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Original research

Effect of obesity, glucose control, lipid profiles, and blood pressure on Lp-PLA2 levels in type 2 diabetes mellitus patients

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ABSTRACT

Background: Diabetes mellitus is a metabolic disorder with cardiovascular complications as its main cause of morbidity and mortality. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a new biomarker of cardiovascular disorders in metabolic diseases. This study aimed to evaluate the influence of glucose control, obesity, lipid profiles, and blood pressure on Lp-PLA2 levels in type 2 diabetes mellitus.

Methods and results: This was a cross-sectional study comprising 60 type 2 diabetes mellitus patients. Body mass index, waist circumference, body fat (BF) percentage, and blood pressure were measured. Fasting plasma glucose, HbA1c, and lipid profile were then analyzed. The Lp-PLA2 levels were determined by enzyme-linked immunosorbent assay method.

Results: Lp-PLA2 had significant positive correlation with plasma glucose, HbA1c, total cholesterol, LDL-C, body fat, systole, diastole, and mean arterial pressure (MAP). Multivariate regression analysis showed that MAP ($\beta = 0.485$, $p = <0.001$), triglycerides ($\beta = 0.224$, $p = 0.048$), and BF ($\beta = 0.225$, $p = 0.051$) predicted the Lp-PLA2 levels in all subjects. Further analysis confirmed that BF ($\beta = 0.559$, $p = <0.001$) and MAP ($\beta = 0.449$, $p = 0.001$) predicted Lp-PLA2 levels in males, while LDL-C ($\beta = 0.525$, $p = 0.002$) and triglycerides ($\beta = 0.390$, $p = 0.015$) predicted the enzyme levels in females.

Conclusion: Lp-PLA2 shows an important association with blood pressure, lipid profile, and obesity, in particular with BF and MAP in males and with LDL-C and triglycerides in females.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder marked by impaired glucose metabolism (Shi and Vanhoutte, 2017). Diabetes is predispose to cardiovascular disease, particularly the atherogenesis process, leading to the acute coronary syndrome. Diabetic macrovascular complication induced by endothelial dysfunction, resembling atherosclerotic lesions, is the main cause of morbidity and mortality (Shi and Vanhoutte, 2017; Zhu, 2016).

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase (PAF-AH), is a member of phospholipase A2 superfamily enzymes (Stankovic and Asanin, 2015). Lp-PLA2 has important roles in hydrolyzing the acetyl group of PAF, generating acetate and lyso-PAF, and in cleaving oxidatively modified lipoproteins of the apolipoprotein B100-containing lipoproteins into oxidized nonesterified fatty acids (oxFFA) and lysophosphatidylcholine (lysoPC) which have pro-inflammatory properties (Burke and Dennis, 2009; Silva et al., 2011; Cojocaru et al., 2010). The main sources of circulating Lp-PLA2 are monocytes/macrophages, T lymphocytes, mast cells, liver cells and, several other cells (Stankovic and Asanin, 2015; Huang et al., 2020).

Due to its inflammatory and pro-atherogenic properties, Lp-PLA2 has been recognized as a new cardiovascular disorder biomarker (Cojocaru et al., 2010; Stefano et al., 2019). Elevation of Lp-PLA2 levels can be used to predict future coronary heart disease (CHD) events in healthy older adults, independent of other CHD risk factors (Daniels et al.,

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2008). Lp-PLA2 levels were also reported having an association with CHD incident among men and women with type 2 DM (Hatoum et al., 2010). It can be used as a novel biomarker of rupture-prone atherosclerotic lesions in the elderly DM and non-DM patients (Fortunato et al., 2014). This enzyme may also be used to predict the incidence of peripheral arterial disease during long-term follow-up (Fatemi et al., 2019). This present study aimed to evaluate the influence of glucose control/levels, obesity, lipid profiles, and blood pressure on Lp-PLA2 levels in type 2 diabetes mellitus.

2. Methods

2.1. Study population and ethics approval

This cross-sectional study was conducted from March to May 2019. Included subjects were the type 2 DM patients diagnosed by the American Diabetes Association (ADA) criteria, who visited the Endocrine Metabolic Outpatient Clinic of dr. Wahidin Sudirohusodo or Hasanuddin University hospital, Makassar, Indonesia, and voluntarily participated in the study with signed informed consent. Subjects who currently had infection, acute or chronic disease, history of regular cigarette smoking, regular alcohol intake, were excluded from the study. The ethical recommendation was approved by Komite Etik Penelitian Kesehatan (Health Research Ethical Committee), of Faculty of Medicine, Hasanuddin University, Makassar, Indonesia (Approval Recommendation Number 191/H4.6.4.5.31/PP36/2019).

2.2. Obesity parameters, blood pressure measurements, and laboratory procedures

Obesity parameters and blood pressure measurements were performed by a single examiner on the same day as blood collection. Bodyweight and height were measured in the morning for calculating the body mass index (BMI, kg/m2). Waist circumference (WC) was measured at the midway level of the iliac crest and the lower border the 12th rib with the subjects in standing position after a normal expiration. Body fat (BF) percentages were measured by bioelectrical impedance analysis (BIA) method, using the Tanita-BC541 (Tokyo, Japan) device. Blood pressure was measured from the arm of seated patients by using Riester mercury sphygmomanometers (Germany) after a 15-minute rest. Systole and diastole pressures were then documented, and mean arterial pressure (MAP) was then calculated by using the formula: MAP = (2 x diastole + systole)/3.

After 10–12 h of the overnight fasting period, venous blood specimens were obtained from each subject by using a vacutainer, collected in Ethylenediamine tetraacetic acid (EDTA) tube for hemoglobin A1c (HbA1c) test (Abx Pentra 400, Horiba, USA) and plain tube, followed by centrifugation for serum separation. The serum was then used for fasting plasma glucose (FPG), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, urea and creatinine tests (Abx Pentra 400, Horiba, USA). The remaining serum was stored at −20 °C until the testing of Lp-PLA2 by enzyme-linked immunosorbent assay method (Bioassay Technology Laboratory, Shanghai, China).

2.3. Statistical analysis

The data normality distribution was determined by the Kolmogorov-Smirnov test. The differences between groups were determined by the Independent T-test (normally distributed data) or Mann-Whitney test (not normally distributed data). Spearman test was used to evaluate the correlation between Lp-PLA2 levels with other parameters because Lp-PLA2 was not normally distributed. Parameters that correlated with Lp-PLA2 with $p < 0.25$ were further included in multivariate regression analyses. All contributed parameters were then normalized in logarithm form for regression analysis. Multivariate regression tests were performed on all subjects, and further on males, females. Results of regression models were shown as β-coefficients, adjusted R-square, and p values. All statistical analyses were performed using the Statistical Package for the Social Sciences, Version 21.0 (SPSS Inc, Chicago, IL, USA) software. Statistical significance was established if p-value ≤0.05.

3. Results

There were 60 subjects recruited in the study, consisted of 31 (51.7%) males and 29 (48.3%) females. The mean of study subjects age was 56.01 ± 10.14 years. Kolmogorov Smirnov test showed that age, total cholesterol, LDL-C, HDL-C, and MAP were distributed normally, while other parameters were not distributed normally. The general characteristics of all, male, and female subjects are presented in Table 1. There was no significant difference in age, FPG, HbA1c, urea, total cholesterol, LDL-C, triglycerides, BMI, BF, systole, diastole, MAP, and Lp-PLA2 between male and female groups. Creatinine, weight, height, and WC were significantly higher in males while HDL-C was higher in females.

Lp-PLA2 levels had a significant positive correlation with FPG, HbA1c, total cholesterol, LDL-C, triglycerides, BF, systole, diastole, and MAP in all subjects (Table 2). In males, Lp-PLA2 significantly correlated with FPG, HbA1c, BF, systole, diastole, and MAP, while in females, it correlated significantly with HbA1c, total cholesterol, LDL-C, triglycerides, systole, diastole, and MAP.

HbA1c, LDL-C, triglycerides, BF, and MAP were included as

Table 1
The general characteristics of all, male, and female subjects.

	Total	Male	Female	p
	n = 60	n = 31	n = 29	
Age (year)	56.01 ± 10.14	55.71 ± 9.78	56.34 ± 1.99	0.811*
FPG (mg/dL)	172.17 ± 73.79	176.26 ± 84.33	167.79 ± 61.76	0.965#
HbA1c (%)	7.90 ± 1.97	7.50 ± 1.90	8.33 ± 1.99	0.097#
Urea (mg/dL)	33.40 ± 20.24	38.48 ± 23.60	27.97 ± 14.40	0.056#
Creatinine (mg/dL)	1.14 ± 0.84	1.40 ± 1.03	0.87 ± 0.45	0.004#
Total cholesterol (mg/dL)	206.80 ± 47.98	203.06 ± 48.47	210.79 ± 47.97	0.538*
LDL-C (mg/dL)	131.93 ± 41.28	134.74 ± 42.27	128.93 ± 40.72	0.590*
HDL-C (mg/dL)	45.22 ± 9.29	42.39 ± 8.02	48.24 ± 9.72	0.013*
Triglycerides (mg/dL)	163.22 ± 98.21	159.42 ± 79.05	167.28 ± 116.60	0.859#
Weight (kg)	65.27 ± 10.38	69.54 ± 9.36	60.70 ± 9.56	0.001#
Height (cm)	159.75 ± 6.01	163.97 ± 4.25	155.24 ± 4.01	<0.001#
BMI (kg/m2)	25.52 ± 3.47	25.89 ± 3.50	25.13 ± 3.45	0.429#
WC (cm)	77.15 ± 7.87	79.26 ± 7.75	74.90 ± 7.47	0.036#
BF (%)	31.25 ± 5.06	31.61 ± 5.02	30.87 ± 5.16	0.579#
Systole (mmHg)	134.33 ± 16.56	131.45 ± 16.34	137.41 ± 16.51	0.182#
Diastole (mmHg)	85.67 ± 8.31	85.16 ± 7.24	86.21 ± 9.42	0.563#
MAP (mmHg)	101.89 ± 9.93	100.59 ± 9.18	103.28 ± 10.66	0.299*
Lp-PLA2 (IU/mL)	17.61 ± 18.26	17.30 ± 17.96	17.93 ± 18.89	0.371#

p-value is used to define the significant difference between male and female groups. FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, BMI = body mass index, WC = waist circumference, BF = body fat, MAP = mean arterial pressure, Lp-PLA2 = lipoprotein-associated phospholipase A2.
* Independent T-Test, # Mann-Whitney Test.

Table 2
Correlation between Lp-PLA2 levels with other parameters in all, male, and female subjects.

	Total		Male		Female	
	p*	r	p*	r	p*	r
Age	0.588	−0.071	0.784	−0.051	0.481	−0.136
FPG	0.002	0.395	0.014	0.436	0.111	0.303
HbA1c	<0.001	0.611	<0.001	0.654	0.004	0.515
Ureum	0.756	−0.041	0.788	0.050	0.580	−0.107
Creatinine	0.599	−0.069	0.844	0.037	0.550	−0.116
Total cholesterol	0.003	0.375	0.452	0.140	<0.001	0.614
LDL-C	0.011	0.324	0.382	0.163	0.004	0.512
HDL-C	0.795	−0.034	0.975	0.006	0.272	−0.211
Triglycerides	0.026	0.288	0.237	0.219	0.033	0.396
Weight	0.597	0.070	0.064	0.336	0.478	−0.137
Height	0.496	−0.09	0.433	0.143	0.193	−0.249
BMI	0.436	0.103	0.190	0.242	0.708	−0.073
WC	0.477	0.094	0.100	0.301	0.592	−0.104
BF	0.001	0.433	<0.001	0.671	0.247	−0.222
Systole	<0.001	0.566	<0.001	0.591	0.020	0.430
Diastole	0.001	0.425	0.038	0.375	0.023	0.421
MAP	<0.001	0.564	0.001	0.553	0.005	0.504

FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, BMI = body mass index, WC = waist circumference, BF = body fat, MAP = mean arterial pressure.
*Spearman Test.

explanatory variables for evaluating their effect on Lp-PLA2 levels (as dependent outcome) in multivariate regression analysis. HbA1c was chosen over FPG in evaluating the glucose control effect due to HbA1c superior correlation with Lp-PLA2. LDL-C and triglycerides were analyzed in evaluating the effect of lipid profiles, while total cholesterol was excluded due to its collinearity effect, and so was HDL, due to its insignificance correlation. BF was the only obesity index that correlated significantly with Lp-PLA2 levels, thus it was included in the analysis. MAP which represented the average of systole and diastole pressure was used in analysis instead of those parameters. All chosen parameters were normalized in the logarithm form for regression analysis.

Multivariate regression analysis showed that the better predictor of Lp-PLA2 levels in all type 2 DM subjects was featured by MAP (β = 0.485, p = <0.001), triglycerides (β = 0.224, p = 0.048), and BF (β = 0.225, p = 0.051). This model explained 37.60% of Lp-PLA2 variability (Table 3).

In male subjects, the better model of multivariate association in determining Lp-PLA2 levels was featured by BF (β = 0.559, p = <0.001) and MAP (β = 0.449, p = 0.001). This model explained 60.4% of Lp-PLA2 variability in male with diabetes (Table 4).

Table 3
Multivariate linear regressions between Lp-PLA2 and glucose control, obesity, lipid profiles, and blood pressure in all type 2 DM subjects.

	Variables	β	p
Model 1 R2 = 37.9%	HbA1c	0.153	0.364
	LDL-C	0.110	0.342
	Triglycerides	0.186	0.107
	BF	0.181	0.142
	MAP	0.349	0.023
Model 2 R2 = 38.1%	LDL-C	0.136	0.227
	Triglycerides	0.198	0.083
	BF	0.224	0.050
	MAP	0.439	<0.001
Model 3 R2 = 37.60%	Triglycerides	0.224	0.048
	BF	0.225	0.051
	MAP	0.485	<0.001

HbA1c = hemoglobin A1c, LDL-C = low density lipoprotein cholesterol, BF = body fat, MAP = mean arterial pressure.
Variables in logarithm form.

Table 4
Multivariate linear regressions between Lp-PLA2 and glucose control, obesity, lipid profiles, and blood pressure in male DM subjects.

	Variables	β	p
Model 1 R2 = 55.8%	HbA1c	0.017	0.928
	LDL-C	−0.007	0.957
	Triglycerides	−0.029	0.853
	BF	0.569	0.001
	MAP	0.435	0.018
Model 2 R2 = 57.5%	HbA1c	0.018	0.926
	Triglycerides	−0.032	0.825
	BF	0.568	0.001
	MAP	0.434	0.016
Model 3 R2 = 59.0%	Triglycerides	−0.028	0.836
	BF	0.573	<0.001
	MAP	0.444	0.001
Model 4 R2 = 60.4%	BF	0.559	<0.001
	MAP	0.449	0.001

HbA1c = hemoglobin A1c, LDL-C = low density lipoprotein cholesterol, BF = body fat, MAP = mean arterial pressure.
Variables in logarithm form.

The better model of multivariate association in order to understand the Lp-PLA2 levels in female subjects was featured by LDL-C (β = 0.525, p = 0.002) and triglycerides (β = 0.390, p = 0.015). This model explained 37.7% of Lp-PLA2 variability in the female with diabetes (Table 5).

4. Discussion

This study showed that there was no significant difference between Lp-PLA2 levels in male and female type 2 DM subjects (17.30 ± 17.96 IU/mL vs 17.93 ± 18.89 IU/mL). Another research reported similar Lp-PLA2 cut-off in diabetes patients. It was reported that Lp-PLA2 levels in patients with a diabetes duration <10 years were 20.2 IU/mL while those with diabetes duration ≥10 years had Lp-PLA2 levels of 20.5 IU/mL (Kotani, 2016). Another study showed that the mean levels of Lp-PLA2 were 13.75 IU/mL in stable angina, 18 IU/mL in acute coronary syndrome, and 14.21 IU/mL in control subjects (Chung et al., 2014). Among patients with ischemic stroke, the mean of Lp-PLA2 levels was 15.58 IU/mL in non-statins users and 9.82 IU/mL in statins users (Alkuraishy et al., 2018).

This current study showed that Lp-PLA2 levels in type 2 DM patients were associated with blood pressure, lipid profile, and obesity index. In all subjects, the factors which had a significant contribution to Lp-PLA2 levels from the strongest to the weakest were MAP, triglycerides, and BF. In males, the contributing factors were BF and MAP, while in females,

Table 5
Multivariate linear regressions between Lp-PLA2 and glucose control, obesity, lipid profiles, and blood pressure in female DM subjects.

	Variables	β	p
Model 1 R2 = 36.9%	HbA1c	0.217	0.493
	LDL-C	0.290	0.209
	Triglycerides	0.391	0.019
	BF	−0.111	0.569
	MAP	0.17	0.464
Model 2 R2 = 38.7%	HbA1c	0.115	0.654
	LDL-C	0.345	0.096
	Triglycerides	0.374	0.020
	MAP	0.198	0.377
Model 3 R2 = 40.6%	LDL-C	0.390	0.032
	Triglycerides	0.387	0.014
	MAP	0.259	0.143
Model 4 R2 = 37.7%	LDL-C	0.525	0.002
	Triglycerides	0.390	0.015

HbA1c = hemoglobin A1c, LDL-C = low density lipoprotein cholesterol, BF = body fat, MAP = mean arterial pressure.
Variables in logarithm form.

the significant factors were LDL-C and triglycerides.

Our findings showed that obesity was a significant contributing factor to Lp-PLA2 levels. Obesity indexes have been shown having a significant association with cardio-metabolic risk factors (Czeczelewski et al., 2020). Interestingly, the only obesity index which had a significant correlation with this enzyme level was BF, especially in male subjects, while it had no significant role in females. Lp-PLA2 is secreted by various cells such as monocyte, macrophages, T lymphocyte, mast cells (Zhu, 2016). Recent finding also reported that human adipocytes were sources of Lp-PLA production in obese and type 2 DM patients (Jackisch et al., 2018). Men tend to have less body fat compared to women, but the apple-shaped body fat distribution in males is associated with higher cardiometabolic risk compared to the pear-shaped distribution in females (Karastergiou et al., 2012). It was also reported that adult women had 48% less waist fat than men (Taylor et al., 2010). Visceral obesity will enhance the lipid overflow-ectopic fat deposition in the liver, epicardial, and muscle and alter the metabolic profile (Despres, 2006, 2012). WC was also reported as a predictor of Lp-PLA2 activity in healthy young adolescents (Silva et al., 2013). We hypothesized that adipocytes in males are more active in secreting Lp-PLA2 levels compared to the females, but further in-vitro and in-vivo investigations should be performed to confirm it.

Lipid profiles had a significant role in the Lp-PLA2 levels. We found that LDL-C and triglycerides in females had a significant contribution to this enzyme level. About 70–80 percent of circulated Lp-PLA2 enzymes are bound to LDL and lipoprotein (a) [Lp(a)] and have an atherogenic role, while the rests are bound to HDL-C that have antiatherogenic action, and to other lipoproteins (Zhu, 2016; Cojocaru et al., 2010). The significant Lp-PLA2 association with triglycerides might reflect this enzyme binding to other remnant lipoproteins besides LDL-C and HDL-C, which were not particularly observed in this study. We did not find the significant correlation of Lp-PLA2 with HDL-C levels, showing that this enzyme binding to HDL-C in diabetes patients might be altered, thus reducing its antiatherogenic property.

One interesting finding also revealed the association between Lp-PLA2 levels and blood pressure. Systole, diastole pressure, and MAP consistently correlated with Lp-PLA2 in males and females. The association remained significant in males, while in females, it was not significant after adjustment of other parameters. Some explanation might describe it. Lp-PLA2 catalysis action would increase the phosphatidylcholine hydrolysis, generating increased oxidative stress, thus enhanced arterial stiffness leading to the increased of blood pressure (Kim et al., 2014).

Glucose control (HbA1c) had a significant correlation with Lp-PLA2 levels both in males and females. Garg et al. reported that FPG and oxidized LDL correlated significantly with Lp-PLA2 in type 2 DM patients (Garg et al., 2015). However, in the current study, after adjustment of the other parameters, the relationship between HbA1c and Lp-PLA2 was attenuated and became non-significant.

This study demonstrated that the contributing factors to Lp-PLA2 levels in males and females with type 2 DM were different. In males, obesity and blood pressure contributed significantly, while lipid profiles contributed to females. Despite these important findings, the cross-sectional design of this study could not explain the causality of these results. Another limitation was the small sample size, thus future larger population studies are needed to confirm and explain the causality.

In conclusion, Lp-PLA2 shows an important association with blood pressure, lipid profile, and obesity, in particular with BF and MAP in males and with LDL-C and triglycerides in females.

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CRediT authorship contribution statement

Liong Boy Kurniawan: Conceptualization, Methodology, Investigation, Resources, Formal analysis, Project administration, Visualization, Writing - original draft, Writing - review & editing. **Herniaty Rampo:** Conceptualization, Methodology, Investigation, Resources, Project administration. **Gita Vita Soraya:** Conceptualization, Methodology, Investigation, Formal analysis. **Endy Adnan:** Conceptualization, Methodology, Investigation. **Tenri Esa:** Conceptualization, Methodology, Investigation. **Yuyun Widaningsih:** Conceptualization, Methodology, Investigation. **Uleng Bahrun:** Conceptualization, Methodology, Supervision. **Mansyur Arif:** Conceptualization, Methodology, Supervision.

Declaration of competing interest

The authors state that they have no conflict of interest.

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