressure, uric acid, and TG level, which were simultaneously found in the patients with high Lp-PLA2 level.

Cavallo-Perin, et al. found an association between increased production of platelet-activating factor (PAF) (production of Lp-PLA2) and enhanced glomerular permeability in micro albuminuric patients with type 1 diabetes (T1D) [24], but in their study, Lp-PLA2 did not correlate with the

Table 3 – Characteristics of patients with and without DKD (NDKD).

Items	Total	NDKD group	DKD group	P value
Patients (number)	1452	867	585	
Gender (n(%) male)	895(61.6)	526(60.7)	369(63.1)	0.128
Age (year)	58.5(12.5)	57(12.1)	60.8(12.9)	<0.001
Duration of diabetes (year)	7.1(6.8)	6.1(6.0)	8.6(7.6)	<0.001
Systolic pressure (mmHg)	131.2(15.1)	128.5(12.9)	135.0(17.0)	<0.001
Diastolic pressure (mmHg)	79.6(9.5)	78.9(8.9)	80.6(10.1)	0.002
BMI (kg/m^2)	24.7(3.4)	24.5(3.3)	25.2(3.5)	<0.001
HbA1c (%)	9.1(2.1)	9.0(2.0)	9.4(2.2)	<0.001
FPG (mmol/L)	8.7(3.0)	8.6(2.9)	8.9(3.2)	0.082
Fast C-peptide (ng/mL)	1.9(1.2)	1.7(1.0)	2.1(1.5)	0.001
C-peptide 120 min (ng/mL)	4.3(2.9)	4.2(2.8)	4.3(3.1)	0.973
Hemoglobin (g/L)	136.4(18.7)	137.4(17.9)	134.7(19.8)	0.044
Total cholesterol (mmol/L)	4.8(1.2)	4.8(1.1)	4.9(1.2)	0.147
Triglyceride (mmol/L)	2.1(2.0)	1.9(1.9)	2.3(2.0)	0.002
HDL-c (mmol/L)	1.32(0.39)	1.33(0.38)	1.29(0.41)	0.039
LDL-c (mmol/L)	2.5(0.8)	2.5(0.7)	2.5(0.8)	0.191
Uric acid (umol/L)	328.7(101.9)	314(91.2)	350.8(112.6)	<0.001
UAER (mg/24 h)	101.1(262.7)	12.2(6.8)	232.8(377.3)	<0.001
Creatinine (umol/L)	72.7(28.3)	65.4(14.8)	83.3(38.2)	<0.001
eGFR ($mL/min/1.73\ m^2$)	102.9(32.0)	110.0(26.9)	92.7(35.8)	<0.001
Lp-PLA2 (ng/mL)	238.4(111.9)	228.2(110.7)	253.5(112.0)	<0.001
Hypertension (n(%))	781(53.8)	390(45.0)	391(66.8)	<0.001
CHD (n(%))	205(14.1)	107(12.3)	98(16.8)	0.021
Carotid plaque (n(%))	903(62.2)	503(58.0)	400(68.4)	<0.001
Use of statins (n(%))	94(6.5)	53(6.1)	41(7.0)	0.515

Lp-PLA2, lipoprotein-associated phospholipase A2.
BMI, body mass index.
FPG, fasting plasma glucose.
HDL-c, high density lipoprotein cholesterol.
LDL-c, Low density lipoprotein cholesterol.
UAER, urine albumin excretion rate.
eGFR, estimated glomerular filtration rate.
DKD, diabetic kidney disease.
CHD, coronary heart disease.
Continuous variables were described as mean (standard deviation).
Categorical variables were described as sample (n) and percentage (%).

concentration of PAF. However, fatty acid, insulin, and adiponectin levels are different in T1D versus T2D patients; therefore, some of these metabolic differences may underlie different pathogenic pathways in T1D versus T2D DKD development [25,26]. Our study, for the first time, showed the association of Lp-PLA2 with DKD, especially with the 24 hrs UAER in patients with T2D. The correlations increased in older patients or patients with long duration of diabetes between Lp-PLA2 and eGFR. Moreover, the correlations between Lp-PLA2 and UAER/eGFR were more significant in patients with hypertension. These results indicated that inflammatory reaction in vessel walls may play important roles in the development of DKD in these patients.

Macroalbuminuria is considered as a disease state characterized by the presence of overt nephropathy and a high probability of chronic kidney disease. We found that the level of Lp-PLA2 was higher in the macroalbuminuria group than in normal group and the microalbuminuria group. Previous studies found lots of proinflammatory molecules, such as IL-18 and TNF-α, highly expressed in patients with macroalbuminuria, which may contribute to maintain microinflammation in renal tissues of patients with DKD [27–29]. Our findings confirmed these results, and may help to may help to indicate that the inflammation is present at the vessel walls of renal tissues.

High fasting C-peptide levels, which indicated insulin resistance [30], were also found in patients with both DKD and high Lp-PLA2 level. Several cross-sectional analyses have shown that individuals with diabetes have higher Lp-PLA2 levels than healthy controls [31–33]. The mechanisms involved inflammatory activity associated with Lp-PLA2's hydrolysis of oxidized phospholipids and the accumulation of PAF in adipose tissue that could potentially increase insulin resistance [33–35]. Insulin resistance plays an important role in the progression of DKD [36,37], thus high Lp-PLA2 level may be a promoter of DKD. According to these studies, it makes sense that statin, a kind of hypolipidemic drugs which inhibits Lp-PLA2 and arteriosclerosis, decreases the albuminuria and UAER significantly [3]. Darapladib, a Lp-PLA2 inhibitor, has been demonstrated to be effective in the treatment of diabetic retinopathy [16], and whether it works in DKD should be further studied.

The duration of diabetes in high Lp-PLA2 group was shorter than the normal group in this study. The high

Table 4 – Associations of Lp-PLA2 with presence of DKD.

	Presence of DKD		
Lp-PLA2 (ng/mL)	OR	95% Confidence interval	P value
Model 1			
Lp-PLA2 < 200	1.000		
Lp-PLA2 ≥ 200	1.661	1.340–2.059	<0.001
Per SD increase	1.002	1.001–1.003	<0.001
Model 2			
Lp-PLA2 < 200	1.000		
Lp-PLA2 ≥ 200	1.711	1.371–2.135	<0.001
Per SD increase	1.002	1.001–1.003	<0.001
Model 3			
Lp-PLA2 < 200	1.000		
Lp-PLA2 ≥ 200	1.327	1.035–1.701	0.026
Per SD increase	1.001	1.000–1.002	0.029
Model 4			
Lp-PLA2 < 200	1.000		
Lp-PLA2 ≥ 200	1.545	1.094–2.180	0.013
Per SD increase	1.002	1.001–1.004	0.010

Model 1: unadjusted. Model 2: adjusted for age, gender, duration of diabetes. Model 3: Model 2 plus adjusted for HbA1c, BMI, total cholesterol, high density lipoprotein cholesterol, triglycerides and low density lipoprotein cholesterol. Model 4: Model 3 plus adjusted for presence of coronary heart disease and carotid plaque, use of statins, and systolic/diastolic blood pressure.

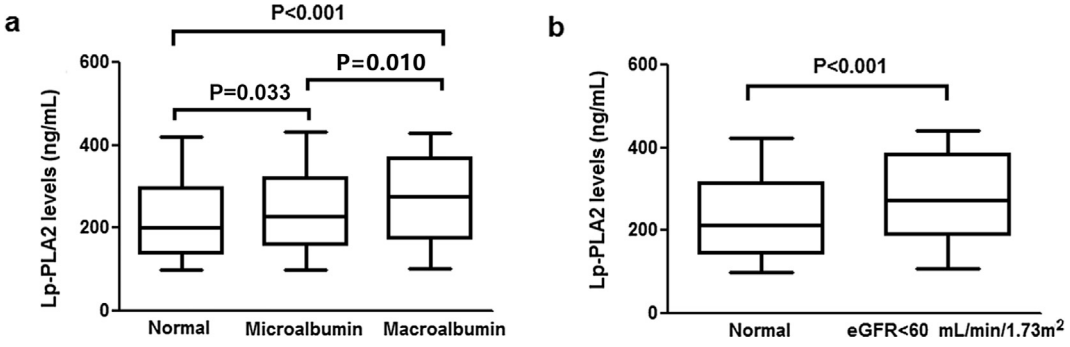

Fig. 1 – Lp-PLA2 levels in group with different UAER/eGFR. (a) Lp-PLA2 levels in normal group (UAER < 30 mg/24 hrs), microalbuminuria group (UAER range from 30 to 300 mg/24 hrs) and macroalbuminuria group (UAER > 300 mg/24 hrs). (b) Lp-PLA2 levels in patients with eGFR ≥ 60 mL/min/1.73 m^2 (normal) and eGFR < 60 mL/min/1.73 m^2. The differences between two groups were analyzed using Mann-Whitney *U* test. The whiskers of the box were showed as 5–95 percentile.

Lp-PLA2 levels in patients with short duration of diabetes attributed to the bad glycemic control, especially in newly diagnosed patients with T2D. However, the incidence of DKD in these patients was quite low. After excluding the newly diagnosed patients with T2D, the duration of diabetes between the low and high Lp-PLA2 groups was similar (7.9 vs. 7.5, P = 0.116). Moreover, the Lp-PLA2 levels in patients with long duration of diabetes were correlated with BMI, which was also a risk factor of DKD.

Our study has some limitations too. Firstly, in accordance with the exclusion criteria, the participants in our study were admitted in our hospital with inadequate glycemic control and thus may not be fully representative of the general T2D population. Secondly, though the Lp-PLA2 mass was considered as the independent predictor of atherosclerotic cardiovascular disease events and cerebrovascular accident [12,22], Lp-PLA2 activity seems more relevant to glycemic control than Lp-PLA2 mass [33]. Thirdly, the data about use of hypertensive agents was not collected by us, which may partially affect the levels of UAER, eGFR, and Lp-PLA2, and the relationship between hypertensive agents and Lp-PLA2 needs further study. Moreover, this is a cross-sectional study and the causal relationship between Lp-PLA2 and DKD needs to be confirmed by further longitudinal prospective studies.

5. Conclusions

Our study indicates that increased plasma level of Lp-PLA2 is associated with incidence and development of DKD in T2D patients. This biomarker is related to inflammation, thereby suggesting potential inflammatory reaction mechanisms underlying DKD. Lp-PLA2 should be considered as a biomarker for early detection and follow-up of DKD. Furthermore, Lp-PLA2 may be a new therapeutic target of DKD.

Table 5 – Associations of Lp-PLA2 with UAER/eGFR in different subjects.

Items	Number	UAER in 24 h		eGFR	
		r	P value	r	P value
All of the patients	1452	0.123	<0.001	−0.710	0.009
Classified by gender					
Male	895	0.140	<0.001	−0.063	0.066
Female	557	0.104	0.014	−0.081	0.064
Classified by age					
<60 years	770	0.134	<0.001	−0.010	0.790
≥60 years	682	0.114	0.003	−0.135	0.001
Classified by duration of diabetes					
<10 years	945	0.105	0.001	−0.034	0.318
≥10 years	507	0.183	<0.001	−0.164	<0.001
Classified by HbA1c					
<9.0%	768	0.134	<0.001	−0.097	0.012
≥9.0%	684	0.093	0.015	−0.078	0.049
Classified by blood pressure					
SBP/DBP < 140/90 mmHg	671	0.051	0.184	−0.026	0.518
SBP/DBP ≥ 140/90 mmHg	781	0.156	<0.001	−0.074	0.045

Lp-PLA2, lipoprotein-associated phospholipase A2.
UAER, urine albumin excretion rate.
eGFR, estimated glomerular filtration rate.

Authors' contributions

XJ.X. and JH.M. are responsible for the conception and design of the study. Y.H. carried out statistical analysis and drafted the manuscript. TT.L., TT.L. B.D and W.Z. collected data. BL. L. and FF.L. approved the final version of the manuscript. JH. M. contributed to obtain funding. Y.H. and JH.M. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosure

There is no conflict of interest in this study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.03.026.

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