Lipoprotein (a) and Arterial Stiffness in Patients with Diabetes Mellitus

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LIPOPROTEIN (A) AND ARTERIAL STIFFNESS IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

Background: *Type 2 Diabetes Mellitus (T2DM) increases morbidity and mortality of cardiovascular disease including atherosclerotic complications. The pathogenesis of atherosclerosis in T2DM is primarily due to changes in lipid profiles and lipoproteins. High levels of lipoprotein (a)/Lp (a) are known to be a risk factor for atherosclerosis. However, the correlation between Lp (a) levels and arterial stiffness has not been widely known.*

Objectives: *To determine the correlation between Lp (a) and arterial stiffness measured by brachial-ankle pulse wave velocity (baPWV) in patients with T2DM in Endocrine Metabolic and Diabetes Unit of RSUD Dr. Soetomo Teaching Surabaya.*

Methods: *The cross-sectional observational analytical research was conducted on T2DM patients aged ≥45 in Endocrine Metabolic and Diabetes Unit of Dr. Soetomo Teaching Hospital from June 2015 to August 2015. T2DM was determined based on the American Diabetes Association (ADA) 2014 criteria. Lp (a) was measured using Latex agglutination testand arterial stiffness was measured by baPWV.*

Results: *Among 39 T2DM patients, 25.6% had Lp (a) ≥30 mg/dL with mean of Lp (a) levels of 21.66±18.67 mg/dL and 94.9% of patients had the mean of baPWV of 16.61±2.57 cm/s. The correlation result of Lp (a) and baPWV showed $p = 0.88$ and $r = 0.026$.*

Conclusion: *There was no correlation between Lp (a) and arterial stiffness (using baPWV measurement) in patients with T2DM.*

KEYWORDS: *lipoprotein (a), arterial stiffness, diabetes mellitus*

INTRODUCTION

Lipoprotein (a) [Lp (a)] is an independent risk factor of atherosclerosis (1,2). Several studies have reported macrovascular complications of T2DM associated with high levels of Lp (a) (3,4). Other studies reported Lp (a) levels in T2DM patients did not change and did not correlate with diabetic status or arterial stiffness (5–8).

The increasing number of T2DM patients in Indonesia especially in Jakarta (5.7% in 1993 to 12.8% in 2001), led to an increase of mortality and high disability derived from macrovascular complications that manifest as atherosclerosis (9).

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There are various ways to measure the arterial stiffness in atherosclerosis, but none of them becomes the gold standard. Arterial stiffness can be measured using carotid femur-Pulse Wave Velocity (cfPWV) and Cardio-Vascular-Index (CAVI) with insignificant results. Brachial ankle-Pulse wave velocity (baPWV) is believed to be the most reliable and the best measurement of artery stiffness (10). A study by Wakabayashi et. al. (11) mentioned that there was a significant correlation between Lp (a) levels and arterial stiffness measured by baPWV.

Therefore, we hypothesize that there is a correlation between Lp (a) levels with arterial stiffness (using baPWV measurements) in patients with T2DM. The study aims to determine the correlation of Lp (a) levels with artery stiffness measured by baPWV in T2DM patient who in Endocrine Unit-Internal Medicine Department of Dr. Soetomo Teaching Surabaya.

METHODS

Population

This study used observational analytic research with cross sectional design. There were 39 patients of T2DM who in the Endocrine Metabolic Unit-Internal Medicine Department of Dr. Soetomo Teaching Hospital who participated in this study. Patients with T2DM were determined based on one of these criteria: clinical history of T2DM or with classic symptom of DM with HbA1c ≥6.5% or fasting venous blood sugar ≥126 mg/dL or glucose ≥200 mg/dL during Oral Glucose Tolerace Test by ADA 2014. The subjects met the inclusion criteria (patients with Type 2 DM; and men and women aged ≥45 years) but not exclusion criteria (patients with hepatic dysfunction, renal function, pregnant women undergo estrogen-progesterone hormone therapy, usage of niacin drugs, patients with infections, patients with chronic inflammatory diseases, and malignant patients). All subjects have agreed and signed the informed consent. Characteristics of subjects such as sex, HbA1c, BMI, hypertension, dyslipidemia, smoking activity were recorded.

Lipoprotein (a) levels were determined by the latex immunoassay method at PRODIA Laboratory Surabaya. The normal value of Lp (a) is <30 mg/dL, while Lp (a) ≥30 mg/dL is considered high (11,12). Arterial stiffness was measured using baPWV in the Diabetes and Nutrition Center of Dr. Soetomo Teaching Hospital Surabaya. Faster pulse wave time obtained compared to normal condition (more than 1350 cm/sec) indicates a vascular rigidity. The baPWV has sensitivity and specificity of 91% and 75%, respectively, in ABI = 0.095. Values were expressed by variable ratio (13).

RESULTS

Analysis on 39 patients with T2DM obtained the mean age of T2DM patients was 59.26 ± 8.03 years, with the youngest age of 46 years and the oldest of 77 years. The female group was higher than the male group with a ratio of 41:59.

The results of Lp (a) examination of 39 samples showed the mean of Lp (a) level was 21.66±18.67 mg/dL with 2 patients had the lowest Lp (a) levels of 2.8 mg/dL and 1 patient with the highest Lp (a) levels of 66 mg/dL. The cut off used for Lp (a) level was 30 mg / dL, thus there were 10 samples with high Lp (a) levels meanwhile most of the sample had normal Lp (a) levels.

The mean of Lp (a) levels in women was higher than the male group; 27.94±22.37 and 17.28±14.57 with the Mann-Whitney test obtained p = 0.16. Therefore, it concluded that there was no difference on the mean of Lp (a) levels in the group of male and female. HbA1c, BMI and smoking variables were tested with an independent-sample t-test. HbA1c's variable analysis test obtained p = 0.93, thus it concluded that there was no difference on the mean of Lp (a) level in the group of HbA1c <7% and the group of HbA1c ≥7%, with mean in each group by 17.28 ± 14.57 and 22.38 ± 18.47. Distribution of lipoprotein (a) levels for each characteristic of subjects are shown in table 1.

The analysis test on hypertension variable obtained p = 0.87, meanwhile the analysis test on the variable of dyslipidemi obtained p = 0.89, it concluded that there was no difference on the mean of Lp (a) level in the group with hypertension and dyslipidemi or undiagnosed group. Test analysis on smoking or non-smoking group obtained p = 0.34, thus there was no difference of Lp (a) level in each group.

The results of baPWV examination showed the mean of the pulse wave of 16.61 ± 2.57 cm/sec. There were 2 patients within normal limits (<1350cm/sec) and most of the samples showed a vascular stiffness; 37 patients with a pulse of ≥1350cm/sec. The distribution of baPWV examination for each characteristic of subjects are shown in table 2.

TABLE 1

Results of Bivariate Analysis and Distribution of Lp (a) on Each Basic Characteristics of Samples

Characteristics Variable	Lipoprotein(a) Mean±SD (mg/dL)	Range Min.	Range Max.	P
Sex				
Male	17.28±14.57	3	66	0.16
Female	27.94±22.37	2.8	52	
HbA1c				
<7%	17.28±14.57	2.8	59	0.93
≥7%	22.38±18.47	3	66	
BMI				
Normal	18.97±19.24	2.8	57	0.69
Overweight	17.5±20.97	2.8	66	
Hypertension				
Yes	21.87±18.74	2.8	66	0.87
No	20.20±20.30	4	52	
Dyslipidemia				
Yes	21.88±18.87	2.8	66	0.89
No	13±0	13		
Smoking				
Yes	11.00±9.9	4	18	0.34
No	19.74±16.28	2.8	66	

TABLE 2.

Results of Bivariate Analysis and Distribution of baPWV on Each Basic Characteristics of Samples

Characteristics Variable	baPWV Mean±SD (cm/detik)	Range Min	Range Max	p
Sex				
Male	17.07±2.14	13.9	21.3	0.31
Female	17.07±2.14	11.5	24.1	
HbA1c				
<7%	15.92±2.37	12.6	21.1	0.35
≥7%	16.82±2.63	11.5	24.1	
BMI				
Normal	16.09±1.57	13.2	18.4	0.42
Overweight	16.72±2.74	11.5	24.1	
Hypertension				
Yes	16.88±2.59	11.5	24.1	0.44
No	14.80±1.60	13.2	16.8	
Dyslipidemia				
Yes	16.65±2.59	11.5	24.1	0.56
No	15.35±0	15.4	15.4	
Smoking				
Yes	20.43±5.20	16.8	24.1	0.20
No	16.41±2.31	11.5	21.3	

The analysis of each variable was obtained as follows: sex p = 0.31, HbA1c p = 0.35, IMT p = 0.42, hypertension p = 0.44, dyslipidemi p = 0.56 and smoking p = 0.20, therefore it concluded that there was no difference between the mean of baPWV value on all characteristic variables (p >0.05).

DISCUSSION

Lipoprotein (a) and arterial stiffness are known as markers associated with atherosclerosis. The influence of Lp (a) with atherosclerosis through 2 mechanisms, namely 1.) The mechanism of atherogenesis through the oxidation process of Lp (a) and uptake Lp (a) by macrophages into the intima tunica, it is similar to LDL and Lp (a) that also causes rupture of atherom plaque. 2.) Thrombosis mechanism through partial homology between apo (a) and plasminogen resulting in binding competition to plasminogen receptors in the endothelium. Lipoprotein (a) also causes PAI-1 to increase; thereby it inhibits plasminogen into plasmin resulting in decreased fibrinolysis process. A study by Tsimikas (14) reported that Lp (a) had a strong relationship with atherosclerosis. Momiyama et al (15) reported the concentration of Lp (a) indicated a correlation with the progression of stenosis and is an independent factor against atherosclerosis. A study by El Gendi et al (16) also reported that Lp levels (a) related to the thickness of the tunica intima carotid artery.

This study showed that Lp (a) and plasminogen competed in the binding process in target cell surface receptors (endothelial cells) and fibrin, and inhibited the fibrinolytic activity of plasminogen (17,18). The formation of plasmin decreased due to the competitive process of Lp (a) to the receptors on the surface of fibrin and targeted cells by some K-IV coffee, thus it caused fibrin and lipid deposits in the vascular wall leads to thrombogenesis processes (17).

Lipoprotein (a) has a high affinity for fibrinogen and fibrin which can inhibit plasminogen to bind. The competitive process of Lp (a) and plasminogen over fibrin is the basis for the formation of atherosclerotic plaque. The fibrinolytic effect of Lp (a) is also determined by apo (a) polymorphism which also describes the activity of lipoprotein fibrin binding to fibrin. The affinity of Lp (a) to fibrin depends on the size and concentration of lipoproteins; the size of Lp (a) is smaller, then the affinity for fibrin is higher (8).

The studies by Kotani et al (19), Wakayabashi et al study (11), Funatsu et al (5) mentioned that the mean values of Lp (a) were 5 mg/dL, 18.6 mg/dL and 16.5 mg/dL respectively. The mean of Lp (a) in this study was 21.66±18.67 mg/dL. Several studies conducted in Japan obtained a lower mean value than this study. This may be due to this research was conducted in different countries, besides the genetic factors also played a role in determining Lp (a) levels.

Although some studies have reported that Lp (a) was correlated with atherosclerosis, this study has not been able to demonstrate the correlation. This might be be due to the number of samples with high Lp (a) level were 25.6% meanwhile the artery stiffness were 94.87%. In addition, this insignificant correlation was also assumed due to the confounding variables that could not be controlled during the sample selection process. This variable consisted of genetic factors, age, sex, BMI, duration of DM, dyslipidemia, and hypertension.

Increased arterial stiffness in T2DM patients may occur in both central and peripheral arteries, baPWV examination may describe the stiffness of the arteries, both central and peripheral. The baPWV sensitivity was 91% and the specificity

was 75% in ABI = 0.095. Whereas in ABI, the sensitivity <0.95 and its specificity decreased (13).

The mean of baPWV in this study was 16.61±2.57 cm/sec, whereas a study by Funatsu et al [5] obtained the mean of baPWV by 18.5±4.8 cm/sec. The study by Funatsu obtained larger baPWV results due to diabetic retinopathy as one of the inclusion criteria, so the study sample had been subjected to microvascular disorders.

The subjects of this study were associated with high risk factors, as indicated by the number of subjects with poor blood sugar control, obesity, hypertension, and dyslipidemia. Although these confounding factors were not reported to affect Lp (a) levels, but these confounding factors greatly affected the stiffness of the arteries.

This study had some limitations namely, the researcher used cross-sectional design thus the examination of Lp (a) levels and arterial stiffness (baPWV) were only performed once, population of T2DM patient in the Outpatient Installation of Metabolic and Diabetes Endocrine Unit-Internal Medicine Department of Dr. Soetomo Teaching Hospital Surabaya in chronic conditions, insufficient sample size, long lifespan, no control group, and could uncontrolled confounding variables due to population limitations.

CONCLUSION

There was no correlation between lipoprotein (a) and arterial stiffness in patients with T2DM, therefore further research is required.

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