Original Research Article

Lipoprotein-associated Phospholipase A_2 Activity contributes to the Coronary Artery Disease with Metabolic Syndrome

ABSTRACT

Background: Coronary artery disease (CAD) is an inflammatory process characterized by atherosclerosis in coronary arteries and it is a major cause of death and disability in developed countries. Lipoprotein-associated phospholipase A2 (Lp-PLA2) has been consistently associated with CAD risk factors and predictive of CVD outcomes; additionally, it is consistently higher among type 2 diabetics than nondiabetics. However, the relationships of circulating Lp-PLA2 activity with incident CAD among patients with metabolic syndrome (MetSynd) have not been examined sufficiently.

Objective: The aim is to determine contribution of Lp-PLA2 to coronary artery disease (CAD) in patients with Metabolic Syndrome (MetSynd)..

Subjects and methods: This is a cohort prospective study based on 412 patients male and female were eligible and aged 25-75 years old patients and gave consent to participate in study. The study included socio-demographics, clinical biochemistry and the presence of co-morbid diseases. The data were analyzed using descriptive and multivariate analyses.

Results: There was a significant difference between MetSynd Positive and normal subjects with respect to age groups, gender, BMI, smoking, nargile use, thyroid, COPD, CAD, hypertension, diabetic and stroke. Also, there was a significant difference between MetSynd versus normal subjects with respect to BMI, Waist Circumference, hemoglobin, HbA1c, vitamin B12, fasting blood glucose, vitamin D, calcium, creatinine, triglyceride, uric acid, ferritin, systolic BP (mm Hg) and diastolic BP (mm Hg), creatine kinase-myocardial band (CK-MB) ($p=0.001$); Lp-PLA2 activity, ($p=0.001$); HOMA-IR index,($p=0.004$), insulin ($p=0.001$); C-reactive protein ($p=0.004$);White blood cell (WBC) ($p=0.008$); Platelet $p= 0.018$) Mean Plate Volume ($p= 0.032$); red cell distribution width ($p=0.001$); and vitamin D levels ($p=0.018$), respectively. The multivariate stepwise regression analysis indicated that Lp-PLA2 ($p<0.001$), BMI (kg/m2) ($p<0.001$), systolic BP ($p<0.001$), MetSynd ($p=0.002$), CK-MB ($p=0.019$), Calcium) ($p= 0.023$), Triglyceride ($p= 0.029$), Total-cholesterol ($p= 0.046$) were considered as risk predictors of the CAD patients after adjusting for age and gender.

Conclusion: Lp-LPA2 contributes to CAD in the presence of MetSynd, as well as Lp-PLA2 could be utilized as a useful predictor in cases of CAD with MetSynd.

Introduction

Coronary artery disease (CAD) is a pathological inflammatory process characterized by atherosclerotic accumulation in the epicardial arteries, and it is the most leading cause of mortality and

morbidity worldwide [1,2]. It has been known for more than half a century that the risk factors for CAD include hypertension, increased levels of low-density lipoprotein cholesterol (LDL-C), type-2 diabetes and smoking. The MetSynd is a cluster of the prediabetic state, abdominal obesity, changes in cholesterol and high blood pressure. İn addition, MetSynd is the most dangerous risk factor for the CAD, stroke and diabetes [3,4].

Inflammation has been increasingly recognised as a critical step in the pathogenesis of both coronary artery disease (CAD) and MetSynd [5-9]. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a novel inflammatory marker associated with MetS, low density lipoprotein (LDL) cholesterol, atherosclerotic disease and incident cardiovascular disease (CVD). Lp-PLA2 has role of proatherogenic, and determine risk factor for CVDr events [10-13]. To the best of our knowledge, it is unclear whether Lp-PLA2 would contribute to CAD in case of MetSyn. CAD is the most leading cause of mortality and morbidity worldwide. The aim of current study was to investigate the role of Lp-PLA2 in prediction of coronary artery disease with respect to MetSynd.

2. PATİENTS AND METHODS

The current study based on cohort design a total of 412 patients and aged from 25 to75 years, cardiology outpatient's were reviewed from January 2019 to November 2021. Patients' demographic, clinical and laboratory data were collected from the hospital. Waist circumference was measured at the level of superior iliac crest, Systolic and diastolic BP was measured in the patient's right arm with a mercury sphygmomanometer.

The study was performed according to the principles of 1975 Declaration of Helsinki and its subsequent revisions. The study protocol was approved by the Istinye University clinical research ethic committee Ethics Committee Decision No. were 2/2021.K-78) and the Clinical Research Ethics Committee of Istanbul Medipol University, Institutional Review Board (IRB# 10840098-604.01.01-E.3193) and (IRB# 10840098-604.01.01-E.8421. Informed consent was obtained from the all patients. Informed consent was obtained from the all patients.

2.1. Lp-PLA2 activity assay

The total plasma Lp-PLA2 activity was measured using an enzyme immunoassay (EIA) kit. LDL-C, HDL-C, HBA1C, TC, TG and FPG levels were measured using colorimetric method. Serum insulin levels were determined by an enzymetic method using A. Insulin resistance was assessed by the homeostasis model assessment equation (HOMA-IR) [15].

2.2. Definition of metabolic syndrome

In our study, MetSynd was defined according to the diagnostic criteria recommended by the Society of Endocrinology and Metabolism of Turkey in accordance with the recommendation of the World Health Organisation (WHO) [6-7] at least one of the following criteria of insulin resistance [16-17] and impaired impaired FPG ≥110 mg/dL, impaired PG tolerance (2h PG ≥140 mg/dL) elevated insulin levels (4th quartile of reference). Plus two or more of the following: Systolic BP ≥140 mm Hg and/or, diastolic BP ≥90 mm Hg; [18]; TG ≥150 mg/dL , and/or HDL-C <35 mg/dL for men and <40 mg/dL for women. Central obesity: waist/hip ratio >0.90 for men and 0.85 for women and/or BMI >30 kg/m2 diagnosed hypertension Microalbuminuria: Urinary albumin excretion rate ≥20 mg/ml or albumin/creatinine ratio ≥30 mg/g

2.3. Coronary Computed Tomography Angiography (CCTA)

Patients were scanned with a 412-slice CT-scanner [19-20] (Philips, Holland) using prospective cohort scanning techniques. All patient's vital signs were monitored during CCTA. Patients received a beta-blocked (50-100 mg oral Metoprolol) one hour prior to scanning if their heart rate was upper than 65 beat/min. The CCTA analysis [19-20]. was performed by an experinced observers blinded to the study. CAD was defined as the occurrence of a visible plaque in at least 1 of 15 coronary segments according to guidelines.

2.4. Statistical analysis

Student-t test and. Chi-square test were used to test for between groups. Multivariate stepwise regression analysis method was used to predict associated risk factors for the CAD. The level $p<0.05$ was considered as the cut-off value for significance.

Results

Table 1 shows socio-demographic characteristics comparison of COVID-19 by MetSynd and normal subjects. There was a significant difference between MetSynd cases and normal subjects with respect to age groups, gender, BMI, smoking cigarette, nargile use, thyroid, COPD, Coronary Artery Disease (CAD), hypertension, diabetic and stroke .

Table 2 presents the baseline values of biochemistry indices by MetSynd cases nd normal subjects. There was a significant difference between MetSynd versus normal subjects with respect to BMI, Waist Circumference, hemoglobin, HbA1c, vitamin B12, fasting blood glucose (mmol/L),

vitamin D (mmol/L), calcium (mmol/L), creatinine (mg/dL), triglyceride (mmol/L), uric acid (mmol/L), ferritin (mmol/L), systolic BP (mm Hg) and diastolic Bp (mm Hg), respectively.

Table 3 gives the clinical biochemical comparison of MetSynd with normal subjects There was a significant difference between MetSynd versus normal subjects including: creatine kinase-myocardial band; (ug/L)(p=0.001); Lp-PLA2 activity, nmol/min/Ml, (p=0.001); HOMA-IR index,(p=0.004), Insulin (µIU/dl) (p=0.001); C-reactive protein (mg/L) (p=0.004);White blood cell (/mm3)(p=0.008); Platelet (103/mm3)(p= 0.018) Mean Plate Volume (mg/L) (p= 0.032); red cell distribution width (mg/L) (p=0.001); and vitamin D levels (p=0.018), respectively.

Table 4 shows the relationship and risk predictors of the Coronary Artery Disease patients using multivariate stepwise regression analysis method. The multivariate stepwise regression analysis indicated that Lipoprotein-associated Phospholipase A2 nmol/min/Ml (p<0.001), Body Mass Index (kg/m2) (p<0.001), systolic blood pressure (p<0.001), metabolic syndrome ATP III (p=0.002), Creatine kinase myocardial band (p=0.019), Calcium (mmol/L) (p= 0.023), Triglyceride (mmol/L) (p= 0.029), Total cholesterol (mmol/L) (p= 0.046) were considered as risk predictors of the CAD patients after adjusting for age and gender.

Table 1. Socio-demographic characteristics of patients by metabolic syndrome (N = 412)

Variables		Metabolic Syndrome cases n = 126 (%)	Normal Subjects n = 286 (%)	*p*-value Significance
Age group				
	<40	34 (27.0)	82 (28.7)	
	40-49	34 (27.0)	45 (15.7)	**0.025**
	=>50	58 (46.0)	159 (55.6)	
Gender				
	Male	89 (70. 6)	150 (52.4)	**0.001**
	Female	37 (29.4)	136 (47.6)	
BMI (25 kg/m$^{2)}$				
	Normal (<25 kg/m^2)	25 (19.8)	91 (40.9)	
	Overweight (29-30 kg/m^2	57 (45.2)	117 (27.3)	**0.037**
	Obese (>30 kg/m^2)	44 (34.9)	78 (30.1)	
Cigarette Smoke				
	Yes	35 (27.8)	49 (17.1)	**0.013**
	No	91 (72.2)	237 (82.9)	
Nargile-smoking	Yes	21 (16.7)	24(8.4)	**0.012**
	No	105 (83.3)	262 (91.6)	

Diabetes				
	Yes	27 (21.4)	30 (10.5)	**0.003**
	No	99 (78.6)	256 (89.5)	
Thyroid				
	Yes	38 (30.2)	113 (24.6)	**0.002**
	No	88 (69.8)	346 (75.4)	
Chronic Obstructive Pulmonary Disease				
	Yes	30 (23.8)	37 (12.9)	**0.005**
	No	96 (76.2)	249 (87.1)	
Hypertension				
	Yes	43 (34.1)	64 (22.4)	**0.009**
	No	83 (65.9)	222 (73.6)	
Coronary Artery Disease				
	Yes	65 (51.6)	103 (36.0)	**0.003**
	No	61 (48.4)	183 (84.0)	
Stroke				
	Yes	32 (25.4)	91 (31.8)	0.201
	No	94 (74.6)	195 (68.2)	
Coronary Heart Failure				
	Yes	43 (34.1)	69 (24.1)	
	No	83 (65.9)	217 (75.9)	**0.025**

Table 2. Clinical biochemistry base data values by metabolic syndrome patients (N= 412)

Variables	Metabolic Syndrome cases = 126 Mean ± SD	Normal subjects = 286 Mean ± SD	P value
BMI kg/m^2	28.52± 4.48	27.04± 4.36	**0.018**
Waist Circumference, cm	104.35±8.34	97.55±11.95	**0.001**
Hemoglobin (g/dL)	11.92± 2.77	12.66± 2.57	**0.009**
HbA1c	5.96±0.91	5.74±0.77	**0.012**
Fasting Blood Glucose (mmol/L)	111.91±45.01	103.07±36.10	**0.050**
Vitamin D (mmol/L)	17.29±7.17	19.47±7.56	**0.006**
Vitamin B12	271.10±125.0	300.8±108.0	**0.016**
Calcium (mmol/L)	8.39±0.77	8.86±0.67	**0.001**
Urea (mg/dL)	53.95±5.11	55.60±4.56	0.738
Creatinine (mg/dL)	0.74±0.16	0.69±0.14	**0.001**
Albumin (mg/dL)	3.44±0.64	3.43±0.58	0.930
Total cholesterol (mmol/L)	193.5±60.40	188.1±56.8	0.386
HDL (mmol/L)	166.5±83.9	203.0±91.6	0.070
LDL (mmol/L)	122.0±44.8	131.0±86.7	0.276
Triglyceride (mmol/L)	172.94±81.57	150.16±95.63	**0.024**
Uric Acid (mmol/L)	6.56±2.31	6.00±1.77	**0.008**
Ferritin (ug/L)	133.62±92.10	191.28±80.71	**0.001**
TSH	1.57±1.12	1.74±1.15	0.151
Systolic Blood Pressure mm Hg	135.82±10.00	133.10±9.18	**0.004**
Diastolic Blood Pressure mm Hg	81.40±6.28	78.00±6.55	**0.001**

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Table 3. Clinical biochemistry baseline value by metabolic syndrome patients (N= 412)patients

Variables	Metabolic Syndrome cases = 126 Mean ± SD	Normal subjects = 286 Mean ± SD	p value
Creatine kinase (ug/L)	40.47± 23.71	38.54± 20.55	0.403
Creatine kinase-myocardial band; (ug/L)	15.21± 8.96	12.74± 5.66	**0.001**
Lp-PLA2 activity (mmol/min/L)	647.92±153.50	593.90±146.27	**0.001**
HOMA-IR index	2.80± 1.63	2.30± 1.59	**0.004**
Insulin (µIU/dl)	11.31±3.88	10.41±4.27	**0.001**
C-reactive protein (mg/L)	13.56±5.01	11.92±7.42	**0.004**
White blood cell (/mm3)	7455.63±1715.00	7906.3±1495.25	**0.008**
Neutrophil (/mm3)	5.435±3.02	5.44±3.17	0.952
Lymphocyte (/mm3)	1.93±0.93	1.98±0.96	0.587
Platelet (103/mm3)	243.31±97.03	267.72±95.57	**0.018**
Mean Plate Volume (mg/L)	9.77±1.15	9.99±0.82	**0.032**
Mean corpuscular volume (mg/L)	85.98±7.84	88.8±5.20	0.542
Red cell distribution width (mg/L)	13.48±1.50	14.26±2.06	**0.001**
Vitamin D 20 (ng/ml)	n (%)	n (%)	
Deficiency <20 ng/ml	86 (68.3)	153 (53.5)	
Insufficiency 20 -30 ng/ml	27 (21.4)	93 (62.5)	**0.019**
Sufficiency>30 ng/ml	13(10.3)	40(14.0)	

Table 4. The relationship and risk predictors of the Coronary Artery Disease patients using multivariate stepwise regression analysis (N=412).

Variables	Regression coefficient	Standard Error	St. Coefficients Beta	t-test value	p-value significance
Lipoprotein-associated Phospholipase A2	-0.146	0.022	-0.147	-6.796	0.001
Body Mass İndex (kg/m2)	-0.020	.005	-0.202	-4.388	0.001
Systolic Blood Pressure mm Hg	-0.013	.002	-0.271	-5.428	0.001
Metabolic Syndrome	0.137	.044	0.176	3.099	0.002
Creatine kinase myocardial band(ug/L)	-0.126	0.056	-0.118	-2.352	0.019
Calcium (mmol/L)	0.082	.036	0.116	2.277	0.023
Triglyceride (mmol/L)	0.220	.010	-0.111	-2.194	0.029
Total cholesterol (mmol/L)	-0.050	0.020	-0.091	-2.001	0.046

Discussion:

This study identified increased total plasma Lp-PLA2 activity in patients with the metabplic Syndrome, especially in those with coronary artery disease when compered to the patients without metabolic syndrome. To point out, our data provided that elevated Lp-PLA2 activity indicates increased risk of CAD with Metabolic syndrome.

The current study revealed that Lp-PLA2 activity was significantly higher in subjects with Metabolic Syndrome in our study. These findings are similar to those from the Bruneck Study [3]. In the current study we have achieved significant associations between metabolic.syndrome ATP III and Body Mass Index (kg/m2), uric acid (mmol/L), ferritin (ug/L),systolic BP mm Hg, diastolic BP mm Hg,CK-MB (ug/L), HOMA-Insulin Resistance, Mean Plate Volume (mg/L),platelet (mg/L), red cell distribution width (mg/L), White Blood Count-WBC (/mm3), vitamin D (ng/ml), hemoglobin A1c (%), vitamin B12, and calcium (mmol/L). Those results are consistents with te Tsimikas et al. Results. [3]. Additionally, this study confirms the strong association between Lp-PLA2 levels and the metabolic syndrome [2, 7].

The Malmö Study findings are consistent with a recent report from the Intermountain Heart Collaborative Study [9], where 42% had the metabolic syndrome. There is observational evidence that Lp-PLA2 may be a useful guide for therapeutic efficacy [21-23]. Lp-PLA2 is complementary to CRP for risk assessment in patients with MetSynd [22-23].. The current results confirmed the

hypothesis that Lp-PLA2 may be a potential risk marker for CAD in the Turkish population. Further, a total of 429 patients in German population with suspected acute coronary syndrome were analysed and Lp-PLA2 turned out to be a more effective risk marker than high sensitivity CRP in these patients. The above different population studies are consistent and confirmed our present study.

Furthermore, Persson et al [7] explored to investigate the role of lipoprotein is associated phosholipase A2 (Lp-PLA2) with the MetSynd, and incident cardiovascular disease (CVD) among Swedish patients. The study results revealed that the cohort study of Lp-PLA2 is associated with the MetS. There is an excellent agrement between Persson et al [7] Sweden study and current study.

In most recent conducted study [25] that use of postmenopausal hormones, not smoking, and having a BMI less than 25 kg/m^2 where favorably confer a beneficial effect on Lp-PLA2 activity. Therefore, Lp-PLA2 activity may represent a novel pathway correlated with increased CAD. Overall, this results are similar and confirmative with our current results outcome.

To the best of our knowledge, the present analysis is the first one studying the contribution of Lp-LPA2 to CAD in the presence of MetSynd, and these findings indicate that Lp-PLA2 may play a role in the process of CAD independently of MetSynd. As well as, we used locally recommendation regarding waist circumference measurement for the diagnosis of MetSynd.

limitations:

The present study has several limitations. Firstly, the study based on a single measurements of plasma Lp-PLA2 which may not reflect the true activity of Lp-PLA2 over time or true expression in coronary artery disease. Secondly, we were unable to rule out the possible impact of aspirin, beta blockers, statins and fibric acid derivatives on Lp-PLA2 activity in the current findings. Thirdly, the study was conducted only with outpatient patients registered in cardiology clinics. This fact limits the generalizability of the results and establishes a need for multicenter studies to achieve a better understanding of such outcome predictors.

Conclusion:

Lp-LPA2 contributes to CAD in the presence of MetSynd, as well as Lp-PLA2 could be utilized as a useful predictor in cases of CAD with MetSynd.

Ethics Committee Approval: The study protocol was approved by the Istinye University clinical research ethic committee Ethics Committee Decision No. were 2/2021.K-78) and the Clinical Research

Ethics Committee of Istanbul Medipol University, Institutional Review Board (IRB# 10840098-604.01.01-E.3193 and IRB# 10840098-604.01.01-E.8421).

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Contributors

AB, AN, contributed to conception, design, organized study, collected data, performed statistical analysis and wrote the first draft of the article, and contributed to the to the interpretation of the data and writing, revised critically and approved final version of manuscript.

ZN and MA, are organized study, collected data, wrote the first draft of the article, and contributed to the interpretation of the data and writing, revised critically and approved final version of manuscript. All authors approved the final version.

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